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Plasmonic biosensors: Towards fully operative detection platforms for biomedical application and its potential for the diagnosis of autoimmune diseases

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ABSTRACT

In-vitro diagnostics (IVD) has become an in-demand area with a high-achievement transformation due to the expansion of new technologies. Technology has grown from time-consuming laboratory techniques to modern automated immunoassays and progressed with real-time sensing through the emergence of biosensor devices. Plasmonic biosensors are one of the most employed optical biosensors and stand out for their versatility and wide range of applications in diagnostic tests. One of the clinical diagnostics areas of growing interest is autoimmune diseases (AD), which have been increasingly prevalent worldwide. There is a rising demand for reliable and early AD diagnosis tools. This review highlights the main challenges for early AD diagnostics and the advanced plasmonic biosensors that have been exploited for AD biomarker detection, including brief descriptions of their analytical performance. Finally, the prospects and trends in this area are outlined, thinking about developing multiplexed platforms capable of addressing the multianalyte nature of one disease.

1. Introduction

Biosensors are becoming progressively an excellent alternative for modernizing biological analyses, impacting medical diagnostic research and healthcare systems [1–3]. *In-vitro* diagnostics (IVD, laboratory tests, and diagnostic technologies) are used around 70 % of the time in clinical practice, shaping the basis for clinical and therapeutic decisions in a similar percentage, especially in emergency departments, oncology, and cardiology specialties [4]. These statistics highlight the relevance of implementing more sensitive and affordable novel methods, with shorter turnaround analysis times and with the potential to be decentralised and bring diagnostics close to the patient. Biosensors hold unique significance in covering those needs. For the last 25 years, a myriad of sensing configurations based on diverse transduction mechanisms have emerged to improve current analytical methods and overcome some of their limitations: shortening analysis and turnaround times, improving sensitivity, and reducing sample volume and manipulation. A biosensor is a self-contained device, including a biological sensing element (enzymes, antibodies, or nucleic acids) capable of interacting with the target analyte in a complex sample, and a transducer. The specific interaction generates a discrete or continuous physicochemical change in the transducer element, which can be further converted into an electrical signal easily monitored over time [5,6]. Electrochemical and optical transducers are, by far, the more extensively sensors studied and the ones offering better performance. The photonic ones, especially those based on refractometric sensing that rely on the evanescent wave working principle [7–9] and operate in a label-free configuration, have achieved exceptional features that are positioning them as next-generation point-of-care sensing devices. Their exceptional performance has been thoroughly demonstrated and they have been employed for diverse applications, at least at the laboratory level. It is in the field of clinical diagnostics where they find the most suitable niche for growth and real implementation.

The evanescent wave-based optical biosensors have reached relevance and maturity mainly due to the success of the plasmonic biosensors, which are based on the surface plasmon resonance (SPR)

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generated on metallic surfaces under specific and easily achieved optical illumination conditions. Besides their evolution in design and configurations, the research has concentrated on developing and implementing real applications demonstrating their advantages over traditional analytical tools for environmental monitoring, food safety, and mainly in the biomedical and clinical fields (diagnosis and therapy follow-up), as cancer, infection diseases, cardiovascular diseases, and brain-related disorders for example [10–21]. Among these main areas of IVD applications, autoimmune diseases (AD) are a remarkable class of disorders with a wide range of heterogeneous conditions and commonly complex diagnoses that may require different techniques. AD comprise chronic disorders with striking effects on morbidity and mortality, involving more than 100 types of diseases with an increasing incidence. There is commonly no single test for each diagnosis as they often rely on the clinical observation of symptoms combined with the identification of several biomarkers in fluids (mainly blood) and possibly tissue biopsy. Compact and novel devices that allow multiple efficient biomarkers detection that can help differentiate one disorder from another, preferably close to the patient, can contribute to early diagnosis and prognosis, prevention of permanent damage in organs and tissues, and patient stratification. Due to the features of plasmonic biosensors, they have also become increasingly attractive in this biomedical field.

This overview focuses on the development of plasmonic biosensors for AD diagnosis, highlighting the main contributions reported in the literature in the last years. We will briefly introduce the basic principles and technology behind plasmonics sensing, describing different configurations and platforms for clinical diagnosis. We will then describe the recent progress in AD detection using plasmonic biosensors. Finally, we will comment on the challenges and emerging future for plasmonic biosensors.

2. Plasmonic biosensors: fundamentals, sensing configurations, and evolution

The fundamental principle behind photonic biosensors, including plasmonics, lies in the generation, under particular conditions, of a confined evanescent field in a waveguide structure [9]. Typically, the evanescent wave can be created when polarised light hits a metal surface or travels through a waveguide under total internal reflection (TIR) conditions. Under these conditions, light is confined, but it partially penetrates the external/outer medium with a lower refractive index (RI), generating an evanescent wave. Depending on the optical transducer, different properties of the guided or reflected light (*i.e.,* wavelength, intensity due to changes in the absorption or dispersion of light, polarisation, or phase) are significantly affected by minute changes in the dielectric medium within the evanescent range, such as those coming from any alteration in the RI. Moreover, the intensity of the evanescent field decays exponentially with distance from the interface (*i.e.,* between 10 and 900 nm approximately, depending on the transducer, the waveguide design and configuration, and the propagating wavelength) making the waveguide surface extremely sensitive. This working principle has proven very helpful for biosensing through the appropriate receptor immobilisation on the surface of the transducer and the subsequent direct and selective analyte capture [22]. Thus, any interaction on the surface (for example, either the attachment of the receptor directly to the surface, or the subsequent analyte binding to the receptor) culminates immediately in a significant change in the RI, which can, therefore, be monitored as it occurs in real-time. Due to the described working principle, the evanescent wave-based optical transducers allow direct detection, without the need for indirectly labelled (i.e., colorimetric, fluorescent, etc.), of virtually any interaction (specific or nonspecific binding) occurring on or close to the surface. As a consequence of the real-time monitoring, this configuration still offers the possibility to extract affinity or kinetics parameters of the interaction event [23]. Depending on the plasmonic transducer and the final configuration of the device, the resolution commonly expressed in refractive index units (RIU) can reach values between 10^{-5}-10^{-8} RIU, and the limit of detection (expressed as the mass density over the surface) as low as 0.01 pg/mm^2 [24,25]. These features commonly reflect analytical sensitivities and detectabilities, employing appropriate receptors with enough affinity, in the low pM-nM range in a direct and amplification-free approach, which is highly competitive for many applications, including clinical diagnosis.

Among the different evanescent-wave-based transducers, surface plasmon resonance (SPR) has become the most common, widely studied, and employed optical biosensor [5,9,26]. The working principle of an SPR biosensor mainly relies on the generation of surface plasmons, produced by the collective oscillation of surface electrons at a metal-dielectric interface, which occurs when light strikes the surface and partially couples with the electrons, generating the evanescent field. Gold (and silver to a much lesser extent, given its lower stability and tendency to oxidation) is the most used metal, as the required excitation conditions can be met in the visible and near-infrared regions, simplifying the optical elements for the plasmon excitation. The plasmons generated are propagated over the surface of thin layers of the metal, and the excitation must be performed under certain optical conditions. Thus, the light wave's vector parallel to the interface $\left(k_x^{light}\right)$ must match the propagation vector of the surface plasmons $\left(k_x^{SPR}\right)$ as described by the following equation [5]:

$$k_x^{SPR} = \frac{2\pi}{\lambda}\sqrt{\varepsilon_d}\sin\theta = k_x^{light}$$

For metals like Au and Ag, these excitation conditions can be met in the VIS and near-IR regions, which simplifies the optical elements needed. For thin-layer films, it is necessary to incorporate coupling elements that allow the appropriate incidence of light. This can be achieved by (i) waveguide structures, where the light is coupled and guided by Total Internal Reflection (TIR) and evanescently penetrates through the metal film, thus exciting the plasmons at the interface; (ii) via diffraction grating couplers, employing periodically structured surfaces and through direct illumination at optimal incident angle; (iii) and the most used one, via prism-coupling in a Kretschmann configuration, where the light passes through a high RI prism and is reflected by TIR generating the evanescent wave that penetrates the metal film and excites the plasmons. Thus, these strategies are based on the effectively excited surface plasmons at the thin metal, and the metal absorbs part of the incident light. In a different design based on fiber-optic SPR, the light is propagated through a fiber core (internally covered with a metal coating) when enters at specific angles, traveling by TIR. Detection of the reflected light relies mainly on angular, intensity, or wavelength interrogation through monitoring one of these parameters over time using spectrophotometers or photodiodes. For angular interrogation, the SPR is excited by a monochromatic light (i.e. lasers, narrow-band LED), and the monitor is related to the shift in the reflected light angle (θ_{SPR}) over time when the RI is changed. Similarly, in wavelength interrogation, polarized broadband light is used to excite the plasmons at a fixed incident angle, monitoring the shift in the plasmonic peak (λ_{SPR}) over time (wavelength over time). For intensity interrogation, the angle and the wavelength of the incident light are fixed, and the monitor is based on the SPR intensity change, commonly where the slope of the resonance curve is maximized. This last mode is used also by the SPR imaging (SPRi), where a multiplexed capabilities can be achieved [27], which facilitates parallel analyses in an arrayed format, and the detection requires a CMOS/CCD camera measuring the intensity distribution over a multispot surface. The intensity changes due to RI changes such as those from a binding event are then detected with digital image processing algorithms. However, the sensitivity of the imaging configuration is slightly worse, although commercialized versions are already reaching limit of detection close to 10^{-6} RIU, similar to conventional SPR.

More than 25 companies commercialized these devices, both conventional SPR and SPRi, since the first instrument introduced by Biacore

(currently Cytiva, United States), with different extents of multiplexed capabilities and performance (i.e. from 1 to 4 channel instruments in conventional SPR, to multispot designs including 24, 48, 96 sensing areas or even more for SPRi technologies. Overall, conventional SPR or SPRi biosensor systems usually involve very bulky equipment including the microfluidic system, fiber or light input connections, a spectrometer or CCD camera/CMOS detectors, and electronics for data acquisition [28]. Moreover, the elevated cost of these instruments and the fact they are not linked to specific IVD applications have constrained their use at the research and innovation level, limiting their implementation in the clinical field by the end user. Reducing size and cost while retaining the performance of high-performance SPR instruments has been a critical goal to further pursue a commercialization route as POC device for dedicated applications.

This challenge can be partially overcome with localised surface plasmon resonance (LSPR)-based instruments since there is no need for optical coupling for exiting the LSPR. In LSPR, metallic nanostructures, smaller than the incident light wavelength, are used for sensing. In this case, the light interacts with these nanostructures (nanorods, nanospheres, nanoshells, nanoholes, etc.), enabling plasmons to oscillate locally around them [29,30]. LSPR sensor chips based on nanostructured substrates (i.e. nanoparticles deposited on top of glass transparent substrates —bottom-up fabrication— or fabricated by top-down nanofabrication methods like lithography) can be manufactured at affordable prices, making them more attractive for POC application. The multiplexed capabilities of LSPR are also more feasible when employing also CCD/CMOS detection elements. Fewer examples of commercialized LSPR-based instruments can be found, although still limited to moderate multiplexing (4–8 channels). During the last decades, enormous efforts have been devoted to improving the plasmonic technology to allow cost-effective miniaturisation and multiplexing capabilities [5,8,26]. Some works address the adaptation of smartphone technology (high--performance cameras, processing power, etc) to plasmonic devices incorporating external low-cost modules that include microfluidics with the transducer chip, additional optical components, and custom-design software, in such a way the cost and integration can be drastically reduced [31–34].

Regarding miniaturisation, integration, and multiplexing aspects, the plasmonic biosensors have been adapted to save reagents and time and facilitate the read-out results, using low-cost components and user-friendly software. As an example of faster analysis due to the simultaneous evaluation, Beeg et al. [35] developed an SPR assay for determination of Infliximab, an antibody against tumour necrosis factor α (TNFα), anti-Infliximab, and TNFα in serum samples, using an array system with six flow channels on parallel strips of the same sensor surface, and performing six injections at the same time. The biosensor assay has broken ground to new SPR arrays for multiple determinations, resulting in cost-effectiveness over commercial enzyme-linked immunosorbent assay (ELISA) kits. Other applications solving clinical challenges [36–38] using plasmonic biosensor technology have attempted integration into POC into POC platforms. For example, using a plasmonic diffraction grating sensor with angular interrogation, Vala et al. [39] proposed a disposable sensor cartridge with 10 independent channels that obtained a resolution of $6{\cdot}10^{-7}$ RIU. In the same way, to do multiple analyses, Zhao et al. [40] reported a prototype of a multichannel fully integrated portable plasmonic biosensor using a comprised optical system of 4 parallel light beams to detect anti-cancer drug (methotrexate) leading the way for promising plasmonic biosensor arrays for clinical users. Fig. 1 summarizes the main components and systems in plasmonic biosensor technology for POC devices, including some reported SPR designs.

Overall, considering the great potential of plasmonics sensing for compact integrated POC devices, its implementation into fully operating commercial devices capable of quantifying analytes from unknown biological samples on a routine basis is still measly advanced. Although the literature reports improvement in configuration and design, none of them reach mature results to further pursue a commercialization with a dedicated specific application. This issue is partly due to the complexity of implementing operative, robust, integrated platforms with the required performance to reach the market, and the custom-biofunctionalized biosensor chips for routine analysis. In this regard, the production of disposable chips integrated in cartridges, with

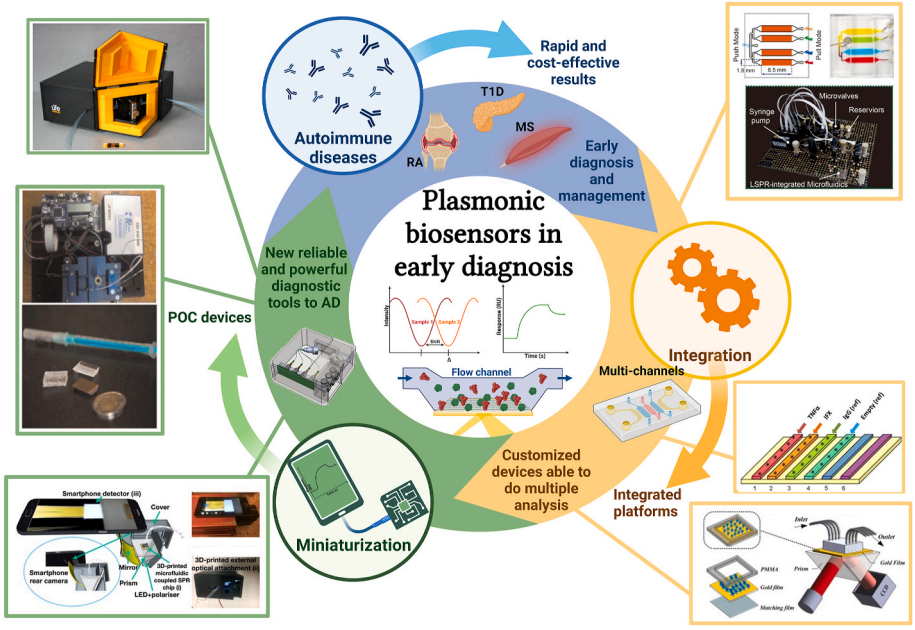

Fig. 1. Schematic representation of the main aspects involved in the development and implementation of the plasmonic biosensors into POC devices for diagnostic purposes, including the study, detection, and monitoring of AD: integration of multi-channels on SPR or LSPR sensors, and representative prototypes of potential integrated POC devices. (RA: rheumatoid arthritis; T1D: type 1 diabetes; and MS: multiple sclerosis). The inserted pictures were adapted from Ref. [41] – Copyright Clearance Center 2020, Royal Society of Chemistry [35]; – Copyright 2019, The Author(s) [39]; – Copyright (2010) with permission from Elsevier [40]; – Copyright (2015) with permission from Elsevier [42]; – Creative Commons License Deed [43]; – Copyright (2022) with permission from Elsevier. Created with Biorender.com.

dedicated microfluidics already biofunctionalized incorporating the bioreceptor is a delicate and crucial aspect, with associated challenges of stability and reproducibility that require specific quality controls. Moreover, translating this to a multianalyte platform, with several bioreceptors incorporated for multiplexed detection considerably complicates and lengthens the development process and the successful implementation in the clinical routine.

3. Plasmonic biosensors for AD diagnosis and follow-up

AD encompasses several diseases whose diagnosis is often complex and slow because the patients exhibit many unspecific symptoms common to other clinical conditions. The body's immune system is vital in protecting us against external agents and pathogens threatening our health. However, under certain circumstances that are not fully understood, the immune system accidently attacks and damages our tissues and organs (especially by aberrant B and T cells), causing inflammation and leading to the development of an AD [44–46]. Reports on the frequencies of the diagnosis of ADs indicate that their incidence and prevalence have increased over the last 40 years [44,47–49]. However, long-term follow-ups are scarce. ADs are classified into: (i) organ-specific; an immune response is directed against a single organ (Addison disease, thyroid diseases, Graves' disease, primary biliary cirrhosis, type 1 diabetes, celiac disease, vitiligo, Crohn's disease), and (ii) systemic, the immune response is against several organs (rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, systemic sclerosis). Thus, AD is a diverse group of conditions affecting individuals of any age with highly varied clinical manifestations, from acute life-threatening organ failure to subtle laboratory alteration, that easily escapes notice [45,47,50,51]. Their diversity is striking and challenges the medical system, becoming an enigma in diagnosing a patient with different signs and symptoms (pain, sore muscles, fatigue, redness, swelling, joint and abdominal pain, recurring low-grade fever, numbness in hands and feet, and skin rashes) [45,47]. Commonly, AD is diagnosed at a stage when the tissue/organ damage is irreversible, and the symptoms are hard to control. As there is no specific laboratory or histological marker for AD, having a diagnosis in the early stages is challenging but crucial for correctly managing the disease,

ADs are diagnosed based on symptoms combined with core laboratory tests. The analysis of circulating autoantibodies produced by the immune system against one or more antigens and tissues of the body and present in the blood is one of the gold standard methods applied in detecting diseases [49,50,52,53]. Despite being produced before the symptom's manifestation, detecting the autoantibodies may be complicated due to their low concentrations, the fact that the corresponding target antigens may have not been identified, and the poor affinity with an identified target [54]. Some autoantibodies are associated with multiple diseases, but others are disease-specific, making them diagnostic markers. Similarly, in some AD, autoantibodies against one specific antigen are involved but, in some others, several antigens (and autoantibodies) might be implicated. It is equally crucial to determine the presence and levels of such autoantibodies and the avidity of the target protein, as this may be involved in the disease progression and severity.

Autoantibodies detection is typically achieved through immunochemical techniques such as ELISA [55], indirect immunofluorescence (IIF) [56], and Western blotting [57]. These traditional methods have been developed for numerous autoantibodies to aid in diagnosing autoimmune diseases. These techniques require bulky and costly equipment, are time-consuming, and commonly rely on specialized staff to perform them, which limits their use only in centralized specialized laboratories. In some cases, the sensitivity might not be good enough in the early stages of the disease, when the autoantibodies concentrations are lower, therefore limiting more efficient diagnostics before more permanent damage has already occurred. Additionally, these methods cannot provide kinetics and affinity information of the biointeraction event, which can be extremely useful in these disorders as they are related to the overall avidity or association of the antibodies for their epitopes. It is also worth mentioning the variability in autoantibody testing, given the increasing number of immunoassays available for their detection (either manual or automated platforms that provide qualitative or semiquantitative results) [58]. Immunoassay-based techniques such as antigen microarrays for the detection of a panel of autoantibodies, or fluid-phase immunoassays, especially interesting for conformational epitopes from autoantigens, have been also explored in the last years however they are not easily adapted for routine clinical testing [59].

Besides autoantibodies, other relevant biomarkers with a suspected role in prognosis and diagnosis are also investigated depending on the disorder, such as different protein markers, like less specific cytokines and interleukins or miRNA [60–62] which can also be detected commonly with immunoassays like ELISA or PCR-based techniques, and extracellular vesicles/exosomes, whose detection requires prior accurate isolation to fully evaluate its role, with different techniques (i.e. ultracentrifugation, ultrafiltration, immunoaffinity chromatography, microfluidics-based strategies, etc), function, and content (i.e. through ELISA, Western blotting, or flow cytometry among others [63].

Overall, for both the detection of autoantibodies and other types of biomarkers, the incorporation of novel technologies that contribute to a more efficient, rapid, and affordable detection remains important and the role of biosensors and the plasmonic ones can become crucial, given their interesting features for clinical diagnostics. In particular, plasmonic biosensors have been developed for the most common autoimmune disorders, and most rely on the detection and affinity studies of autoantibodies although they have been implemented for other types of biomarkers.

The detection strategies considered for those more relevant autoimmune diseases, like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), celiac disease (CD), Crohn's disease, and multiple sclerosis (MS), will be detailed in the following sections. We have summarized the information provided in the reported bibliography in Table 1 including the most relevant aspects such as type of plasmonic device, biomarker and bioreceptor employed for the detection, type of information (quantification of biomarker, study of kinetics and affinity parameters, biofluid employed, analysis of real samples, etc).

3.1. Plasmonic biosensors applied to the diagnosis of rheumatoid arthritis

RA is an inflammatory, chronic, and systemic AD affecting about 1 % of the world population. As with other AD, it is predominant in females (2:1 to 3:1 female to male ratio) and typically develops between 30 and 50 years [97,98]. Usually, the rheumatoid factor (RF) is a common biomarker employed in the diagnosis and could be found in up to 80 % of RA patients. The RF are autoantibodies directed against the Fc portion of immunoglobulin (Ig), but in clinical practice, IgM RF is the most employed [99]. However, these autoantibodies could appear in other inflammatory conditions that trigger chronic antigenic stimulation. The anti-citrullinated protein epitopes autoantibodies (ACPA) are another biomarker widely employed for disease diagnostics due to their excellent predictive value [50,52,99] together with anti-carbamylated protein (anti-CarP) [100]. ACPA response is very heterogeneous among individual RA patients, and it has become relevant the assessment of ACPA profiles for multiple citrullinated antigens and relating them with clinical features, which may be helpful in patient's classification and personalizing therapy.

Based on this, most examples employing plasmonic biosensing have addressed the detection of ACPA, to profile affinity of ACPA for different citrullinated peptides. SPR imaging (SPRi) which allows multiple simultaneous and fast real-time analysis is a powerful tool for this purpose. Lokate et al. [64] demonstrated the usefulness of an SPRi biosensor, which allows a high level of multiplexed detection for the

Table 1
Overview of the plasmonic biosensors implemented for autoimmune diseases (AD) diagnosis, study, and monitoring.

AD	Plasmonic device	Target Biomarker	Immobilized ligands	Matrix	*Performance /Purpose of assay*	Working range	Analysis Time / Sample Volume	Ref.
RA	SPRi 24-spot array Commercial instrument	ACPA	LCP	Diluted serum (1:50) Human patient samples	LOD = 0.5 pM	ND	ND / 400 μL	[64]
RA	SPRi 36-spot array Commercial instrument	ACPA	Cit-P	Purified Serum samples Human patient samples	Affinity (K_D) determination	125–2000 nM	10 min / 500 μL	[65]
RA	SPRi 48-spot array Commercial instrument	ACPA	Cit-P	Diluted serum Human patient samples	Antibody profiling	ND	ND/ND	[66, 67]
RA	SPR 4 channel Commercial instrument	ACPA	Cit-P	Purified antibodies in buffer Human patient samples	Affinity (K_D) determination	31.25 – 2000 nmol/L	~6 min / 60 μL	[68]
RA	SPRi Commercial instrument	Anti-CCP	MIP	Buffer solution	LOD: 0.177 RU/mL	ND	ND / ND	[69]
RA	LSPR -Au NP- TFBG optical fiber biosensor	CCPs	Antibody (anti-CCP)	Buffer solution	LOD: 1 ng/mL	1-1000 ng/mL	4-10 min/ND	[70]
RA	SPR Commercial Instrument	Agalacto-IgG	PVL	Purified Serum Human patient patients	Qualitative comparison (patients vs control)	ND	5 min / 210 μL	[71]
RA	SPR Comercial Instrument	Anti-GPI	GPI	Diluted Synovial fluid (1/100) Human patient samples	Qualitative comparison (patients vs control)	ND	~3 min / ND	[72]
JIA	SPR Commercial Instrument	Anti-ADA	ADA	Diluted Serum 1:100 Human patient samples	Qualitative comparison (treated patients vs control)	5 – 200 μg/mL	10 min / 90 μL	[73]
RA	SPR Commercial Instrument	Chemokine (CXCL12)	Lentiviral particles	Buffer solution	Affinity/kinetic analysis	25 – 400 nM	10 min / ND	[74]
RA	SPR Custom-made device-2 channels	Chemokine (CXCL12)	LVPX4	Undiuted urine Human patient samples	LOD ≈ 5 nM	5 – 40 nM	5 min / 350 μL	[75]
RA, SLE	Dark-field imaging LSPR -Au-Nanorods chips (8 channels)	Cytokines:IL2, IL4, IL6, IL10, IFN-γ, TNF-α)	Specific antibodies	Serum samples spiked Human patient samples	LOD ~6.4–20.5 pg/mL	5 – 20 pg/mL	40 min / ~1 μL	[76]
RA, SS	SPR Commercial Instrument	CD5	Specific antibody	Diluted serum (1:10)	LOD: 1.04 nM (direct assay) LOD: 8.31 fM (mAuNPs amplification)	ND	10-20 min/ ND	[77]
SLE	SPR Commercial instrument	Anti-ds(DNA)	ds-DNA	Control serum	Kinetic studies	mAb standards: 0.078–16.4 nM	~7 min / 90 μL	[78]
SLE	SPR Commercial Instrument	Anti-ds(DNA)	ds-DNA	Diluted Serum (1/100) Human patient samples	Specificity: 98% Sensitivity: 83%	ND	ND / 90 μL	[79]
SLE	SPR Commercial Instrument	Anti-ds(DNA)	ds-DNA	Diluted Serum (1/100) Human patient samples	Diagnostic efficiency = 0.8	ND	ND / 90 μL	[80]
SLE	SPR Commercial Instrument	Anti-CRP mCRP	Complement Factor H	Buffer solution	Inhibition assay No LOD provided	1.56 – 50 nM	4 min / 200 μL	[81]
SLE (LN)	SPRi Commercial Instrument	Autoantibodies for C1 complex complements (-C1q, C1r, C1s andC1-Inh)	C1q, C1r and C1s	Purified Plasma Human patient samples	Qualitative assessment of binding	0 – 300 μg/mL	10 min / ND	[82]
APS	SPR Commercial Instrument	Anti-CL	aminocardiolipin	Diluted Serum (1/10) Human patient samples	Specificity: 100% Sensitivity (100%)	ND	~10 min / 100 μL	[83]
APS	SPR Commercial Instrument	Anti-β2GPI	β2GPI	Diluted Serum (1/90) Human patient samples	Qualitative Affinity estimation (K_D≈ nM) Qualitative diagnostic specificity and sensitivity	ND	9 min / ND	[84]
SLE, RA AIH	SPRi Commercial instrument	Anti-hnRNP A2/B1	Overlapping hnRNP peptides	Diluted serum (1/8000) Human patient samples	Kinetics evaluation (K_{off})	ND	~30 min / 120 μL	[85]
T1D	SPRi Commercial Instrument	Anti-GAD	GAD	Buffer solution	K_d ≈ 1.37 nM LOD ≈ 30-40 ng/mL	ND	~16 min / 200 μL	[86]

(*continued on next page*)

Table 1 (*continued*)

AD	Plasmonic device	Target Biomarker	Immobilized ligands	Matrix	*Performance /Purpose of assay*	Working range	Analysis Time / Sample Volume	Ref.
T1D	SPR Commercial Instrument	Anti-GAD	GAD	Buffer solution	LOD: 196.5 ng/mL LOD: 2.2 ng/mL (+AuNP) LOD: 0.03 ng/mL (AuNP + enzyme precipitation)	0.1 – 2 μg/mL 0.1 – 2 μg/mL 0.1 – 100 ng/mL (AuNP strategy)	45 min / 150 μL	[87]
T1D	LSPR in a fabricated nanoledge device	Anti-insulin	insulin	Buffer solution and control human serum	LOD≈ 0.1 ng/mL	0.1 – 10 ng/mL	Few min / ND	[88]
CD	LSPR- Plastic optical Fiber	Anti-tTG	tTG	Diluted control serum	Detectability: ~nM	30 – 3000 nM	~5 min / ND	[89]
CD	SPR Custom-made device	GIP	Gliadin (+ specific Mab)	Undiluted urine Human patient samples	Competitive assay LOD: 2 ng/mL	3.6-56 ng/mL	15 min / 200 μL	[90]
MS	SPRi Home-built instrument	Anti-gangliosides: Anti-GT1b, anti-GM, and anti-GA1	GT1b, GM, GA1 gangliosides	Control human serum, diluted 1:10	$LOD_{anti\text{-}GT1b}$: 8.2 ng/mL $LOD_{anti\text{-}GM}$: 11.3 ng/mL $LOD_{anti\text{-}GA1}$: 17.6 ng/mL	1 – 100 ng/mL	40 min / ND	[91]
MS	SPRi Home-built instrument	Anti-gangliosides: Anti-GT1b, anti-GM, and anti-GA1	GT1b, GM, GA1 gangliosides	Control human serum, undiluted	$LOD_{anti\text{-}GT1b}$: 4.5 ng/mL $LOD_{anti\text{-}GM}$: 5.6 ng/mL $LOD_{anti\text{-}GA1}$: 6.6 ng/mL	1 – 100 ng/mL	120 min / ND	[92]
MS	SPR Commercial Instrument	Antibodies against CSF114(Glc)	Glycopeptide CSF114 (Glc)	Diluted Serum (1:100 and 1:50) Human patient samples	Sensitivity: 36% Specificity (95%)	ND	~6 min / ND	[93]
MS	SPR Commercial Instrument	Antibodies against CSF114(Glc)	Glycopeptide CSF114 (Glc)	Diluted serum (1:100 and 1:50 Human patient samples	ND	1.25–20 μg/mL	5 min / 150 μL	[94]
MS	SPRi Commercial Instrument	miRNA-422 miRNA-223 miRNA-126 miRNA-23a	Complementary DNA probes	Human serum (control)	LODmiRNA-422: 0.55 pM LODmiRNA-223: 0.88 pM LODmiRNA126: 1.19 pM LODmiRNA23a:1.79 pM	1 – 500 nM (direct assay) 0.05 – 100 nM (amplification with Ab-NP)	120 min / 550 μL	[95]
MS	LSPR Custom-made setup (AuNP-based chip)	miRNA-17	Complementary DNA probe	Buffer solution	LOD: 1nM (direct assay) LOQ: 10 nM (direct assay) LOD 1 pM (HCR amplification)	0.001 – 1 nM (amplification)	30 min / 50 μL	[96]

ADA: Adalimumab; AIH: autoimmune hepatitis; anti-CL: anti-cardiolipin; Anti-ds(DNA): anti-double-stranded (ds)DNA autoantibodies; APS: antiphospholipid syndrome; AuNP: Gold nanoparticles; CCP: cyclic citrullinated peptides; Cit-P: citrulline-containing peptides; CD: celiac disease; CRP: C-reactive protein; EVs: extracellular vesicles; GAD: glutamic acid decarboxylase-65KDa isoform; GIP: gluten immunogenic peptides; GPI: glucose 6-phosphate isomerase; HCR: hybridization chain reaction; JIA: Juvenile idiopathic arthritis; LCP: Linerar citrullated peptides; LVPX4: Lentiviral particles bearing CXCR4; LN: Lupus nephritis; LSPR: Localised SPR; MS: Multiple sclerosis; NP: Nanoparticles; PD-1: cell death protein-1; PVL: *Psathyrella velutina* lectin; RA: Rheumatoid arthritis; SA: sialic acid; SLE: Systemic lupus erythematosus; SPRi: SPR imaging; T1D: type 1 diabetes; TFBG: Tilted-fiber Bragg Grating; tSPR: transmission SPR spectroscopy; tTG: transglutaminase; β2GPI: β2-glycoprotein I.

quantification of ACPA (Fig. 2A) in 50 RA patients and 29 control volunteers, being able to detect an antibody concentration as low as 0.5 pM in linear citrullinated peptides-arrayed sensor chips (24-spot array chips), and differentiated them from healthy individuals or patients suffering other AD (i.e. SLE or osteoarthritis). Taking advantage of the possibility of extracting association and dissociation binding parameters with the biosensor platform, Szarka et al. [65] evaluated the binding affinities of ACPA towards different synthesised citrulline-containing peptides, also employing a commercial SPRi instrument. The ACPA has a straight relation with the RA onset and progression, but knowledge is limited on the ligand binding affinities of the autoantibodies with several citrulline-peptide species. Based on the plasmonic analysis, the author concluded that 92 % of sera bound to citrulline-vimetin and all samples attached to the multi-epitope peptide (designed by the authors) on the sensor chip, allowing the development of better diagnostics and novel therapies for RA. Other examples show similar strategies with plasmonic biosensors as core elements to identify ACPA profiles against panels of citrullinated peptides for RA patients or early arthritis patients [66,67] and to characterise their affinity [68].

Other innovative strategies involve the development of new receptors for targeting these autoantibodies [69] or novel plasmonic devices [70]. Thus, Dibekkaya et al. [69] prepared a cyclic citrullinated peptide (CCP)-imprinted polymer based on acrylamide for its incorporation on a plasmonic sensor. With this strategy, the authors created a specific template, immobilized adequately on a gold sensor surface, able to interact with ACPA with significant affinity and specificity when compared with IgM and BSA. There are other plasmonic biosensors for RA implemented for the detection of different autoantibodies for other antigens like agalacto-IgG in serum [71] or glucose 6-phosphate isomerase in synovial fluid [72] validating them in RA patients and healthy donors' sera samples. Interestingly, the SPR has been employed also to assess the immunogenicity of therapeutic antibodies, like adalimumab, by assessing the generation of autoantibodies against the drug and their affinity in treated RA patients [73].

Besides autoantibodies, there are other biomarkers known as multi-biomarker disease activity, which could be employed for RA diagnosis, such as the antibody against tumour necrosis factor receptor (anti-TNF), C-reactive protein (CRP), and other chemokines [52,99,101]. Some of them, like CRP, are involved in innate immune response, acute and chronic inflammatory states, and infectious processes. The TNF is a critical cytokine, a signalling protein of acute and chronic inflammation, related to several disorders such as RA and Crohn's disease [102]. Its detection, relevant for many conditions and disorders, requires significantly low levels of detectability and has been attempted with plasmonic biosensors [103]. For example, Predabon et al. [104] described a gold nanohole plasmonic array biosensor using cysteamine/biotin/streptavidin/TNF-α antibody as bioreceptor layer, detecting the TNF-α by the monitoring of the transmitted light intensity. This biosensor reached a concentration detectability of only 17 pg mL^{-1} (0.32 pM) in rat blood serum, opening new opportunities for

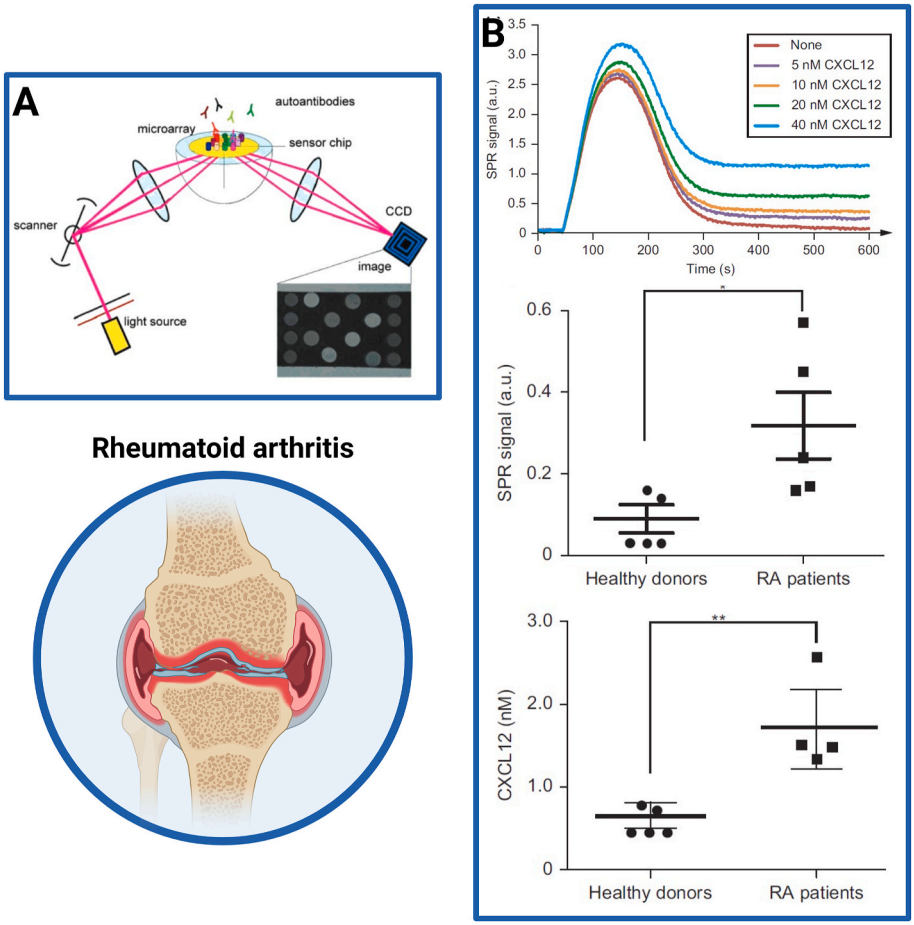

Fig. 2. Examples of plasmonic biosensors for RA diagnosis: (a) schematic representation of an SPRi optical configuration for the detection of ACPA, where the specific citrullinated peptides were chemically anchored on the surface of the plasmonic chips (adapted with permission from Ref. [64] – Copyright 2007, American Chemical Society). (b) Detection of CXCL12 chemokine with lentiviral particles expressing CXCR4 immobilized on the surface of gold plasmonic chips. The image shows real-time sensorgrams of spiked urine (from healthy donors) with CXCL12 biomarker at different concentrations (top), and comparative results of SPR and ELISA (middle and bottom) for urine samples from 5 healthy donors and five patients with active RA, respectively (adapted from Ref. [75] – Copyright (2013) with permission from Elsevier). Created with Biorender.com.

ultrasensitive TNF-α detection. Together with a set of interleukins, TNF-α was also detected in a nanoplasmonic biosensor, exploiting the localised resonance on gold nanorods, and employing a multiplexed approach for the simultaneous detection of a panel of 6 biomarkers, with specific antibodies immobilized on the gold nanorods, in serum samples (as low as 1 μL volume), at pg/mL level, extremely sensitive considering the label-free design of the biosensor assay [76]. Although not evaluated in the specific context of AD, the biosensor could be easily transferred to analyse serum patients suffering from RA, for example. On the other hand, for the chemokines, Vega et al. [74] focused on the CXCL12, the only ligand for the CXCR4 receptor (in humans, the CXCR4/CXCL12 is implicated in cancer, some infectious, and also in RA), due to the high levels found in synovial and bone tissue of RA patients. An innovative strategy based on lentiviral particles presenting specific bioreceptors for CXCL12 [105] attached to the plasmonic chip surface was employed for the direct, and label-free detection, including a proof of concept for CXCL12 detection in urine samples from RA patients (Fig. 2B). Interestingly, the strategy allowed more than 150 evaluation cycles with the same plasmonic chip, achieving a detectability in the 5–40 nM range (50–400 ng mL^{-1}). Another recent example describes the implementation of an SPR immunosensor for the detection of the CD5 biomarker, linked to different non-inflammatory diseases, but also to several AD, like RA and the Sjogren's syndrome, with elevated levels in serum compared with healthy individuals. Employing specific antibodies as receptors a direct assay strategy allowed the detection of the biomarker in the nM range. However, incorporating a second antibody labelled with magnetoplasmonic nanoparticles labelled with a second antibody, a sandwich-like assay drastically enhanced the detectability 6 orders of magnitude, reaching values of 8.3 fM [77]. The assay was even tested in diluted serum and showed good levels of accuracy.

3.2. *Plasmonic biosensors for the diagnosis of systemic lupus erythematosus*

SLE is a systemic AD that potentially causes damage to any organ of the body and is one of the most heterogeneous illnesses treated by physicians, with an incidence of 0.3–31.5 in 100,000 per year [106]. Despite the severity, SLE mortality declined after the corticosteroid era, and nowadays, the survival is about 15 years in 85–95 % of the cases [78]. Due to its systemic nature and clinical features, its early diagnosis and management are complicated.

Over the years, various biomarkers have been described for SLE, using classification criteria for SLE, including the number of white blood cells, platelets, hemolytic anaemia with reticulocytotic, proteinuria, and the presence of autoantibodies, such as antinuclear antibodies (ANA), DNA antibodies, and Smith antibodies [106]. Among them, the double-stranded(ds) DNA autoantibodies have high specificity for SLE and could be helpful in terms of guiding the early diagnosis of this AD [79]. Buhl et al. [78] employed a covalent immobilizing dsDNA strategy (i.e. through biotin-streptavidin moiety for robust biofunctionalization) on the gold plasmonic chip and characterised the binding (kinetic and affinity measurements) with different antibodies in a SPR device (Fig. 3A). The assay was optimized for and validated with real SLE patient serum samples, and showed significant differences with control patients, demonstrating the use of autoantibodies against dsDNA as a candidate for SLE diagnostics (98.2 % specificity at a sensitivity of 83.3 %) [79]. Fiegel et al. [80] further analysed the diagnostic accuracies of the SPR-based method and compared with four commercial anti-dsDNA immunoassays. The authors evaluated 50 patients with SLE, 39 patients with other ADs, and 20 healthy controls. The overall diagnostic accuracy was considered satisfactory and similar to the commercial assays, and the biosensor may add a new analytical method beneficial in the clinical monitoring of SLE. Other examples using SPR biosensing have attempted to either characterise the affinity of autoantibodies for different antigens (complement component C1q, the phospholipid, and beta 2-glycoprotein I) [82] (Fig. 3B) or to establish a detection method (*i.e.* for CRP autoantibodies), employing a one-step inhibition assay, but not in-depth biosensor assay development have been reported [81].

Other common autoantibodies commonly monitored in some AD, including SLE (but also in RA and autoimmune hepatitis (AIH) are the ANA against the heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1. Employing also an SPRi with multiplexed capabilities and a

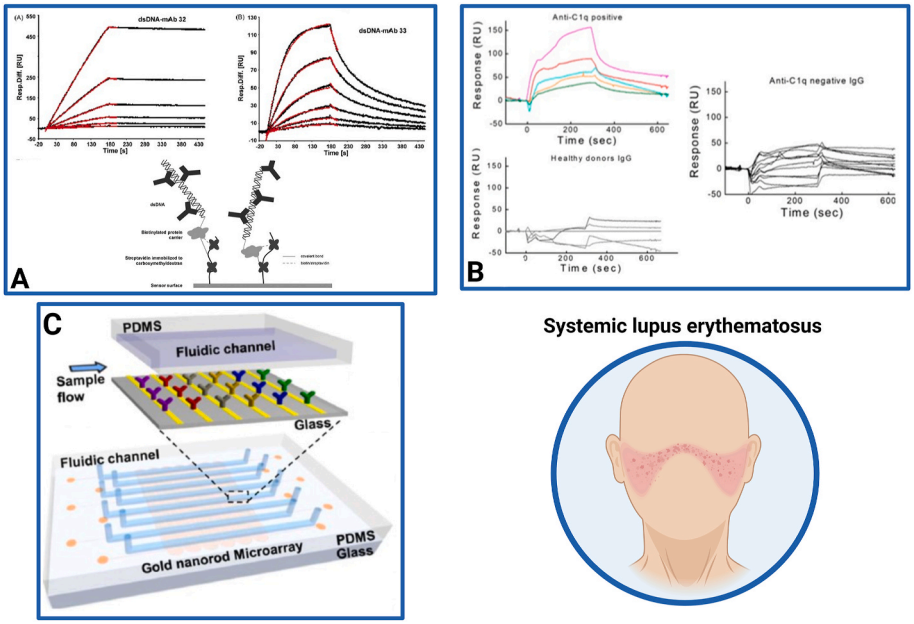

Fig. 3. Examples of plasmonic biosensors for SLE diagnosis: (a) a chip design representation described by the author for a commercial SPR and the representative sensorgrams obtained of two monoclonal antibodies studied (mAb32 and mAb33) for different dsDNA concentrations (adapted from Ref. [78] – Copyright (2009) with permission from Elsevier). (b) SPR sensorgrams for patients' samples positive and negative for anti-C1q autoantibodies (as determined previously by reference method-ELISA) and healthy volunteers. The data shown correspond to purified samples containing only IgGs. Adapted from Ref. [82]. (c) a schematic of a LSPR microarray integrated into a microfluidic chip with eight parallel microfluidic channels for six cytokine biomarker detection in serum samples (adapted with permission from Ref. [76] – Copyright 2015, American Chemical Society). Created with Biorender.com.

dedicated biofunctionalization based on PEGylated modified gold surface with a panel of hnRNP protein peptides, a detection strategy was implemented for identifying biomarkers relevant to these autoimmune disorders (SLE, RA, AIH) through the high throughput evaluation of multiple sera (positive and controls) and the evaluation of dissociation constants (K_{off} values) which provide useful information about the stability of the interaction of the autoantibodies and different amino acid sequences within the protein [85].

Like other AD and despite their lower specificity, cytokines can also be employed as a complementary disease biomarker as described for RA, and their evaluation is reported with nanoplasmonics label-free, multiplexed detection [76] (Fig. 3C). The LSPR biosensor allowed a quantitative cytokine measurement at 5–20 pg mL^{-1}, using 1 μL of serum sample.

It is essential to highlight that about 25 % of patients with AD tend to suffer an additional AD [107], and that is the case for some SLE patients. Sometimes, one-third of cases of SLE are complicated by antiphospholipid syndrome (APS), a thrombo-inflammatory disease. APS is characterised by the presence of antiphospholipid antibodies, such as anticardiolipin and anti-β2-glycoprotein I autoantibody (anti-β2GPI) [108]. Schlichtiger et al. [83], employed plasmonic sensor chips modified with aminocardiolipin and studied 21 patients with APS, 21 healthy control, and 10 patients positive for syphilis. Applying cutoff values generated from healthy controls, it was possible to detect anti-cardiolipin (aCL) autoantibodies in patient sera with confirmed APS with 100 % diagnostic specificity and 100 % sensitivity, outperforming conventional ELISA (sensitivity of 85.7 %). Similarly, Metzger et al. [84] evaluated a plasmonic biosensor modified with human β2GPI the presence of 30 patients with APS, 9 with SLE, 10 with positive results to syphilis, and 20 with parvovirus B19 infection, respectively. Comparing the results with the ELISA test, the proposed biosensor presented a high specificity. All sera of SLE patients, positive syphilis, or parvovirus B19 infection were negative for β2GPI-specific APLs.

3.3. Plasmonic biosensors for diagnosis of the diagnosis of type 1 diabetes

Diabetes mellitus is a chronic disease characterised by insulin deficiency due to the non-functioning pancreas cells, affecting the body's ability to use glucose from digested foods [109]. There are two types of diabetes: T1D, caused by the autoimmune destruction of the insulin-producing β-cells, becoming then the individual insulin-dependent, and type 2, caused by the dysfunction in insulin production of β-cells, increasing hepatic glucose output and insulin resistance [110,111]. In 2021, about 8 million individuals worldwide had T1D diagnosed (64 % were aged 20–59 years) [112]. At the moment of the T1D diagnosis, about 85 % of the β-cells mass has been lost, and it would be extremely complicated to do any intervention or attempt to reverse its progression at a late stage [110].

The current diagnostic biomarkers of T1D still depend on hyperglycemia (high glucose level or glycated hemoglobin), but this is not sensitive and specific, considering that these tests and symptoms could diagnose different types of diabetes. Thus, to differentiate T1D from type 2 diabetes and other subtypes, it is possible to evaluate the presence of specific autoantibodies, such as the islet-cell cytoplasmic, the glutamic acid decarboxylase (GAD), the insulin, the zinc transporter, and the insulinoma 2-associated antibodies, respectively [110]. Most of the examples of plasmonic biosensors indeed have focused on GAD [113] or insulin autoantibodies, as a highly reliable tool to characterise them (stability of the interaction, affinity and kinetic parameters …) or to implement detection assays for diagnostics [113,86]. Nogues et al. [86] employed an SPRi to characterise affinity and kinetics of GAD65 autoantibodies, the major autoantibody found in patients diagnosed with T1D (about 80 %). A strategy of surface biofunctionalization that minimised nonspecific adsorption on the sensor surface was optimized using a custom-designed self-assembled monolayer (SAM) with purified GAD65 antigen in such a way that reliable data could be obtained (K_{on} and K_{off} values). Using a conventional plasmonic biosensor with the signal enhanced by colloidal gold nanoparticles functionalised with HS-OEG_3-COOH, horseradish peroxidase (HRP), and anti-IgG, Cao et al. [87] demonstrated the capability of detecting the anti-GAD antibody with a very low limit of detection (LOD = 200 fM), demonstrating a higher sensitivity compared to previous reports due to the amplification scheme employed. Bagra et al. [88] described a nanoledge plasmonic chip (SiO_2, Ti, and Au) functionalised with cystamine (SAM) and human insulin to identify anti-insulin antibodies using transmission spectroscopy based on extraordinary optical transmission and LSPR. This device was able to detect the anti-insulin antibodies of T1D in buffer and serum at the range between 100 pg mL^{-1} to 100 ng mL^{-1}.

3.4. Plasmonic biosensors applied to the study and diagnosis of other autoimmune diseases

Plasmonic biosensors have also been employed for other relevant autoimmune disorders. For example, celiac Disease (CD) is one of the most common ADs, with a prevalence of 0.5–1% of the population [114,115]. It is a chronic disorder mediated by an immune response generated by gliadin, a protein found in rye, barley, and wheat [116]. The most common biomarkers for its diagnosis are the autoantibodies anti-gliadin (AGA) and anti-tissue transglutaminase (anti-tTG), despite their poor specificity (approximately 50 % of patients with non-celiac gluten sensibility is positive for AGA [117]). Cennamo et al. [89] reported a plastic optical fiber as a low-cost plasmonic biosensor for anti-tTG detection able to evaluate in a range of concentrations between 30 and 3000 nM under optimized conditions. Another example where plasmonic biosensors have been successfully applied is not for diagnosing the disease itself, but for monitoring gluten intake, which can be crucial in some situations, such as treatment follow-up in the elderly and children. The plasmonic biosensor assay relied on detecting toxic peptides from the degradation of gliadin, which can be detected and quantified by employing specific antibodies directly in urine without any sample treatment. A competitive assay was implemented with the biosensor reaching a LOD of 1.6 and 4.0 ng mL^{-1} using two different specific monoclonal antibodies. The assay was validated with 21 urine samples with a controlled intake of gluten-containing food at very low quantities. Besides that, the biosensor showed promising storage stability of 6 months, becoming an excellent alternative in non-invasive CD follow-up [90].

Another AD that affects young adults is Multiple Sclerosis (MS), a chronic inflammatory neurodegenerative autoimmune disorder known to be extremely difficult to diagnose accurately [118,119]. MS affects less than 0.1 % of the world population, and the current diagnosis is based on characterising the damage to the central nervous system by scanning scar tissues or plaques, indicating some trauma or autoimmune attack, and on the clinical history [120,92]. The most relevant biomarkers for MS are related to gangliosides and sulfatides, cell membrane components of the myelin sheath.

Malinick et al. [91] used an SPRi for screening 3 ganglioside antibodies, employing background-free biofunctionalized sensor chips based on perfluorodecyltrichlorosilane (PFDTS) layer covered with the different gangliosides in self-assembled pseudo-myelin sheath, allowing their detection with a LOD of few ng mL^{-1} and a working range of 1–100 ng mL^{-1} in 10 % diluted serum (Fig. 4A). Taking advantage of the high throughput capabilities and the sensitivity, this strategy has been later expanded and combined with machine learning models for data processing to characterise interactions and cross-reactivities of three autoantibodies with multiple ganglioside antigens and establishing direct assays, this time in whole serum, with no amplification, with a very competitive LOD between 4.5 and 6.6 ng mL^{-1} (around 30.5 pM) [92]. Serum circulating anti-glycopeptide antibodies, also considered a valuable biomarker for MS patients stratification and therapy follow-up, have been the target in a plasmonic diagnostic biosensor assay, and validated for glycopeptide CSF114(Glc) with real MS patients, allowing

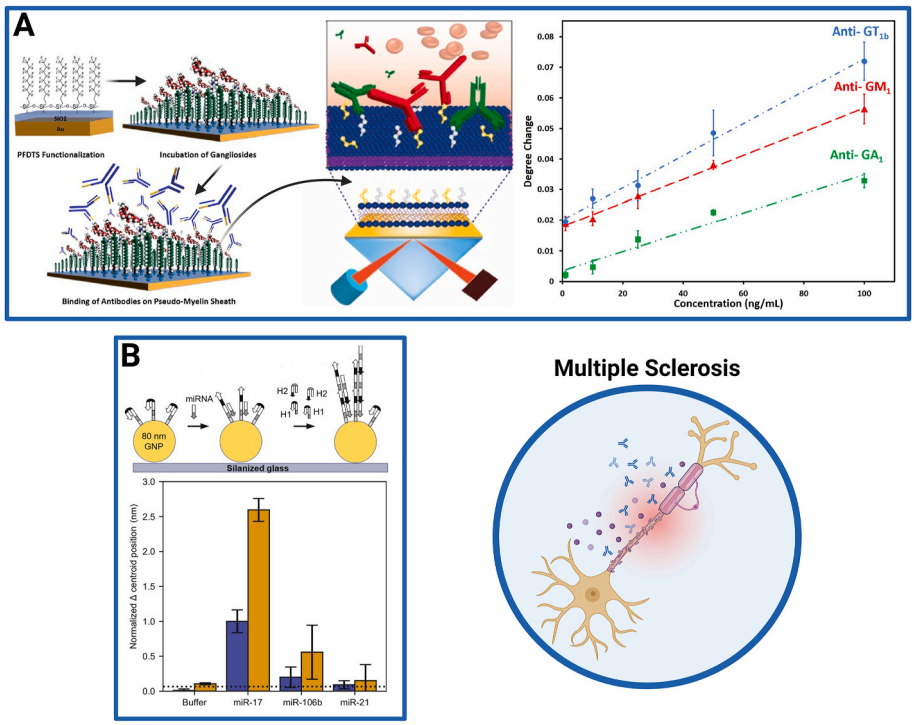

Fig. 4. Examples of plasmonic biosensors for MS diagnosis: (a) a schematic representation of the chip surface functionalization steps with three different gangliosides (GT1b, GM and GA1) and the detection scheme for MS specific antibodies in serum (anti-gangliosides: Anti-GT1b, anti-GM, and anti-GA1). The calibration curve for direct assays obtained of each antibody in PBS is shown (adapted with permission from Ref. [91] – Copyright 2020, American Chemical Society). (b) Scheme of the working principle of the proposed biosensor based on LSPR sensing of gold nanoparticles with hybridization chain reaction (HCR), and the specificity test using the miRNA-17 probe compared with other probes (miRNA106b and miRNA-21) (blue bars: miRNA sequence detection; orange bars: overall response performing HCR) (adapted from Ref. [96] – Copyright (2020) with permission from Elsevier). Created with Biorender.com.

a faster, equally reliable method than ELISA for their detection, with a diagnostic specificity of 95 % and sensitivity of 36 %, respectively [93,94]. Finally, as in many other diseases including inflammatory diseases, the expression levels of miRNA has revealed as highly relevant biomarkers. Their detection, especially challenging for their features (short oligonucleotides, low concentrations, etc) has also been described employing label-free plasmonic biosensors with good levels of detectability. For MS few examples have already been reported. For example, Sguassero et al. developed an SPRi-based strategy based on the direct hybridization of miRNAs using complementary probes that reached detectabilities in the nM range but that could be drastically reduced below 1 pM through the inclusion of an amplification step with gold nanoparticles labelled with an antibody targeting the DNA/RNA moiety. With this optimized strategy multiple miRNAs (4 different sequences) from total RNA extracted from blood at low concentrations were detected [95]. Another example, based on LSPR measurements with gold nanoparticles-based plasmonic chip employed a different amplification strategy based on hybridization chain reaction (HCR), an enzyme-free isothermal amplification strategy based on the triggered self-assembly of two DNA hairpins in solution in the presence of a specific target sequence (see Fig. 4B) [96]. Although not tested with real samples or complex media like serum, the approach developed reached a LOD as low as 1 pM.

4. Conclusions and future perspectives

Plasmonic biosensors have fully demonstrated their potential in the biomedical field, especially in invitro diagnostics, as attractive analytical tools to improve disease diagnosis. Currently, there are a vast number of reported examples where different SPR and LSPR biosensing prototypes have been employed at the research laboratory level for the detection of hundreds of biomarkers, reaching excellent levels of sensitivity and specificity according to the clinical requirements. This success has required intense efforts in the biosensing aspects, especially in the biofunctionalization of sensor chips with delicate bioreceptors and the individual and particular conditions for the specific detection of the biomarkers. This has also been reflected in many examples related to autoimmune diseases from different perspectives: for disease diagnostics, through the rapid, sensitive, and reliable detection of specific biomarkers, but also from a more global perspective of disease study, which involves the use of plasmonic biosensors for biomarkers discovery, investigation on biological mechanisms and behavior of the disease, or for therapeutic monitoring. The detection of specific autoantibodies, as hallmark biomarkers, remains the main field of application with more relevant results. In this regard, the high throughput capabilities of SPR imaging, and the inherent advantages that real-time label-free monitoring offer have positioned this configuration as highly convenient for studying antibodies-autoantigen interactions, identifying potential new biomarkers, or stratifying the patients. Plasmonic biosensing overcomes the limitations that end-point-based techniques like immunoassays have, which cannot provide information on the interaction events. From a diagnostic perspective, besides autoantibodies detection, other relevant biomarkers (protein biomarkers, generic inflammatory markers, genetic markers like miRNA, etc.) have been also reported. In most cases the detectabilities reached meet the clinical requirements, being highly competitive with the most conventional techniques currently employed, like immunoassays. Thus, plasmonic biosensors reveal themselves as attractive options for different autoimmune disorders diagnostics and monitoring. Early diagnosis of AD is crucial to preventing permanent tissue and organ damage and worsening of patient's quality of life, facilitating the management of the disease at an early stage, and overall, reducing the incidence of premature death and decreasing the pressure on the health system. Almost all AD have reported biomarkers (autoantibodies, proteins, peptides, etc.), which can contribute to improving

diagnosis. However, none of them rely on one single biomarker, as their specificity is relatively moderate. Some of the biomarkers mentioned in this review are related to one or more AD, or even also to non-autoimmune diseases. The absence of specific biomarkers makes the combination of a panel of biomarkers even more necessary, as this would help increase the specificity and sensitivity of the diagnosis. Combining individual techniques for multiple analytes detection (multiple immunoassays, and/or adding genomic PCR-like techniques for genetic markers) is not suitable for routine and effective diagnostics. Thus, the multianalyte approach (1 single instrument for several analytes) for monitoring different types of biomarkers remains crucial for this subset of disorders, to enhance the diagnostic specificity and sensitivity. In this regard, plasmonic biosensors, either those based on imaging detection techniques or those relaying in conventional SPR with multichannel designs are excellent options for this purpose as demonstrated at the laboratory level, for example for multiple autoantibodies detection, or multiple inflammatory markers. Even the levels of sensitivity that can be achieved make feasible the incorporation of amplification-free direct detection of oligonucleotides, which enables the combination of mixed biomarkers in one single device.

Yet, the currently plasmonic commercialized instruments seem to have challenging features, especially in terms of cost and dimensions, to envisage rapid incorporation into the clinical routine, either for AD or for any other application. Additionally, they are generic instruments, versatile for different applications but not specifically designed for a single one. Nevertheless, the technology level of maturity is high, and it is indeed evolving rapidly to solve these restrictions, aiming to increase portability and affordability (i.e. employing low-cost light sources and detection elements, like mini-spectrometers, affordable CMOS elements, disposable, easy-to-use cartridges for chip incorporation, etc) and achieve more realistic, out-of-the-lab devices that can be operated at the Point-of-Care. Not sacrificing performance (sensitivity, reliability) in the name of integration is essential and also challenging for miniaturized designs. Moreover, besides the technological efforts on integration, the biosensing component, related to the incorporation of one or different receptors (highly demanded in many clinical conditions including AD diagnosis) within the same sensor chip is still challenging from a mass production perspective and on many occasions can be the limiting factor. This is a critical aspect to address in diagnostics, and also in particular in the case of AD. However, this should be the final aim of this technology: generating a combined device with excellent performance in combination with ready-to-use, already biofunctionalized sensor chips, integrated into convenient cartridges, for each desired application to be used in daily routine.

In summary, it is still critical to fill the gap between laboratory designs and prototypes and final products, shaped into point-of-care diagnostic devices, integrated in such a way that they can contribute to a faster, more efficient, and affordable diagnosis, while providing alternatives to more efficient disease management (i.e. monitoring the disease progression or the applied treatment) in decentralised centers, reducing the health care cost. The advantages that plasmonic devices can provide once fully implemented are undeniable in terms of turn-around time of analysis and cost for disorders with complex diagnoses such as AD diseases, and we should expect innovative solutions soon to reach the market, as the segment of optical biosensing is increasing attention and investment towards POC achievement.

CRediT authorship contribution statement

Juliana Fátima Giarola: Writing – review & editing, Writing – original draft, Conceptualization. **M.- Carmen Estevez:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Laura M. Lechuga:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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