Review

Recent Advances in Biosensors for Diagnosis of Autoimmune Diseases

Ahlem Teniou [1], Amina Rhouati [1] and Jean-Louis Marty [2],*

[1] Bioengineering Laboratory, Higher National School of Biotechnology, Constantine 25100, Algeria
[2] UFR Sciences, Universitéde Perpignan Via Domitia, 66860 Perpignan, France
* Correspondence: jlmarty@univ-perp.fr (J.-L.M.)

Supplementary Material

Table S1: Comparison between the reported biosensor technologies for the diagnosis and monitoring of autoimmune diseases.

Method of detection	Target	Limit of detection	Linear range	Real samples	Refs
Celiac disease					
Electrochemical (CV)	TGA	1.8 ng/mL	0.005 - 1 µg/mL	Serum	[1]
Electrochemical (LSV)	TGA	260 ng/mL	0.26 - 6.9 µg/mL	Serum	[2]
Electrochemical (SWV)	DGPA	/	0.033 - 1.0 µg/mL	Serum	[3]
Electrochemical (CV)	TGA	0.72 U/mL	0.25 - 8.54 U/mL	Serum	[4]
Electrochemical (Chronoamperometry)	TGA IgA	4.6 U/mL	0 - 100 U/mL	Artificial human plasma	[5]
Electrochemical (DPV)	TGA	2.4 U/mL	3 - 100 U/mL	serum	[6]
Electrochemical (EIS)	AGA	46 ng/mL	0 - 1 µg/mL	Serum	[7]
Electrochemical (Amperometry) + Optical (SPR)	AGA	33 ng/mL	0 - 10 µg/mL	Serum	[8]
Piezoelectric (QCM)	TGA	1300 ng/mL	1300 -12,000 ng/mL	Serum	[9]
Electrochemical (CV)	TGA IgA TGA IgG AGA IgA AGA IgG	2.45 U/mL 2.95 U/mL 3.16 U/mL 2.82 U/mL	0 - 100 U/mL		[10]
Electrochemical (DPV)	TGA	1 U/mL	3 - 40 U/mL	Serum	[11]
Electrochemical (Chronoamperometry)	TGA	2 U/mL	3 – 100 U/mL	Serum	[12]
Electrochemical (CV) + Optical (ECL)	TGA	0.5 ng/mL	1.5 ng/mL - 10 µg/mL	Serum	[13]
Optical (SPR)	TGA	/	30–3000 nM	Serum	[14]
Electrochemical (Amperometry) + IoT	TGA	3.2 AU/mL (IgA) 1.4 AU/mL (IgG)	0 - 30 AU/mL	Serum	[15]
Multiple sclerosis					
Electrochemical (Amperometry)	Anti-MBP	0.016 ng/mL	0.05 - 50 ng/mL	Serum	[16]
Electrochemical (EIS)	Osteopontin	0.98 fg/mL	0.05 - 10,000 pg/mL	Serum	[17]
	Anti-IL 12 antibodies	5 pg/mL	0 - 100 pg/mL	Serum	[18]
	anti-IL-12 antibodies	3.5 pg/mL	0.1 - 500 pg/mL	Fetal Bovine Serum	[19]
	Anti-MBO	0.1495 ng/mL	0.4875 - 2500 ng/mL	Serum and CSF	[20]
	Anti-MBP	0.18 ng/mL	/	Serum	[21]
Electrochemical (DPV)	MBP, Tau	0.3 nM (MBP) 0.15 nM (Tau proteins)	58 - 227 nM (MBP), 0.5 - 15.1 nM (Tau protein)	Blood sample and/or CSF	[22]
Fluorescence	miR-145	0.016 nM	0.1 nM - 1.6 nM	Serum	[23]

spectrophotometer					
Electrochemical (OFET)	MBP	1 ng/mL	1 - 500 ng/mL	/	[24]
Electrochemical (DPV)	miR-155	10 aM	10 aM – 1 µM	Serum	[25]
	BDNF	9 pg/mL	10 - 40 pg/mL	Fetal bovine serum	[26]
Optical (Lateral flow)	Osteopontin	0.1 ng/mL	10 - 500 ng/mL	Serum	[27]
Rheumatoid arthritis					
Optical (ECL)	Anti-CCP	0.2 pg/mL	0.001 - 15 ng/mL	Serum	[28]
Electrochemical (CV)	Anti-CCP	15 pg/mL	8 - 250 pg/mL	Serum	[29]
Electrochemical (EIS)	Anti-CCP	0.82 U/mL	1 - 800 U/mL	Serum	[30]
Optical (SERS)	Anti-CCP	0.18 U/mL	0–25 U/mL	Serum	[31]
Electrochemical (Amperometry)	IL-6	0.42 pg/mL	0.97 - 250 pg/mL	Serum	[32]
Optical (Colorimetry)	IgM-RF	4.15 IU/mL	/	Serum	[33]
Electrochemical (EIS)	IgM-RF	0.22 IU/mL	1 - 200 IU/mL	Serum	[34]
Electrochemical (amperometry)	IgM-RF + Anti-CCP	0.8 IU/mL (RF) 2.5 IU/mL (CCPA)	/	Serum	[35]
Electrochemical (SWV)	Anti-CCP	0.16 IU/mL (in PBS) 0.22 IU/mL (in human serum)	0.25 – 1500 IU/mL	Serum	[36]
Electrochemical (SWV+CV)	Anti-CCP	/	0.125 - 2000 pg/mL	Serum	[37]
Electrochemical (EIS)	IL-6	0.33 pg/mL	1 pg/mL - 15 mg/mL	Serum	[38]
Electrochemical (DPV)	TNF-α	0.52 pg/mL	1 - 100 pg/mL	Serum	[39]
Electrochemical (EIS)	TNF-α	0.67 pg/mL (in PBS) 0.78 pg/mL (in human serum)	1 - 1000 pg/mL	Serum	[40]
Electrochemical (EIS)	TNF-α	60 pg/mL	500 pg/mL - 100 ng/mL	Serum	[41]
Lupus erythematous systemic					
Electrochemical (Amperometry)	BAFF and APRIL	0.33 pg/mL (BAFF) 16.4 pg/mL (APRIL)	1.1 - 100 pg/mL (BAFF) 0.05 - 20 ng/mL (APRIL)	Serum	[42]
Electrochemical (Amperometry)	BAFF and APRIL	0.08 ng/mL (BAFF) 0.06 ng/mL (APRIL)	0.24 - 120 ng/mL (BAFF) 0.19 - 25 ng/mL (APRIL)	Serum	[43]
Piezoelectric (QCM)	Anti-TRIM21 and anti-TROVE2 autoantibodies	0.01 U/mL (anti-TRIM21) 0.005 U/mL (anti-TROVE2)	0.32 - 7.17 U/mL (anti-TRIM21) 0.07 - 1.46 U/mL (anti-TROVE2)	Serum	[44]
Electrochemical (Amperometry)	anti-dsDNA	8 µg/mL	/	Serum	[45]

Abbreviations: TGA: transglutaminase-antibody; **DGPA:** antibody against deamidated gliadin peptides; **AGA:** anti-gliadin antibody; **QCM:** quartz crystal microbalance; **IgA:** immunoglobulin A; **IgG:** immunoglobulin G; **tTG:** tissue transglutaminase; **IoT:**

Internet of things; **Anti-MBP:** autoantibodies against myelin basic protein; **IL:** interleukin; **EIS:** Electrochemical impedance spectrometry; **CSF:** cerebrospinal fluid; **miR:** micro-RNA; **BDNF:** brain-derived neurotrophic factor**; Anti-CCP:** Anti-cyclic citrullinated peptide antibody; **ECL:** electrochemiluminescence; **RF**: Rheumatoid factor; **TNF-α:** tumor necrosis factor alpha; **BAFF:** B-cell activation factor; **APRIL:** a proliferation-induced ligand; **Anti-dsDNA:** Anti-double stranded DNA; **CV:** cyclic voltammetry; **LSV:** linear sweep voltammetry; **OFET:** Organic Field Effect Transistor; **DPV:** differential pulse voltammetry; **SWV:** Square wave voltammetry; **SPR:** Surface plasmon resonance; **SERS:** surface-enhanced Raman scattering

20
21
22
23
24
25
26

References

1. Habtamu, H.B., et al., *Electrochemical Immunosensor Based on Nanoelectrode Ensembles for the Serological Analysis of IgG-type Tissue Transglutaminase.* Sensors, 2019. **19**(5): p. 1233.

2. Rosales-Rivera, L.C., et al., *Disulfide-modified antigen for detection of celiac disease-associated anti-tissue transglutaminase autoantibodies.* Analytical and Bioanalytical Chemistry, 2017. **409**(15): p. 3799-3806.

3. Puiu, M., et al., *A modular electrochemical peptide-based sensor for antibody detection.* Chemical Communications, 2014. **50**(64): p. 8962-8965.

4. Longo, S., et al., *Nanoelectrode ensemble immunosensor platform for the anodic detection of anti-tissue transglutaminase isotype IgA.* Journal of Electroanalytical Chemistry, 2022. **906**: p. 115984.

5. González-López, A., M.C. Blanco-López, and M.T. Fernández-Abedul, *Micropipette tip-based immunoassay with electrochemical detection of antitissue transglutaminase to diagnose celiac disease using staples and a paper-based platform.* ACS sensors, 2019. **4**(10): p. 2679-2687.

6. Martín-Yerga, D. and A. Costa-García, *Towards a blocking-free electrochemical immunosensing strategy for anti-transglutaminase antibodies using screen-printed electrodes.* Bioelectrochemistry, 2015. **105**: p. 88-94.

7. Rosales-Rivera, L., et al., *Electrochemical immunosensor detection of antigliadin antibodies from real human serum.* Biosensors and Bioelectronics, 2011. **26**(11): p. 4471-4476.

8. Wajs, E., N. Fernández, and A. Fragoso, *Supramolecular biosensors based on electropolymerised pyrrole–cyclodextrin modified surfaces for antibody detection.* Analyst, 2016. **141**(11): p. 3274-3279.

9. Manfredi, A., et al., *Piezoelectric immunosensor based on antibody recognition of immobilized open-tissue transglutaminase: An innovative perspective on diagnostic devices for celiac disease.* Sensors and Actuators B: Chemical, 2014. **201**: p. 300-307.

10. Neves, M.M.P.S., et al., *Multiplexed electrochemical immunosensor for detection of celiac disease serological markers.* Sensors and Actuators B: Chemical, 2013. **187**: p. 33-39.

11. Martín-Yerga, D., et al., *Enhanced detection of quantum dots by the magnetohydrodynamic effect for electrochemical biosensing.* Analyst, 2017. **142**(9): p. 1591-1600.

12. Nanni, P.I., et al., *Staple-Based Paper Electrochemical Platform for Celiac Disease Diagnosis.* ChemElectroChem, 2018. **5**(24): p. 4036-4045.

13. Habtamu, H.B., et al., *A sensitive electrochemiluminescence immunosensor for celiac disease diagnosis based on nanoelectrode ensembles.* Analytical chemistry, 2015. **87**(24): p. 12080-12087.

14. Cennamo, N., et al., *An innovative plastic optical fiber-based biosensor for new bio/applications. The case of celiac disease.* Sensors and Actuators B: Chemical, 2013. **176**: p. 1008-1014.

15. Giannetto, M., et al., *An integrated IoT-Wi-Fi board for remote data acquisition and sharing from innovative immunosensors. Case of study: Diagnosis of celiac disease.* Sensors and Actuators B: Chemical, 2018. **273**: p. 1395-1403.

16. Guerrero, S., et al., *Monitoring autoimmune diseases by bioelectrochemical detection of autoantibodies. Application to the determination of anti-myelin basic protein autoantibodies in serum of multiple sclerosis patients.* Talanta, 2022. **243**: p. 123304.

17. Zhou, S., et al., *Ti3C2Tx MXene and polyoxometalate nanohybrid embedded with polypyrrole: Ultra-sensitive platform for the detection of osteopontin.* Applied Surface Science, 2019. **498**: p. 143889.

18.   La Belle, J.T., et al., *A cytokine immunosensor for multiple sclerosis detection based upon label-free electrochemical impedance spectroscopy.* Biosensors and Bioelectronics, 2007. **23**(3): p. 428-431.

19.   Bhavsar, K., et al., *A cytokine immunosensor for Multiple Sclerosis detection based upon label-free electrochemical impedance spectroscopy using electroplated printed circuit board electrodes.* Biosensors and Bioelectronics, 2009. **25**(2): p. 506-509.

20.   Derkus, B., et al., *Myelin basic protein immunosensor for multiple sclerosis detection based upon label-free electrochemical impedance spectroscopy.* Biosensors and Bioelectronics, 2013. **46**: p. 53-60.

21.   Derkus, B., et al., *Alginate and alginate-titanium dioxide nanocomposite as electrode materials for anti-myelin basic protein immunosensing.* Sensors and Actuators B: Chemical, 2014. **192**: p. 294-302.

22.   Derkus, B., et al., *Simultaneous quantification of Myelin Basic Protein and Tau proteins in cerebrospinal fluid and serum of Multiple Sclerosis patients using nanoimmunosensor.* Biosensors and Bioelectronics, 2017. **89**: p. 781-788.

23.   Mansourian, N., M. Rahaie, and M. Hosseini, *A Nanobiosensor Based on Fluorescent DNA-Hosted Silver Nanocluster and HCR Amplification for Detection of MicroRNA Involved in Progression of Multiple Sclerosis.* Journal of Fluorescence, 2017. **27**(5): p. 1679-1685.

24.   Song, J., et al., *Influence of Bioreceptor Layer Structure on Myelin Basic Protein Detection using Organic Field Effect Transistor-Based Biosensors.* Advanced Functional Materials, 2018. **28**(37): p. 1802605.

25.   Shariati, S., A. Ghaffarinejad, and E. Omidinia, *Early detection of multiple sclerosis (MS) as a neurodegenerative disease using electrochemical nano-aptasensor.* Microchemical Journal, 2022. **178**: p. 107358.

26.   Ayankojo, A.G., et al., *Electrochemical sensor based on molecularly imprinted polymer for rapid quantitative detection of brain-derived neurotrophic factor.* Sensors and Actuators B: Chemical, 2023. **397**: p. 134656.

27.   Mukama, O., et al., *A highly sensitive and specific lateral flow aptasensor for the detection of human osteopontin.* Talanta, 2020. **210**: p. 120624.

28.   Zhao, Y., et al., *Label-free ECL immunosensor for the early diagnosis of rheumatoid arthritis based on asymmetric heterogeneous polyaniline-gold nanomaterial.* Sensors and Actuators B: Chemical, 2018. **257**: p. 354-361.

29.   Zhou, B., et al., *Immunosensing the rheumatoid arthritis biomarker through bifunctional aldehyde-amine linkers on an iron oxide nanoparticle seeded voltammetry sensor.* Nanomaterials and Nanotechnology, 2022. **12**: p. 18479804221085103.

30.   Chinnadayyala, S.R. and S. Cho, *Electrochemical immunosensor for the early detection of rheumatoid arthritis biomarker: Anti-cyclic citrullinated peptide antibody in human serum based on avidin-biotin system.* Sensors, 2020. **21**(1): p. 124.

31.   Chon, H., et al. *Highly sensitive immunoassay of anti-cyclic citrullinated peptide marker using surface-enhanced Raman scattering detection.* in *International Conference on Nano-Bio Sensing, Imaging, and Spectroscopy 2015.* 2015. SPIE.

32.   Zhang, C., et al., *Microfluidic electrochemical magnetoimmunosensor for ultrasensitive detection of interleukin-6 based on hybrid of AuNPs and graphene.* Talanta, 2022. **240**: p. 123173.

33.   Veigas, B., et al., *Antibody modified gold nanoparticles for fast colorimetric screening of rheumatoid arthritis.* Analyst, 2019. **144**(11): p. 3613-3619.

34.   Chinnadayyala, S.R., et al., *Label-free electrochemical impedimetric immunosensor for sensitive detection of IgM rheumatoid factor in human serum.* Biosensors and Bioelectronics, 2019. **143**: p. 111642.

72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119

35.   Guerrero, S., et al., *Electrochemical biosensor for the simultaneous determination of rheumatoid factor and anti-cyclic citrullinated peptide antibodies in human serum.* Analyst, 2020. **145**(13): p. 4680-4687.

36.   Selvam, S.P., S.R. Chinnadayyala, and S. Cho, *Electrochemical nanobiosensor for early detection of rheumatoid arthritis biomarker: Anti-cyclic citrullinated peptide antibodies based on polyaniline (PANI)/MoS2-modified screen-printed electrode with PANI-Au nanomatrix-based signal amplification.* Sensors and Actuators B: Chemical, 2021. **333**: p. 129570.

37.   Ma, J., et al., *Label-free Electrochemical Immunosensor for Sensitive Detection of Rheumatoid Arthritis Biomarker Anti-CCP-ab.* Electroanalysis, 2022. **34**(4): p. 761-771.

38.   Tertiş, M., et al., *Label-free electrochemical aptasensor based on gold and polypyrrole nanoparticles for interleukin 6 detection.* Electrochimica Acta, 2017. **258**: p. 1208-1218.

39.   Hosseini Ghalehno, M., M. Mirzaei, and M. Torkzadeh-Mahani, *Electrochemical aptasensor for tumor necrosis factor α using aptamer–antibody sandwich structure and cobalt hexacyanoferrate for signal amplification.* Journal of the Iranian Chemical Society, 2019. **16**(8): p. 1783-1791.

40.   Yagati, A.K., M.-H. Lee, and J. Min, *Electrochemical immunosensor for highly sensitive and quantitative detection of tumor necrosis factor-α in human serum.* Bioelectrochemistry, 2018. **122**: p. 93-102.

41.   Arya, S.K. and P. Estrela, *Electrochemical immunosensor for tumor necrosis factor-alpha detection in undiluted serum.* Methods, 2017. **116**: p. 125-131.

42.   Arévalo, B., et al., *Simultaneous electrochemical immunosensing of relevant cytokines to diagnose and track cancer and autoimmune diseases.* Bioelectrochemistry, 2022. **146**: p. 108157.

43.   Arévalo, B., et al., *Binary MoS2 nanostructures as nanocarriers for amplification in multiplexed electrochemical immunosensing: Simultaneous determination of B cell activation factor and proliferation-induced signal immunity-related cytokines.* Microchimica Acta, 2022. **189**(4): p. 143.

44.   do Nascimento, N.M., et al., *Label-free piezoelectric biosensor for prognosis and diagnosis of Systemic Lupus Erythematosus.* Biosensors and Bioelectronics, 2017. **90**: p. 166-173.

45.   Fagúndez, P., et al., *An electrochemical biosensor for rapid detection of anti-dsDNA antibodies in absolute scale.* Analyst, 2018. **143**(16): p. 3874-3882.