## Supplementary Information

**Electrochemical Sensing of Blood Proteins for Mild Traumatic Brain Injury (mTBI) Diagnostics and Prognostics: Towards a Point-of-Care Application**

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### SI-1: Full list of published electrochemical strategies for the detection of blood protein biomarkers relevant to mTBI.

Publications related uniquely to a specific application other than blood analysis (e.g. measurements in saliva, sweat, urine, muscle-on-tissue designs etc.) or aimed specifically at electronics development have been omitted, with very few exceptions (detection of VCAM-1 in diluted urine\(^1\), sequentially multiplexed amperometry for IL-6 detection\(^2\), detection of CRP in synthetic urine using molybdenum-based electrode\(^3\)). The search has been limited to scientific publications in peer-reviewed journals with one exception: a patent by Kumta et al.\(^4\) has been included due to a very small amount of publications related to EC detection of UCH-L1. Research publications having accomplished multianalyte detection (a few biomarkers measured simultaneously or sequentially using the same sensing strategy) are denoted as ‘MuxT’ in *Column 5 (‘Label/Detection solution’)*, label-free approaches are marked as ‘Label-free’ in the same column. To note, ‘Label-free’ in indicates the assays that include no additional incubation step(s) with the label/labelled antibody after the final incubation with the target analyte (T). That is, either no redox label is required or the redox-label has been already incorporated into the design of the sensor. NOTE: Information about biotin/streptavidin labelling as well as blocking steps (in vast majority of cases using bovine serum albumine) is omitted in *Column 4 (‘Surface modification/Bioreceptor functionalization/Assay format’).*

| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/reaction mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) Linear vs target concentration (c), if not stated otherwise (e.g., vs lgc.) |
|-----------------------|------------------------------------------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------|--------------------------|----------------------------------|
| BDNF                  | CPA 2018\(^5\)                          | Carbon SPE (DPI microfluidics, gap 19 µm) | AuNPs/pTTBA/(EDC+NHS)/Ab\(_2\)/T/Ab\(_2\)/[EDC+NHS]/TBO/pTTBPA/AuNPs/carbon SPE#2 | TBO                                                                                 | T / 20 min, 35 °C | Buffer HS | 0.015 ng mL\(^{-1}\) <0.1 ng mL\(^{-1}\) (1) | 0.004–0.6 ng mL\(^{-1}\) |
| Brain-derived         |                                          |                                  |                                                              |                                                                                  |                                                                                   |        |                          |                                   |
| neurotrophic          | DPV \(^6\)                              | Au np-wrinkled film (electroless deposition) | Cystamine/GA/Ab/T | Label-free [Fe(CN)]\(^{3+/4-}\) | T / 30 min, 37 °C | Buffer HP | 0.2 ng mL\(^{-1}\) <0.5 ng mL\(^{-1}\) (1) | 0.1–2 ng mL\(^{-1}\) |
| factor                |                                          |                                  |                                                              |                                                                                  |                                                                                   |        |                          |                                   |
| Biomarker (Target, T) | Technique | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution | Analysis time and Incubation parameters | Sample | Lower Detection Limit (1) | Range (2) | Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgCt) |
|----------------------|-----------|---------------------------------|---------------------------------------------------------------|-------------------------|----------------------------------------|--------|--------------------------|-----------|--------------------------------------------------------------------------------|
| DPV                  | Graphene SPE | AuNPs/L-Cysteine/(EDC+NHS)/Ab/T/ Abc/(EDC+NHS)/AQ | AQ | Buffer HS | 1.5 ng mL⁻¹ | <20.7 µg mL⁻¹ (1) | 0.01-150 µg mL⁻¹ |
| SWV                  | GCE       | PDANS/Ab/T/BSA-Ab₂-Cu₂(PQ4)₂-NPs (nanoflowers) | BSA-Ab₂-Cu₂(PQ4)₂-NPs, Na₂MoO₄, SWV in 0.5 M H₂SO₄ | Buffer HS | 1.26 pg mL⁻¹ | <0.3 µg mL⁻¹ (1) | 5 pg mL⁻¹-1 ng mL⁻¹ (vs lgCt) |
| EIS µPAD             | Carbon SPE | CS/GA/CDP-choline/T | Label-free [Fe(CN)₆]³⁻ | Buffer HP | 0.001 mg L⁻¹ | <0.1 mg L⁻¹ (1) (est. Fig. 5) | 0.005-500 mg L⁻¹ (vs lgCt) |
| SWV                  | Au IDEs microfab. | (4-ATP+cysteamine)/GA/Ab/T | Label-free [Fe(CN)₆]³⁻ /MuxT | T / 5 min | Buffer | <5.9 pM (1) | 5.9 pM-58.9 nM (vs lgCt) |
| EIS                  | Au (highly ordered wire arrays, microfab.) | MPA/(EDC+NHS)/Ab/T | Label-free [Fe(CN)₆]³⁻ | Buffer | 2.25 fg mL⁻¹ | 3 fg mL⁻¹ (EIS) | 4.5 fg mL⁻¹ (SWV) |
| EIS                  | Au | (microfluidic ID-zigzag biochip) | 11-FcC/GRO/CBMA/(EDC+NHS)/Ab/T | Buffer (TBACIO₃ in CAN and H₂O) HS | 18.3 pM | 50-50’000 pM (vs lgCt) | 5’000-500’000 pM (vs lgCt) |
| DPV                  | Au DE    | Fc-Peptide/(EDC+NHS)/Apt/T | Label-free | Buffer (TBACIO₃ in CAN and H₂O) HS | 7.2 pM | 10-5000 pM (vs lgCt) |
| DPV                  | CPE      | CPE-IL/ZnO-MPC*/(EDC+NHS)/Ab/T | Label-free [Fe(CN)₆]³⁻ | Buffer (TBACIO₃ in CAN and H₂O) HS | 5 pg mL⁻¹ | <10 ng mL⁻¹ (1) | 0.01-1000 ng mL⁻¹ (vs lgCt) |
| DPV                  | CPE      | Zr-tdc-IL (MOF)/(EDC+NHS)/Ab/T | Label-free [Fe(CN)₆]³⁻ | Buffer (TBACIO₃ in CAN and H₂O) HS | 0.2 ng mL⁻¹ | Two linear ranges: (I) 0.5-50 ng mL⁻¹ (II) 50-600 ng mL⁻¹ | Non-linear (vs lgCt) signal increase up to ca. 10⁻⁸ M |
| Conductometry        | CuPT-PPy nanowire mesh | NIPAAm-AM/Apt/CRP Polymer | Label-free | Buffer (TBACIO₃ in CAN and H₂O) HS | 9.03 × 10⁻¹³ g mL⁻¹ | <700 ng mL⁻¹ (1) (est. Fig. 6) | Non-linear (vs lgCt) signal increase up to ca. 10⁻⁸ M |
| EIS/DPV              | GCE      | PEI-Fc/Ab/T | Label-free EIS redox probe: [Fe(CN)₆]³⁻/²⁻ DPV | 20 µL T / 2 h, 4 °C | Buffer (RT plasma dil 1:1000) | 2.5 ng mL⁻¹ (EIS) | 0.5 ng mL⁻¹ (DPV) | 0.005-150 ng mL⁻¹ |

**CRP C-reactive protein (2018-2020)**
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) |
|-----------------------|-------------------------------------------|-----------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------|--------------------------|---------------|
| CRP (2018-2020) C-reactive protein | | | | | | | | |
| EIS μPAD (origami PAD) 2019 | Au DE | NH2-Ni-MOF(c)/AuNSs/Ab/T/Apt/ssDNA2/ MeB-DNA2 duplex | Label-free [Fe(CN)]3/2- | Buffer HS dil: 1:10 | 15 ng mL-1 | <5 µg mL-1 (1) (dilution 1:4) | 0.05-100 µg mL-1 (vs IgC) |
| EIS μPAD (origami PAD) 2019 | Carbon SPE | AuNP s/L-cysteine/[EDC+NHS]/Ab/T | Label-free [Fe(CN)]3/2- | Buffer HS dil: 1:10 | 17 ng mL-1 | <0.932 ng mL-1 (1) | 0.047-23.6 µg mL-1 |
| CPA 2018 | Carbon SPE | AuNP s/L-cysteine/[EDC+NHS]/Ab/T | Label-free [Fe(CN)]3/2- | Buffer HS dil: 1:10 | 17 ng mL-1 | <0.932 ng mL-1 (1) | 0.047-23.6 µg mL-1 |
| EIS 2018 | [EDC+NHS]/Ab/T | Mo | Label-free | Buffer HS dil: 1:10 | 100 pg mL-1 | 0.1-1000 ng mL-1 (vs IgC), non-linear part incl.) |
| Capacitive (impedance derived) 2020 | Graphene nanoplate SPE | PANI-PA/Ab/T | Label-free; Reagentless | Buffer FB5, dil. 1:100 | 0.5 µg mL-1 | Tested in 2 µg mL-1 | 145 |
| EIS (SFI) 2019 | ZnO-CuO composite nano-surface | Ab/T | Label-free | Buffer <1 ng mL-1 (1) | n/a, ca. from <1 ng mL-1 to 10 ng mL-1 (vs IgC); (est. Fig. 7)
| EIS (SFI) 2019 | Au IDEs microfab. (wave-shaped microgel. array) | DTSP/Ab/T | Label-free [Fe(CN)]3/2- | Buffer HS dil: 1:100 | 0.025 ng mL-1 | 0.01-10000 ng mL-1 (vs IgC) |
| EIS (SFI) 2019 | MHDA/[EDC+NHS]/Ab/T | Label-free [Fe(CN)]3/2- | Buffer* *Rabbit blood, dil. 1:10 only BNP-target | 3 µg mL-1 | Up to 10 µg mL-1 shown (vs IgC) |
| EIS/CV 2020 | Carbon film | MWNT4s (multiple-bent)/Ab/T | Label-free [Fe(CN)]3/2- | Buffer 40 pM (EIS) (~4.5 µg mL-1) similar (CV) | 10-1000 ng mL-1 (EIS) |

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### Notes
- **FED (DG-ISET) 2018**
  - Sensing area: high-K HfO2
  - Sensing area: (a) H2O2/OH/APTES/GA/Ab/T/GOx-Ab2
  - (b) "Extended gate": Off-chip enzymatic reaction in a 96-well ELISA plate. [End-point H-ELISA]
- **EIS µPAD (or FED architecture)**
  - Sensing area: high-K HfO2
  - Sensing area: (a) H2O2/OH/APTES/GA/Ab/T/GOx-Ab2
  - (b) "Extended gate": Off-chip enzymatic reaction in a 96-well ELISA plate. [End-point H-ELISA]
| Biomarker  | Technique Publication year and reference | Transducer | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flo w rate/Other | Sample | Lower Detection Limit \( (\text{1}) \) | Range \( (\text{2}) \) Linear vs target concentration \( (c_T) \), if not stated otherwise (e.g., vs \( lgC_T \)) |
|---|---|---|---|---|---|---|---|---|
| CRP C-reactive protein (2018-2020) | **EIS** 2020\(^{(3)}\) | Au DE | MUA/(EDC+NHS)/Ab/T | Label-free \([\text{Fe(CN)}_6]^{3/4-}\) | T / 30 min | Buffer | 3.7 pg mL\(^{-1}\) (32 FM) | 200-5000 ng mL\(^{-1}\) (vs \( lgC_T \)) |
| Dielectric voltammetry 2019\(^{(3)}\) | Microfluidic chip drive unit: Si/GaN/AIGaN Sensing area (separated gate): Si/GaN/Au | Sensing area: Thiolated Apt/T | Label-free MuxT | 4 \( \mu L \) / 5 min | Purified T (4\% BSA) HS dil. 1:1000 | 0.14 \( \mu g \) mL\(^{-1}\) \(<3 \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.1-0.5 \( \mu g \) mL\(^{-1}\) (vs \( lgC_T \)) |
| **FED (FET)** 2019\(^{(3)}\) | CTA/pHEMA/Ab/T | Label-free [Fe(CN)]\(^{3/4-}\) | T / 2 h; T / 15 min*: * dil. FBS, higher T concentrations | Buffer FBS undil. or dil. 1:10, 1:20 | 7.02 pg mL\(^{-1}\) (62 FM) <0.2 \( \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.2-3.15 \( \mu g \) mL\(^{-1}\) |
| CPA 2019\(^{(3)}\) | Carbon SPE (dual probe) | MBs/Ab\(_{1}\)/T/Ab\(_{2}\)-HRP | HRP, \( H_2O_2 \) MuxT | 50 \( \mu L \) / 5 min | Buffer HP dil. | 8 ng mL\(^{-1}\) \(<1.7 \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.01-5 \( \mu g \) mL\(^{-1}\) (working range, sigmoid vs \( lgC_T \)) |
| RPS (B) 2019\(^{(4)}\) | Nanocarriers: SPBs | Peptide-Apt/Non-binding DNA/T | Label-free MBs with Apt (or DNA) / 30 min / 1 h | Buffer | n/a | Low \( \mu M \) range: ca. 0.5-2.5 \( \mu M \) \( (\text{estimated from Fig. 4}) \) |
| **FED (FET)** 2019\(^{(3)}\) | Si/SiO\(_2\)/CeO\(_2\) | Ab/T | Label-free | 20 \( \mu L \) / 30 min | Buffer HS | 0.1 \( \mu g \) mL\(^{-1}\) \(<1 \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.1-2.5 \( \mu g \) mL\(^{-1}\) (working range, not linear) |
| **PEC** 2019\(^{(3)}\) | GCE | PNS-777 MOF/AuNPs/Capture strand/ HT/Primer/Padlock probe+dNTPs/T4 ligase+T-phi29 polymerase | Zr-based MOF (PNS-777) as photopactive material | T: MBs+(EDC+NHS) / 1 h; MBs with amino Apt / 1 h; Primer / 2 h, 37 °C; 50 \( \mu L \) T / 30 min, 25 °C | Buffer HS dil. 1:50 | 16 FM | <100 FM \( (\text{1}) \) | 50 FM–50 nM (vs \( lgC_T \)) |
| **PEC (CBP)** 2019\(^{(4)}\) | ITO | NiS/pCOFs/AgNPs/Apt/T | Label-free pCOFs (as photopactive material) \( H_2O_2 \) | 10 \( \mu L \) Apt / 30 min, 37 °C | Buffer HS dil. 1:10 | 0.1 \( ng \) mL\(^{-1}\) \(<20 \) ng mL\(^{-1}\) \( (\text{1}) \) | 0.5-100 \( ng \) mL\(^{-1}\) \( (3.5 \text{ pM-710} \text{ pM}) \) |
| CPA 2020\(^{(3)}\) | Carbon SPE (8 multiplexed units) | MBs/Ab\(_{1}\)/T/Ab\(_{2}\)-HRP | HRP, \( H_2O_2 \), HQ | MBs with Ab\(_{1}\) / 15 min T / 5 min Complete assay (after Ab\(_{1}\) immobilization): 15 min | Buffer Whole blood dil. 1:10 HP dil. 1:10 | 1.5 \( ng \) mL\(^{-1}\) \(<1 \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.005-1 \( \mu g \) mL\(^{-1}\) (vs \( lgC_T \), non-linear) |
| EIS non-farad. 2020\(^{(3)}\) | Nano-ZnO and ZnO/CuO nitrocellulose membrane | Ab/T | Label-free | 40 \( \mu L \) T / 10 min | Buffer | 2.5 \( ng \) mL\(^{-1}\) (nano-ZnO) | 16 \( ng \) mL\(^{-1}\) (nano-ZnO) | 0.1-15 \( ng \) mL\(^{-1}\) (vs \( lgC_T \), non-linear) |
| CPA 2020\(^{(3)}\) | Carbon SPE (microfluidic) | rGRO/NI/PtNPs micromotors/Ab\(_{1}\)/T/Ab\(_{2}\)-HRP | HRP, \( H_2O_2 \), HQ | 10 \( \mu L \) T / 5 min | Buffer HP HS | 0.8 \( \mu g \) mL\(^{-1}\) \(<3 \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 2–100 \( \mu g \) mL\(^{-1}\) (vs \( lgC_T \)) |
| SWV 2020\(^{(3)}\) | Carbon SPE | Aryldiazonium/(EDC+NHS)/Ab/T | Label-free \([\text{Fe(CN)}_6]^{3/4-}\) | T / 1h | Buffer | <0.1 \( \mu g \) mL\(^{-1}\) \( (\text{1}) \) | 0.01–10 \( ng \) mL\(^{-1}\) |
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution | Analysis time and Incubation parameters | Sample | Lower Detection Limit (1) | Range (2) |
|----------------------|------------------------------------------|----------------------------------|---------------------------------------------------------------|--------------------------|-----------------------------------------|--------|--------------------------|----------|
| CRP                  | EIS 2020<sup>12</sup>                    | Au                               | Fc-Peptide/EDC+NHS/Ab                                         | Label-free               | Redox-tagged peptide / 16h; EDC+NHS / 30 min; Ab / 1h; T / 30 min | Buffer | 240 pM Peptide 2 300 pM Peptide 3 | 0.5-10 nM (non-linear) |
| GFAP                 | CPA 2020<sup>13</sup>                    | GCE                              | Chitosan/AuNPs/IL-MoS<sub>2</sub>T/Ab-ir NPs-GRO-DN           | Label-free               | 10 µL Ab / overnight T / 60 min at 37 °C | Buffer | HT dil. 1:1000 | 3.3 pg mL<sup>1</sup> <5 ng mL<sup>1</sup> (1) | 0.01–100 ng mL<sup>1</sup> |
| EIS                  | Au MDEA (a) Au MECS (b) (microfabrication) | DTSP/Ab/T                         | DTSP/Ab/T                                                     | Label-free               | T / 30 min                               | Buffer | 1 pg mL<sup>1</sup> | 1 pg mL<sup>1</sup>–100 ng mL<sup>1</sup> | 0.8–400 pg mL<sup>1</sup> |
| EIS                  | FED (OFET) 2014<sup>45</sup>            | Si/SiO<sub>2</sub>            | MIP-MWCNTs: [MWCNTs+AlBN+ DMAA+AEDEP+EGMA[GAPF]]/agarose film/(SDS+HCl)/EDTA | Label-free               | 50 µL T / T accumulation (prior to EIS) | Buffer | 0.04 µg mL<sup>1</sup> | 0.2–10 µg mL<sup>1</sup> |
| EIS                  | Drive:Si/SiO<sub>2</sub>/Pentacene/Au Sensing: Si | Sensing: (PS-MA+PEG)/Ab/T | Sensing: (PS-MA+PEG)/Ab/T | Label-free               | Drain current almost constant after 30 min | Buffer | 1 ng mL<sup>1</sup> | 0.5–100 ng mL<sup>1</sup> |
| EIS                  | Graphene SPE                           | NaOH(OH)/PEI/GA/Ab/T           | Label-free                                                     | T / 30 min               | Buffer                                  | Buffer | 1 pg mL<sup>1</sup> | 1 pg mL<sup>1</sup>–100 ng mL<sup>1</sup> (vs IgG<sub>C</sub>) |
| GM-CSF               | CPA 1999<sup>13</sup>                   | Carbon SPE                      | EDC/Ab/(free + ALP-labelled T) (competitive assay) | ALP                     | T / 30 min Complete assay: 35 min       | Buffer | 0.1 µg mL<sup>1</sup> | 1.1–30 µg mL<sup>1</sup> |
| h-FABP               | CPA 1996<sup>12</sup>                   | Pt (Clark type oxygen probe)   | Immunosandwich on nitrocellulose: CDI/Ab/T/Ab<sub>2</sub>-GOx | GOx                     | 100 µL T / 10 min, 37°C T / 10 min, 37°C | Buffer | 5 ng mL<sup>1</sup> | 5-80 ng mL<sup>1</sup> |
| Heart-fatty acidic binding protein | CPA 1997<sup>13</sup>                   | Graphite SPE                    | Ab<sub>2</sub>/Ab<sub>1</sub>-ALP                              | ALP                     | Complete assay: 20 min                   | HP     | 10 ng mL<sup>1</sup> (Fig. 5-7<sup>13</sup>) | 10–350 ng mL<sup>1</sup> |

| Incubation parameters | Linear vs target concentration (c<sub>T</sub>) if not stated otherwise (e.g., vs lgC<sub>T</sub>) |
|-----------------------|---------------------------------------------------------------|
# Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) Linear vs target concentration (c), if not stated otherwise (e.g., vs lgC) |
|----------------------|----------------------------------------|-------------------------------|-----------------------------------------------|-------------------------------------------------|------------------------------------------|---------|-----------------|---------------------------------|
| **h-FABP Heart-fatty acidic binding protein**… | CPA 2002 | Carbon SPE | Ab₂/T/Ab₂-ALP | ALP PAPP | 150 µL (T+Ab₂-ALP)/ 45 min, 37°C Complete assay: 50 min | Buffer | 1 ng mL⁻¹ | 4-250 ng mL⁻¹ (vs lgCₚ) 10-250 ng mL⁻¹ (vs lgCₚ) 4-250 ng mL⁻¹ (vs lgCₚ) |
| | SWV 2012 | GCE | GRONR₅/EDC-NHS/Ab₂/T/Ab₂/GA/TiP-Zn²⁺-probe | TiP-Zn²⁺-probe MuxT | 20 µL T / 60 min; 20 µL Ab₂- TiP-Zn²⁺ probe / 60 min | Buffer | 3 fg mL⁻¹ | <1.7 µg mL⁻¹ (1) |
| | EIS 2012 | Au (microfabrication) | MUA/[EDC+NHS]/Ab/T [mSAM] (MUA+MCOH)/[EDC+NHS]/Ab/T [hSAM] | Label-free [Fe(CN)₆]³⁻/²⁻ | T / 30 min, 37°C | Buffer | 117 pg mL⁻¹ [mSAM] 524 pg mL⁻¹ [hSAM] Similar, with decreased sensitivity |
| | Capacitive EIS 2015 | Au IDEs (microfabrication) | MUA/[EDC+NHS]/Ab/T [mSAM] (MUA+MPOH)/[EDC+NHS]/Ab/T [hSAM] | Label-free [Fe(CN)₆]³⁻/²⁻ | Microfluidic platform: 50 µL T / 30 min | Buffer | 0.836 ng mL⁻¹ [mSAM] 0.968 ng mL⁻¹ [hSAM] 98 pg mL⁻¹~100 ng mL⁻¹ (vs lgCₚ) |
| | ASV (DPASV) 2017 | GCE | CD-GS/Ab₂/T/Ab₂-ZnO-MWCNTs/CdS | ZnO-MWCNTs/CdS pH 5 prior to DPV MuxT | 6 µL T /1 h, 37°C; 6 µL Ab₂-ZnO-MWCNTs / 40 min, 37°C; 8 µL [Cd(NO₃)₂ + TAA] / 15 min, 37°C | Buffer | 0.3 fg mL⁻¹ | <5 pg mL⁻¹ (1) |
| **IL-6 Interleukin 6 (2018-2020)** | EIS 2018 | PPy-NWs layer | PPyPAC/[EDC+NHS]/Ab/T | Label-free | T / 30 min | Buffer | 0.36 pg mL⁻¹ | 21 |
| | DPV 2018 | GCE | AMCs/CTIL/Ab₂/T/[OAMs+APTES]/ACP/[EDC+NHS]/Ab₂-HRP Ab₂-HRP/[EDC+NHS]/ACP /[OAMs+APTES] 1-NPP, H₂O₉ | T / 30 min, 4 °C Ab₂-HRP/ACP/OAMs / 40 min, 4 °C | Buffer | 0.32 fg mL⁻¹ | 10 fg mL⁻¹~90 ng mL⁻¹ (vs lgCₚ) |
| | SWV 2018 | GCE | CP[PPC/[EDC+NHS]/Ab₂/T/Ab₂-GRO-NB | NB MuxT | T / 30 min Ab₂-GO-NB / 30 min | Buffer | 5 pg mL⁻¹ | <50 pg mL⁻¹ (1) |
| | CPA (Bead-based ELISA) 2018 | Au (microfabrication) Microfluidic multiplexed assay | WE: CTPEG₁₀/[EDC-NHS]/Ab₁ Recognition probe on MBs: Ab₂-HRP HRP TMB, H₂O₂ Suggested for MuxT | T with 10 µL bead solution / 30 min; MB-T mixture kept in each channel at the sensor / 10 min | Buffer | 2.6 pg mL⁻¹ | 5 pg mL⁻¹ linear between ca. 40 and 1000 pg mL⁻¹ (vs lgCₚ) (estimated from Fig. 6) |
| | FED (OECT) 2018 | Drive: Kapton/PEDOT:PSS Sensing: Au wire | Sensing area: EG₄COOH/[EDC+NHS]/Ab/T rc-membrane: GA/protein G/glycine/Ab/T | Label-free | Re. preconc.: 1 mL of T/ 2h; T release in detection buffer: 30 min (100 µL) Gate with T / 1 h | Buffer | 220 pg mL⁻¹ | n/a |
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) |
|----------------------|------------------------------------------|----------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------|--------|------------------------|-----------------|
|                      |                                          |                                  |                                                               |                                                                                   |                                                               |        |                        |                  |
| IL-6                 | EIS 2018\(^{[3]}\)                      | Graphite SPE Magneto-immunosensors | Recognition probe on MBs: Protein G/[EDC+NHS]/Ab/T           | Label-free [Fe(CN)]\(^{3-}\)                                                     | 10 µL (T+MBs, suspension 1:1) /30 min, 20°C   | Buffer | H2 dil. 1:100          | 0.3 pg mL\(^{-1}\) <100 pg mL\(^{-1}\) (1) | 1 pg mL\(^{-1}\)-1 µg mL\(^{-1}\) (linear at low concentrations only) |
|                      | EIS 2018\(^{[4]}\)                      | GCE                              | pABA/[EDC+NHS]/pATP/AuNPs/Apt/T                              | Label-free [Fe(CN)]\(^{3-}\)                                                     | 15 µL T / 60 min                                           | Buffer | H2 dil. 1:1           | 1.66 pg mL\(^{-1}\) <2 pg mL\(^{-1}\) (1) | 5 pg mL\(^{-1}\}-100 ng mL\(^{-1}\) (vs IgC\(^{a}\)) |
|                      | FED [GFET] 2019\(^{[5]}\)               | Si/SiO\(_2\)/Graphene            | PASE/Apt                                                    | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 10 min                                              | Buffer | H2 dil. 1:1           | 2.78 pg mL\(^{-1}\) (139 FM) | 1.5 pM-100 nM (non-linear) |
|                      | DPV 2019\(^{[6]}\)                      | Au (needle microelectrode)        | Sulfo-LC-SPDP/DTT/Ab/T                                      | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 2.5 min                                              | Buffer | H2 <20 pg mL\(^{-1}\)  | <100 pg mL\(^{-1}\) (1) (linear) | 0-80 pg mL\(^{-1}\) (non-linear) |
| IL-8                 | EIS 2020\(^{[7]}\)                      | ITO                              | PPy-NHS/Ab/T                                               | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 45 min                                               | Buffer | H2 dil. 1:10          | 10.2 fg mL\(^{-1}\) <0.6 pg mL\(^{-1}\) (1) | 0.03-22.5 pg mL\(^{-1}\) |
|                      | EIS 2020\(^{[8]}\)                      | ITO                              | PPCE/IL-6 receptor/T                                       | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 30 min                                               | Buffer | H2 dil. 1:10          | 6 fg mL\(^{-1}\) <0.9 pg mL\(^{-1}\) (1) | 0.02-16 pg mL\(^{-1}\) |
|                      | EIS 2021\(^{[9]}\)                      | ITO                              | AB/epoxy-substituted-PPy/Ab/T                              | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 45 min                                               | Buffer | H2 dil. 1:5           | 3.2 fg mL\(^{-1}\) <1 pg mL\(^{-1}\) (1) | 0.01-50 pg mL\(^{-1}\) |
|                      | EIS (SFI) 2018\(^{[10]}\)               | ITO                              | Star polymer SPGA-M@Super 9\(^{a}\) carbon black-PVDF composite/Ab/T | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 45 min                                               | Buffer | H2 dil. 1:200         | 3.3 fg mL\(^{-1}\) <26 pg mL\(^{-1}\) (1) | 0.01-3 pg mL\(^{-1}\) |
|                      | EIS 2018\(^{[11]}\)                     | ITO                              | NH\(_4\)OH:H\(_2\)O\(_2\):H\(_2\)O/PHA/[EDC+NHS]/Ab/T     | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 30 min                                               | Buffer | H2 dil. 1:50          | 6 fg mL\(^{-1}\) <26 pg mL\(^{-1}\) (1) | 0.02-3 pg mL\(^{-1}\) |
|                      | SWV 2019\(^{[12]}\)                     | Carbon SPE                       | PEI-AuNPs/GA/Ab\(_T\)/PEI-AuNPs-Ab\(_2\)-Ag\(^{b}\)        | PEI-AuNPs-Ab\(_2\)-Ag\(^{b}\) MuxT                                             | 2 µL T / 40 min; 2 µL PEI-AuNPs-Ab\(_2\)-Ag\(^{b}\) / 40 min | Buffer | pH (4.5)              | 1 fg mL\(^{-1}\) <2.5 pg mL\(^{-1}\) (1) | 0.5-100 pg mL\(^{-1}\) (vs IgC\(^{a}\)) 2.5-50 pg mL\(^{-1}\) |
| ASV (LSASV) 2018\(^{[13]}\) | SWV 2019\(^{[12]}\)                     | Carbon/MWCNTs AJPE               | Ab\(_{2}\)/T/Ab\(_{2}\)-ALP/Ag\(^{c}\)                    | AgNO\(_3\), AA; Stv-ALP as catalyst for Ag\(^{+}\) reduction                    | T / 2 h, Ab\(_{2}\) / 2 h 10 s constant E before LSV     | Buffer | 0.3 ng mL\(^{-1}\)    | 1.25-10 ng mL\(^{-1}\) |                  |
|                      | DPV 2020\(^{[14]}\)                     | ITO                              | β-Ag\(_{2}\)(MoO\(_4\))/[EDC+NHS]/Ab/T                  | Label-free [Fe(CN)]\(^{3-}\)                                                     | T / 10 min                                               | Buffer | 90 pg mL\(^{-1}\)     | 1 fg mL\(^{-1}\)-40 ng mL\(^{-1}\) (non-linear/two linear ranges) |                  |
| ASV (SWASV) 2020\(^{[15]}\) | GCE (Hg film-modified)                  | MBs/[EDC+NHS]/Ab/T TCEP treated T | TCEP-treated T/ Maleimide-mod.DNA QDs                       | 50 µL MBs/DNA-QD+250 µL HNO\(_2\) (RT) / 1 h; N\(_2\) / 15 min                  | Buffer | H2 dil. 1:10          | 3.36 fg mL\(^{-1}\) <5 fg mL\(^{-1}\) (1) | 5-5000 fg mL\(^{-1}\) (vs IgC\(^{a}\)) |
|                      | CV 2007\(^{[16]}\)                      | SiO\(_2\) nanowires Microfluidic chip | APTMS/Ab\(_{2}\)/T/ALP-Ab\(_{2}\) | ALP/pNPP/MuxT                                                                     | 3 µL T / 2 h; Ab\(_{2}\) / 2h; Stv-ALP / 30 min<; 30 µL pNPP / 20 min, RT | Buffer | Lung serum            | ~ ag mL\(^{-1}\) 1 pg mL\(^{-1}\) (1) | n/a |
|                      | SWV 2012\(^{[17]}\)                     | Au DE                            | (FRGG+TBAP/McCN)/[EDC+NHS]/Fc-Ab/T                         | Label-free MuxT                                                                  | T / 15 min                                               | Buffer | <1 pg mL\(^{-1}\)     | 0.001-50 ng mL\(^{-1}\) (vs IgC\(^{a}\)) |                  |
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit [1] | Range [2] Linear vs target concentration (\(c_0\), if not stated otherwise) (e.g., vs lgC_0) |
|-----------------------|------------------------------------------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------|-------------|---------------------------|-----------------------------------------------|
| IL-10 Interleukin 10 Continuation >> | EIS 2012<sup>29</sup> | HfO<sub>2</sub> | TESUD/Ab/T | Label-free | T / 30 min, 4°C Total volume: 10 mL | Buffer | 0.1 pg mL<sup>-1</sup> | 0.1-20 pg mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| EIS 2015<sup>30</sup> | Al<sub>2</sub>O<sub>3</sub> | APTES/MWCNTs/(EDC+NHS)/Ab/T | Label-free [Fe(CN)<sub>6</sub>]<sup>3-/4-</sup> | 50 µL T / 30 min, 4°C | Buffer | <0.5 pg mL<sup>-1</sup> (1) | 0.5-500 pg mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| EIS 2016<sup>31</sup> | Au (microfabrication) Microfluidic chip | MHD(A/EDC+NHS)/Ab/T | Label-free [Fe(CN)<sub>6</sub>]<sup>3-/4-</sup> | T / 30 min, 4°C | Buffer | n/a | 1–15 pg mL<sup>-1</sup> (non-linear) |
| EIS 2017<sup>32</sup> | Au (microfabrication) | CMA/(EDC+NHS)/Ab/T | Label-free [Fe(CN)<sub>6</sub>]<sup>3-/4-</sup>/MuxT | T / 30 min, 4°C 15 min for detection | Buffer | 0.3 pg mL<sup>-1</sup> | 1–15 pg mL<sup>-1</sup> |
| EIS 2020<sup>33</sup> | Graphene ID AIP | EDC+NHS/T | Label-free [Fe(CN)<sub>6</sub>]<sup>3-/4-</sup>/MuxT | 100 µL T / 30 min Complete assay: 33 min | BIS dil. 1:1000 | | 46 pg mL<sup>-1</sup> | 0.1-2 g mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| EIS 2020<sup>33</sup> | Si/SiO<sub>2</sub>/Si<sub>3</sub>N<sub>4</sub>-(Spy-PPy) | CMA/(EDC+NHS)/Ab/T | Label-free | T / 30 min, 4°C | Buffer | 0.347 pg mL<sup>-1</sup> | 1-10 pg mL<sup>-1</sup> |
| DPV 2013<sup>34</sup> | GCE | Au-NGR/Ab/T/HRP-Ab<sub>2</sub>-GA-PDA-GRO | HRP Thi/H<sub>2</sub>O<sub>2</sub> | 10 µL T / 1 h, 37°C; 50 µL HRP-Ab<sub>2</sub>/PDA-GRO / 50 min, 37°C | Buffer | 0.11 pg mL<sup>-1</sup> | <0.4 ng mL<sup>-1</sup> (1) | 0.0005-50 ng mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| DPV 2013<sup>34</sup> | Au DE | Thiolated DNA/MCH/Collagen-like Pept (5) (target-induced degradation) | Label-free [Fe(CN)<sub>6</sub>]<sup>3-/4-</sup> (5) APMA for T activation; Captopril for modulating T (T+APMA) / overnight, 37°C WE with activ; T / 2 h, 37°C | Captopril / 30 min, 37°C | Buffer | 0.1 µg mL<sup>-1</sup> | 0.1-1 µg mL<sup>-1</sup> |
| ASV (SWASV) 2013<sup>37</sup> | Au thin film (PDM-AuNPs composite) | Pept-SH/AuNPs-DNA-(EDC)-CdS<sub>2</sub>Te<sub>0.6</sub>QDs (target-induced cleavage) | CdS<sub>2</sub>Te<sub>0.6</sub>QDs; HNO<sub>3</sub>; Bl<sup>2+</sup> prior to SWV (pH 5.2) | 100 µL T / 2h, 37°C 200 µL HNO<sub>3</sub> / 2h | Buffer (pH 5.2) | 0.63 pg mL<sup>-1</sup> | <1.7 ng mL<sup>-1</sup> (1) | 1-500 pg mL<sup>-1</sup> |
| FED (FET) 2013<sup>38</sup> | SiO<sub>2</sub> | APTES/CA/FN (target-induced degradation) | Label-free CaCl<sub>2</sub> | Measurement 3 h after addition of (T+CaCl<sub>2</sub>) | Buffer | <150 ng mL<sup>-1</sup> (1) | Only 150 ng mL<sup>-1</sup> executed |
| FED (FET) 2013<sup>38</sup> | SiNWs (zigzag structure) | TESBA/peptide)<sup>39</sup> TESBA/peptide/DNA/AuNPs<sup>40</sup> (target-induced cleavage) | Label-free | T / conductance change registered after 20 s<sup>2</sup> and 13 s<sup>2</sup> | Buffer | ca. 1 pM<sup>39</sup> ca. 0.1 pM<sup>40</sup> | 1 pM-100 nM (vs lgC<sub>0</sub>), 100 FM-10 nM (vs lgC<sub>0</sub>) |
| PEC (CBP) 2014<sup>31</sup> | TiO<sub>2</sub>-NTs | CdS:Mn/CdTe-QDs/Ab<sub>2</sub>/T/Ab<sub>2</sub>/SiO<sub>2</sub> | Ab<sub>2</sub>@SiO<sub>2</sub> label; TiO<sub>2</sub>-NTs/ CdS:Mn/CdTe-QDs | 20 µL T / T, 37°C 20 µL Ab<sub>2</sub>@SiO<sub>2</sub> / 1 h, 37°C | Buffer | 3.6 fg mL<sup>-1</sup> | 10 fg mL<sup>-1</sup>-500 pg mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| DPV 2015<sup>40</sup> | Au DE | 9-MN/Fc-Pept (target-induced cleavage) | Label-free APMA for T activation | T in TCNB buffer; 20 µL T with APMA / 1 h, 37°C WE with activated T / 1 h, RT | Buffer | 0.3 ng mL<sup>-1</sup> | 1-200 ng mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| DPV 2015<sup>40</sup> | GCE | Au/issDNA<sub>2</sub>-pPipNP-Pept-SH/issDNA<sub>2</sub> ssDNA<sub>2</sub>-Thi (target-induced cleavage) | Label-free H<sub>2</sub>O<sub>2</sub> | T / 2 h, 37°C | Buffer | 0.32 pg mL<sup>-1</sup> | <0.1 pg mL<sup>-1</sup> (1) | 1 pg mL<sup>-1</sup>-10 pg mL<sup>-1</sup> (vs lgC<sub>0</sub>) |
| Biomarker | Technique | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution | Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters | Sample | Lower Detection Limit | Range (2) |
|-----------|-----------|-------------------------------|---------------------------------------------------------------|--------------------------|---------------------------------------------------------------|----------------------------------------|---------|----------------------|-----------|
| MMP-2   | EIS       | Au (microfabrication) | Microfluidic chip | Pept-SH (target-induced cleavage) | Label-free/MuxT (MMP-2, MMP-7) | Substrate/medium | Buffer | 0.5 pg mL⁻¹ | 0.1–400 ng mL⁻¹ (non-linear, impedance reduction vs c₁) |
|          | DPV 2015¹⁴ | GCE                          | Au/Pept-SH/Stv-Thi-Pt-Pd-mhCeO₂/NS-NPs (target-induced cleavage) | Thi-Pt-Pd-mhCeO₂/NS-NPs | H₂O₂ | Buffer | 0.078 pg mL⁻¹ | <1 ng mL⁻¹ (1) |
|          | DPV 2016²⁵ | GCE                          | GCE: Au/CB[7]²⁻ released MεB Probe: MBs/(EDC+NHS)/Pept-SH/AuNPs-DNA (target-induced cleavage) | MeB-DNA²⁺/Exo III | 20 µL (Probe+T)/ 40 min, 37°C (Cleaved-Pept/AuNPs-DNA, + MeB-DNA²⁺)/ 60 min, 37°C; Exo III / 60 min, 37°C; | Buffer | 0.15 pg mL⁻¹ | 0.5 pg mL⁻¹:10 ng mL⁻¹ (vs lgC₇) |
|          | DPV 2016²⁶ | GCE                          | Au/Fc-Pept; Probe: (CB[7]⁻²⁻)-PtnPs with Fc-HRP)/(CB[7]⁻²⁻)-PtnPs with Fc-GOx | (target-induced cleavage) | T / 50 min, 37°C | Buffer | 0.03 pg mL⁻¹ | 0.1 pg mL⁻¹:20 ng mL⁻¹ (vs lgC₇) |
|          | CPA 2017²⁸ | ITO                          | K-GS@CS@C₆H₅NBF₄/GA/Ab/T/GA/ ssDNA/|ssDNA,|ssDNA,|ssDNA,|ssDNA, | Buffer | 35 fg mL⁻¹ | 100 fg mL⁻¹:10 ng mL⁻¹ (vs lgC₇) |
|          | SWV 2018²⁹ | GCE                          | Au-rGRO-pMeB-Pept-Sh/(EDC+NH₃)/PtnPs-amFc-BSA (target-induced cleavage) | Label-free/ | 60 µL T / 3 h | Buffer | <0.01 ng mL⁻¹ | <0.5 ng mL⁻¹ (1) |
|          | SWV 2019³⁰ | GCE                          | PANI gel/AuNPs/Pept-Sh/CS-AuNPs-Pt(II)/ Na-tartrate gel (target-induced cleavage) | Label-free/ | [Fe(CN)]₆³⁻/²⁻ | Buffer | 0.4 pg mL⁻¹ | 1 pg mL⁻¹:1 μg mL⁻¹ (vs lgC₇) |
|          | PEC (CBP)| 2020³¹ | ITO                          | Fe₃O₄@SiO₂/(EDC+NH₃)/Ab/T/Ab₂/ TiO₂-AgNPs | TiO₂-Ag NPs/Ab₂ | Buffer | 0.34 fg mL⁻¹ | 1 fg mL⁻¹:100 pg mL⁻¹ (vs lgC₇) |
|          | MT3       | DPV 2013³² | GCE                          | K₀₂[Fe(CN)₆]₃⁻:CS-GA/C-dots+Nafion/Ab/T | Label-free/ | T / 60 min, 37°C | Buffer | 2.5 pg mL⁻¹ | 5 pg mL⁻¹:20 ng mL⁻¹ |
|          | NCAM      | DPV 2020³³ | GCE                          | MIP (pABA + PolySi₈) | [Fe(CN)]₆³⁻/²⁻ | T in p-ABA solution (buffer, pH 9.0) / 60 min | Buffer | “Probe-type”: 4.74 ng mL⁻¹ (vs lgC₇); “Sandwich” 0.47 ng mL⁻¹ In SI, n/a |

(2) Lower Detection Limits/
Range, if not stated otherwise (e.g., vs lgC₇)
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) | Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC_T) |
|----------------------|----------------------------------------|----------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------------------------|----------|-------------------------------------------------------------------------|
| NFL Neurofilament light | EIS 2020\(^{104}\) Au (microfabrication) | MAC/GMA/Ab/T | Label-free \([\text{Fe(CN)}_6]^{3-/4-}\) | n/a | KCl | 5.21 ng L\(^{-1}\) | 1-50 µg L\(^{-1}\) |
| | PEC (no bias) 2020\(^{105}\) Pt NWs on FTO (biocathode) | (MUA+MCH)/Ab Photoanode: FTO/BiVO\(_4\)/FeODH | Label-free | 60 µL T / 1 h, RT | Buffer HP dil. 1:10 | 38.2 fg mL\(^{-1}\) | n/a | 0.1-1000 pg mL\(^{-1}\) (vs lgC\(_T\)) |
| NGB Neuroglobin | CV 2020\(^{106}\) Au DE | np-Au/MCH/TMSE/T (a) | H\(_2\)O\(_2\) and Cyt c as redox partners/substrates | n/a | Buffer | Qualitative study: strategy for exploring the molecular basis of NGB coupled with electron transfer |
| | | GCE | rep@POAP (electro-catalytic oxidation of T by NO) | NO (physiological level) | Detection: 1-2 min | Buffer | sub-µM | sub-µM-10 µM range |
| | DPV 2018\(^{108}\) GCE | PC/AuNA/ MVIMBf\(_3\)/MIP-Poly(DPIMBr)/T | T / 15 min | Buffer HS dil. 1:100 | 2.6 pg mL\(^{-1}\) | <7.7 ng mL\(^{-1}\) | 1 pg mL\(^{-1}\) |
| | | Graphite SPE | GR nanosheets/PpPD/AuNPs/Ab/T | Label-free AA | T / 60 min | Buffer HS | 0.3 ng mL\(^{-1}\) | <11 ng mL\(^{-1}\) |
| | | Au DE (3D-SICPC-modified) | 3Dm-gro-PANI/[EDC+NHS]/T | Label-free \([\text{Fe(CN)}_6]^{3-/4-}\) | 10 µL T / 40 min, 37°C | Buffer HS dil. | 0.1 µg mL\(^{-1}\) | <0.5 ng mL\(^{-1}\) |
| | | SWV 2018\(^{111}\) GCE | CS-Fc/AuPd-MWCNTs/GA/Ab/T | H\(_2\)O\(_2\) | 20 µL T / 50 min, 37°C | Buffer (pH 6.5) HS | 0.48 pg mL\(^{-1}\) | <1 ng mL\(^{-1}\) |
| | | SWV 2018\(^{112}\) Carbon SPE | pTMB-Au|PD-SA-AuNPs-Ca\(^{4+}\) hydrogel/Ab/T | Label-free H\(_2\)O\(_2\) / MuxT | 10 µL T / 45 min, 37°C | Buffer (pH 6.5) HS | 2.3 pg mL\(^{-1}\) | <1.7 ng mL\(^{-1}\) |
| | | | PANI hydrogel/AuNPs/Ab/T|Ab\(_2\)-AuNPs-THI-gRO-Hem/ H\(_2\)O\(_2\) | 80 µL T / 45 min, 37°C; 40 µL Ab\(_2\)-AuNPs-THI-gRO-Hem / 37°C | Buffer HS | 0.026 pg mL\(^{-1}\) | <1 ng mL\(^{-1}\) |
| | | | Alginate/PANI/hydrogel/GA/Ab/T/ [Nanogel/Cu@AuNPs] | Probe: Cu@AuNPs | 200 µL probe with T / 1 h | Buffer (pH 5.5) HS | 4.6 pg mL\(^{-1}\) | <3.3 ng mL\(^{-1}\) |
| | | | PPY-polTHI-hydrogel with GOGx/AuNPs/Ab/T | Label-free; H\(_2\)O\(_2\); Glucose; GOGx doping | T / 50 min | Buffer HS | 0.65 pg mL\(^{-1}\) | <5.5 ng mL\(^{-1}\) |
| | | | PPB-PEDOT-AuNPs/SH-Apt/T | Label-free MuxT | 20 µL T / 1 h | Buffer HS | 10 pg mL\(^{-1}\) | <1.25 ng mL\(^{-1}\) |

**NOTE:** The table provides a summary of various electrochemical detection methods used for biomarker detection, including the transducer type, surface modification techniques, detection solution, analysis time and incubation parameters, sample type, lower detection limit, and concentration range. Each method is detailed with specific parameters and detection limits, highlighting the versatility and precision in biomarker detection.
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution | Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters | Sample | Lower Detection Limit | Range (2) | Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC) |
|----------------------|--------------------------------------|----------------------------------|---------------------------------------------------------------|-----------------------|-----------------------------------------------------------------|---------------------------------------------|--------|---------------------|---------|-----------------------------------------------------------------|
| DPV 2019117          | GCE                                  | AuNPs/Ab/T/TB/ WP6@PdPt PCONs/Ab2 | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| SWV 2019118          | Au wires                              | Au QCM chips                      | **Surface modification/ Bioreceptor functionalization/ Assay format | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| SWV 2019119          | GCE                                  | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| SWV 2019120          | GCE                                  | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| SWV LFA (with SERS)  2019121 | FTO                                  | AgNPs/Au/ NBA/Ab/T | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| EIS 2019122          | ITO                                  | P(ThiPh-gMAm)/GA/ Ab/T            | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| EIS (SFI) 2019123    | Au DE                                | MHDA/(EDC+NHS)/Ab/T               | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| EIS (SFI) 2019124    | Au DE                                | MHDA/(EDC+NHS)/Ab/T               | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| ASV (LSASV) 2019124  | GCE                                  | 3D-GRS/CS/GA/Ab/T/Ab2-OMCSi-AuNPs/ 3D-GRS/AuNPs | **Label** | **Detection solution** | **Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc.** | **Analysis time and Incubation parameters** | **Sample** | **Lower Detection Limit (1)** | **Range (2)** | **Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgC)** |
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and incubation parameters Volume/Target or label/Time/Temperature/Flow rate/Other | Sample | Lower Detection Limit (1) | Range (2) | Linear vs target concentration (c), if not stated otherwise (e.g., vs lgC) |
|-----------------------|------------------------------------------|---------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------|---------------------------|--------|---------------------------------------------------------------|
|                       |                                         |                                 |                                                               |                                                                                   |                                                                                                   |        |                           |        |                                                               |
| **NSE** |                                                                 |                                 |                                                               |                                                                                   |                                                                                                   |        |                           |        |                                                               |
| Neuron-specific enolase (2018-2020) Continuation =>                                                                 |                                 |                                                               |                                                                                   |                                                                                                   |        |                           |        |                                                               |
|                      | Poten. 2019[15]                         | pH electrode (commercial)       | Immunoassay immobilization on PS-microplates: Ab₂/T/Ab₂-GOx-LS | GOx-LS; Triton X-100 (to release GOx), Glucose | [T + Ab₂-GOx-LS] [50+50 µL/well] / 35 min; Glucose / 10 min | Buffer | 8.1 pg mL⁻¹ <0.5 ng mL⁻¹ | 0.01-100 ng mL⁻¹ (dynamic linear range: pH vs lgC) | 0 2-100 ng mL⁻¹ (vs lgC) |
|                      | PEC (CBP) 2019[16]                      | ITO                             | NiWO₄-NiStr/Ab/T                                             | Label-free Uric acid | PEC measurement: 150 s with 20 s light on/off cycles | Buffer | 0.12 ng mL⁻¹<10.7 ng mL⁻¹ | 77-723 ng mL⁻¹ (vs lgC) | 10 90-300 ng mL⁻¹ (vs lgC) |
|                      | DPV 2020[17]                            | GCE                             | Au@MOFs/(EDC+NHS)/Ab₂/T/Ab₂-Au@Pd⁺Pt NCbs/MnO₂ UNs          | MnO₂ UNs/Au@Pd⁺Pt NCbs label* HQ, H₂O₂ | 6 µL MnO₂ UNs/Au@ Pd⁺Pt NCbs-Ab₂ / 1 h | Buffer | 4.17 fg mL⁻¹<0.7 ng mL⁻¹ | 10 fg mL⁻¹–100 ng mL⁻¹ (vs lgC) | 10 fg mL⁻¹–50 ng mL⁻¹ (vs lgC) |
|                      | DPV 2020[18]                            | GCE                             | Fc-g-Au@Pd-P(BBY)/TCEP+APT₁/T/Apt₂/AuPt NA/T/Thr/GrO       | Thi and Fc as signal probes | Fc-g-Au@Pd-P(BBY)/TCEP+APT₁ with T / 60 min, 37°C, Apt₂/AuPt NA/T/Thr/GrO / 60 min, 37°C | Buffer | 30 fg mL⁻¹ n/a | 100 fg mL⁻¹–50 ng mL⁻¹ (vs lgC) | 100 fg mL⁻¹–100 ng mL⁻¹ (vs lgC) |
|                      | SWV 2020[19]                            | Au wires                        | AuNPs-MIPs (epitope-mediated)                                | Label-free [Fe(CN)₆]³⁻₂⁻ | 2 mL T / 15 min | HS dill: 1:2 | 25 /200 pg mL⁻¹ (w/wo Au NPs) | 25–4000 / 50–500 pg mL⁻¹ (w/wo Au NPs) (non-linear) | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) |
|                      | EIS 2020[20]                            | ITO                             | P(Pyr-Epx)/Ab/T                                              | Label-free [Fe(CN)₆]³⁻₂⁻ | T / 30 min | Buffer | 6.1 fg mL⁻¹ <1.2 pg mL⁻¹ | 0.02-7.5 pg mL⁻¹ | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) |
|                      | EIS 2020[21]                            | ITO                             | Str(PGMAs)/Ab/T                                              | Label-free [Fe(CN)₆]³⁻₂⁻ | T / 45 min | Buffer | 9.1 fg mL⁻¹ <1.2 pg mL⁻¹ | 0.03-6 pg mL⁻¹ | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) |
|                      | EIS 2020[22]                            | Au DE                           | Zr-TAPP/Ab/T                                                 | Label-free [Fe(CN)₆]³⁻₂⁻ | T / 50 min | Buffer | 7.1 fg mL⁻¹ <10 fg mL⁻¹ | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) |
|                      | CPA 2021[23]                            | GCE                             | AuPt NSNs/Ab₂/Ab₂/ Au-CuO₂@CeO₂                               | Au-CuO₂@CeO₂/Ab₂ H₂O₂ | 6 µL T / 40 min, RT | Buffer | 31.3 fg mL⁻¹ <15 ng mL⁻¹ | 50 fg mL⁻¹–100 ng mL⁻¹ (vs lgC) | 50 fg mL⁻¹–100 ng mL⁻¹ (vs lgC) |
|                      | DPV 2013[24]                            | Pencil graphite Microfluidic chip (PMMA) | WE (graphite): PMMA/OH(NaOH)/NH₃/PEI/GA/Ab₂/T/Ab₂/ALP-lg | ALP PAR | 20 µL T / 30 min, 37°C; 20 µL Ab₂ / 20 min, 37°C (flow rate 120 µL h⁻¹) | Buffer | 0.1 pg mL⁻¹ <0.1 pg mL⁻¹ | 0.1–100 pg mL⁻¹ | 10 fg mL⁻¹–200 pg mL⁻¹ (vs lgC) |
|                      | SWV 2014[25]                            | Au DE                           | (Capture peptide+TCEP)/(T+CaCl₂)/(signal peptide+Cu²⁺)       | OPD; Cu²⁺ as catalyst for OPD oxidation | T / 2.5 h, 30°C | Buffer | 0.1 nM <0.2 nM | 0.1–25.6 nM (vs lgC) | 0.1–25.6 nM (vs lgC) |
|                      | OSWV 2014[26]                           | Au DE                           | (DPTA+NAC)/Cu²⁺/His₂-RAGE VC1 or C2/T                       | Label-free | 10 µL T / 30 min | Buffer | 0.52 pM | 1–100 µM | 1–200 µM (vs lgC) |

**S100B**

**S100B calcium-binding protein**
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flo w rate/Other | Sample | Lower Detection Limit (1) | Range (2) | Linear vs target concentration (cT), if not stated otherwise (e.g., vs lgCt) |
|----------------------|------------------------------------------|----------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------|------------------------|----------|---------------------------------------------------------------|
| S100β S100 calcium-binding protein | OSWV 2016[147] | Au DE | (DPM+NAC)/Cu2+/His2-RAGE VC1 or C2/T (a) (DPM+MBT)/Cu2+/His2-RAGE VC1 or C2/T (b) | Label-free | 10 µL T Solutions deoxygenated | Buffer HP dil. 1:2 | 2.6 pm (a) 4.9 pm (b) | 2.6-20 pm (a) 4.9-20 pm (b) | 0.9 pm (a) 2.7 pm (b) |
|                      | DPV 2017[158] | Graphene SPE | Electrografted reduced FRGG/GA/Ab/T | Label-free [Fe(CN)6]3-/4- | T / 45 min, 4°C | Buffer HS (and CSF) | 1 pg ml-1 1 pg ml-1 | 1 pg ml-1-10 ng ml-1 (vs lgCt) | 1 pg ml-1-10 ng ml-1 (vs lgCt) |
|                      | EIS 2018[20] | Au IDE (microfluidic ID-zigzag biochip) | (4-ATP+cysteamine)/GA/Ab/T | Label-free [Fe(CN)6]3-/4-/MuxT | 5 min (flow rate 25 µL min-1) | Buffer | 10 ng ml-1 10 ng ml-1-10 µg ml-1 (vs lgCt) | 10 ng ml-1-10 µg ml-1 (vs lgCt) |
|                      | FED (FEED) 2018[160] | Carbon SPE | SWCNTs-Nafion-GA/Ab/T | HRP Reagentless | T / 60 min Ab2 / 40 min | HS | 10 fg ml-1 10 fg ml-1-10 ng ml-1 | 10 fg ml-1-10 ng ml-1 |
|                      | SWV LFA (with SERS) 2019[21] | FTO | AgNPs/Au/4-MBA/Ab/T | Label-free MuxT | T / 30 min | Buffer (pH 6.5) | 10 pg ml-1 50 pg ml-1-1 µg ml-1 | 50 pg ml-1-1 µg ml-1 |
|                      | EIS (SFI) 2019[46] | Au DE | MHDA/(EDC+NHS)/Ab/T | Label-free [Fe(CN)6]3-/4-/MuxT | Optimal Z-t measurement: 15 s | Buffer 5- 25 and 90% blood and plasma | 2-5 pg ml-1 Recoveries; 14-67 pg ml-1 in 90% blood | 0.1-2800 pg ml-1 |
|                      | PEC (CBP) 2019[60] | ITO | rGRO-AuNPs/3-ICT-sol-gel-film/Ab/T/Ab/(EDC+NHS)/CdS-QDs | Csds-QDs AA | 5 µL T / 30 (45 min Buffer; 20 µL T / 30 min (HS) 6 µL Csds-QDs / 30 min | Buffer HS | 0.15 pg ml-1 <100 pg ml-1 (1) | 0.25-10000 pg ml-1 (vs lgCt) |
|                      | CSV (DPCSV) 2020[24] | Au DE | Recognition probe: MBs/Au/Ab/T | Label-free | 50 µL T / 30 min | Buffer Horse plasma | 10 pM <250 pM (1) | 10 pM-100 nM (non-linear) |
|                      | EIS 2014[42] | Au DE | Lip-NHS/Tau-protein/T | Label-free [Fe(CN)6]3-/4- | 5 µL T / 2h | Buffer | 0.2 µM 0.1-1.0 µM | 2N4R (tau441) |
|                      | DPV 2017[43] | Carbon SPE | GRO/(ECD+NHS)+(+DMAP)/pPG/GA/Ab/T/Ab/(pP+S+MUA)/(ECD+NHS)/pPG | PbS-NCs-probe; HNO2 for NCs ionization/ MuxT | 1 mL in a cell (Buffer); 10 µL T / 30 min (HS) 6 µL PbS-NCs drop-casted (HS); 15 min with HNO3 | Buffer HS dil. 1:100 | 0.15 nM <0.5 nM (1) | 0.15-250 nM (non-linear) |
|                      | EIS 2017[44] | Au (microfabrication) | DTSSP/Protein G/Ab/T | Label-free [Fe(CN)6]3-/4- | T / 25 min | Buffer HS | 0.03 µM 0.01 µM | 0.01 pM-10 nM 2N4R (tau441) |

**Continuation ->**
| Biomarker (Target, T) | Technique Publication year and reference | Transducer (or FED architecture) | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution Substrate/redox probe/ mediator/catalyst/ signal enhancer/pH modulator etc. | Analysis time and Incubation parameters Volume/Target or Label/Time/Temperature/Flo w rate/Other | Sample | Lower Detection Limit | Range (2) Linear vs target concentration (c_T), if not stated otherwise (e.g., vs lgC_T) |
|-------------------------|------------------------------------------|----------------------------------|-------------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|------------------------|-----------------------------------------------|
| DPV 2018\(^{145}\) Au (microfabrication) | (SATA+Ab)/Thiolated pGluA/T (a) (SATA+Ab)/T (b) | Label-free \[^{[Fe(CN)]}_{3}^{3-}\]/MuxT | 20 µL T / 30 min Buffer (pH 6.2) | 0.968 pM (a) 9.68 pM (b) 0.968-454 pM (a,b) (vs lgC_T) |
| DPV 2018\(^{146}\) Au DE | MPA/(EDC+NH3)/Ab/T/AuNPs-SH-Apt | Label-free \[^{[Fe(CN)]}_{3}^{3-}\] | T / 45 min Buffer HS dil. 1:100 | 0.42 pM <1.5 pM (1) 0.5-100 pM 1N3R (tau381) |
| EIS 2018\(^{4}\) Multiarray of vertically aligned Pt wires | Cysteamine/ GA/Ab and(or) Apt/T | Label-free/[Fe(CN)]\(^{3-}\)/Suggested for MuxT | 2 µL T / 5 min Buffer | 0.001 pg mL\(^{-1}\) 0.001-10 pg mL\(^{-1}\) |
| EIS 2018\(^{147}\) Au DE | Lipoic acid/(EDC+NH3)/Ab/n-butylamine/hexanethiol/T | Label-free/[Fe(CN)]\(^{3-}\)/Suggested for MuxT | T / 1h Buffer | 0.7 pM <1 pM (1) 1-100 pM 2N4R (tau441) |
| DPV 2019\(^{148}\) GCE | CGR/Thi/AuNPs/Apt/T | Label-free | 20 µL T / 30 min Buffer HS dil. 1:100 | 0.7 pM <1 pM (1) 1-100 pM 2N4R (tau441) |
| DPV 2020\(^{149}\) Au | MWNTs/rGRO/CS/Ab/T/AuNPs | Au NP \[^{[Fe(CN)]}_{3}^{3-}\]/T with AuNPs / 4 h, 4°C; T- AuNPs conjugate with WE / 30 min, 4°C Buffer HS | 0.46 FM <1.5 fM (2) 0.5-80 FM (vs lgC_T) 2N4R (tau441) |
| EIS 2020\(^{150}\) GCE | SL-rGRO@PTSA/Cu\(^{2+}\)/ (EDC+NH3)/Ab/T | Label-free/[Fe(CN)]\(^{3-}\)/Suggested for MuxT | 6 µL T / 30 min, 4°C Buffer HS dil. 1:1000 | 75 FM <2.5 pM (1) 0.08-80 pM (vs lgC_T) 2N4R (tau441) |
| SWV 2020\(^{151}\) Au (mini pillar-based sensor) | Au nanodendrites/Ab/T | Label-free Ru(NH\(_3\))\(^{3+}\)/MuxT | 10 µL Ab / 4h at RT 10 µL T / 4h at RT Buffer HS | 7.14 10\(^{-11}\) mg mL\(^{-1}\) 10\(^{-10}\)-10\(^{-7}\) mg mL\(^{-1}\) (vs lgC_T) |
| EIS 2020\(^{152}\) PET-ITO | rGRO/Au NP/11-MUA/(EDC+NH3)/Ab/T | Label-free \[^{[Fe(CN)]}_{3}^{3-}\] | T / 60 min, dark Buffer HS | 0.091 pg mL\(^{-1}\) <10 pg mL\(^{-1}\) (1) 1-500 pg mL\(^{-1}\) 2N4R (tau441) |
| FED (FET) 2020\(^{153}\) Sensing : Glass/Ti/Au (microfluidic chamber) | Sensing area: Au/COOH-EG\(_{2}\)-thiol/PEG/(EDC+NH3)/Ab/T | Label-free Complete assay: 30 min Buffer (CSF) | 1 pM (~10 pM) | 1 pM-10 nM (Fig. 2) (1) 2N4R (tau441) |
| CPA 2020\(^{154,155}\) Carbon SPE\(^{153}\) Dual SPCE\(^{153}\) | pABA/(EDC+NH3)/3D-Au-PAMAM/GA/Ab/T/Ab\(_{2}\)-HPR | Ab\(_{2}\)/HRP HO/\(\text{H}_2\)\(_{2}\) MuxT | T / 1h Ab\(_{2}\) / 60 min Buffer HP | 1.7 pg mL\(^{-1}\) 2.3 pg mL\(^{-1}\) (>pg mL\(^{-1}\) (1) 8-5000 pg mL\(^{-1}\) 2N4R (tau441) |

\(^{1}\) Linear vs target concentration (c_T), if not stated otherwise (e.g., vs lgC_T).
| Biomarker (Target, T) | Technique (or FED architecture) | Transducer | Surface modification/ Bioreceptor functionalization/ Assay format | Label Detection solution | Analysis time and Incubation parameters | Sample | Lower Detection Limit | Range (2) |
|-----------------------|---------------------------------|-------------|---------------------------------------------------------------|--------------------------|-----------------------------------------|--------|------------------------|-----------|
| Tau protein(s) / T-Tau | ELA-PEC (2021)                  | Carbon paste electrode | AuNPs-MoSe₂/MCH/Apt/T/Ab/Protein G-AP | Protein G-AP AAP, Mg(NO₃)₂ | 35 µL T / 30 min, 37°C; 35 µL Ab / 60 min, 37°C; 35 µL Protein G-AP / 60 min, 37°C; [AAP+Mg(NO₃)₂] / 60 min, 37°C | Buffer | 0.3 fM | 0.5 fM-1.0 nM (vs lgCₜ) |
| Total tau (P- + non-phosphor.) | DPV (2017)                      | Au (microfabrication) | MPA/(EDC+NHS)/Ab/T | Label-free [Fe(CN)₆]₃⁻/⁴⁻ | T / 3h | Buffer | 1000 pg mL⁻¹ | 1000-100000 pg mL⁻¹ |
| Continuation => | PEC (2020)                      | FTO         | Mo:BiVO₄/FeOOH/Ab₂/T/Ab₂-HRP | Ab₂-HRP DAB | 70 µL T / 1h, RT; 30 µL Ab₂ / 1h DAB / 10 min | Buffer | 1.59 fM | ~fM to >10⁶ fM (vs lgCₜ) (Buffer, HP, Fig. 4) |
| | FED (GFET) (2020)              | Si/SiO₂     | APMES/rGRO/PBASE/Ab/T | Label-free MuxT | 20 µL T / 30 min | Buffer | n/a | 100 fg mL⁻¹-100 ng mL⁻¹ (vs lgCₜ) |
| | UCH-L1 Ubiquitin C-terminal hydrolase | EIS (2018) | Multiarray of vertically aligned Pt | Label-free [Fe(CN)₆]₃⁻/⁴⁻ | The suggested array has been patented for the detection of UCH-L1, GFAP and tau-proteins. However, the array has been tested in detail for tau-protein detection only. | | | | |
| | SWV (2019)                     | Graphene SPE | pNE/Ab (a) pDE/Ab (b) | Label-free [Fe(CN)₆]₃⁻/⁴⁻ | 50 µL T / 30 min | Buffer | 1.91(a) 0.70 (b) pg mL⁻¹ | 0.1 pg mL⁻¹-100 ng mL⁻¹ (vs lgCₜ) (a) |
| | VCAM-1 Vascular cell adhesion protein 1 | EIS (2017) | DTSP/Ab/T or DTSP/Ab₂/T/Ab₂ | Label-free | 50-100 µL T / 15 min | Buffer | 8 fg mL⁻¹ | 8 fg mL⁻¹-800 pg mL⁻¹ (vs lgCₜ) |
(1) Lowest reported LDL using EC detection methods; ‘<x’ corresponds to the lowest concentration analyzed within the working range of the sensor (employing standard addition method and/or a reference material/method for validation, with a decent recovery), actual LDL being possibly lower than the indicated value. Redox couple \([\text{Fe(CN)}_6^{3-/4-}]\) indicated if used. (2) The upper limit of the range indicated often presents the maximum concentration explored but not the upper detection limit. Please consult original paper for details. (3) Increase in diameter of a sub-micron latex colloid upon binding to an unlabelled specific antibody results in changes in pore resistance. Particles passing through the pore displace the conducting fluid in that pore. (4) Enzyme cascade amplification: GOx catalyses glucose to gluconic acid with concomitant formation of \(\text{H}_2\text{O}_2\) for accelerating the redox reaction of Fc in the presence of HRP and PtNPs. (5) Collagen in the complex is being degraded by MMP-2. The inhibition effect of captopril to MMP-2 can be revealed by the electrochemical signal. With the increase of MMP-2 concentration more collagen molecules will be digested, thus a larger amount of electrochemical probe \([\text{Fe(CN)}_6^{3-/4-}]\) can get closer to the electrode leading to an increase of the electrochemical signal. (6) Application for the target detection in urine has been exceptionally noted here, due to the fact that no other publications have been found on the electrochemical detection of VCAM-1 biomarker. For Column 7 ‘Sample’: Dilution factor (‘dil.’, if indicated) corresponds to the primary dilution of the sample to be analyzed and does not account for the further dilution steps implied by the suggested protocol (mixing with the redox probe/mediator/labelling solution/signal enhancer/detection buffer/etc.). pH of the (detection) buffer is indicated, if significantly different from clinical ranges in blood samples (ca. 7.5). ABBREVIATIONS: see last Page. For more detailed information on EC strategies for the detection of CRP biomarker readers should refer to the review articles by Bakirhan et al.\textsuperscript{161}, Sohrabi et al.\textsuperscript{162}, Dhara and Mahapatra\textsuperscript{163} and Chen et al.\textsuperscript{164}. As of December 2020 no EC detection strategies have been found on the following biomarkers: BMX (bone marrow tyrosine kinase on chromosome X), CKBB (creatine kinase B type), ICAM-1 (intracellular adhesion molecule-1), MDA-LDL (malondialdehyde modified low density lipoprotein), NFM (neurofilament medium), Nogo-A (neurite outgrowth inhibitor protein), pNF-H (NF-H) ((phosphorylated) neurofilament heavy protein), E-selectin (E-selectin), SNTF (calpain-derived αII-spectrin N-terminal fragment) and Ub (ubiquitin).
**Summary of Key Observations and Outstanding Challenges**

A total number of 127 publications on EC techniques and protocols for 19 different mTBI protein biomarkers were compiled (Table 3 and SI-1).

- **Techniques**
  - EIS (35 entries) followed by DPV (29) and SWV (23) were the most frequent EC methods employed for determining mTBI relevant blood proteins concentrations.

- **Assay performance**
  - 99 publications report measurement data obtained in complex matrix (e.g., HS, HP, etc.), but the vast majority did so under significantly diluted sample conditions and/or compromised analytical performance characteristics. Sample dilution may be a feasible approach to reduce NSB (see SI-3), but this brings up additional requirements to sample preparation (e.g., microfluidic cartridge design) or operator usability aspects, the latter not being ideal for POC diagnostic testing. While reproducibility of results is indicated in many of the publications, only few have determined accuracy and precision data with real/clinical samples (e.g., goal of CV < 6% in laboratory medicine), with multiple reagent/sensor lots, with a statistically significant patient sample number and by systematically comparing performances against a reference method. In this context the question comes up to which degree the impressive detection limits (LDL) reported can be confirmed in real-world situations to reliably differentiate brain injured from healthy individuals based on physiological cutoffs (CO).

- **Diagnostic Specificity / Multiplexing**
  - It is primarily an mTBI biomarker discovery and validation rather than sensor development task to improve the diagnostic specificity (i.e., reduce the number of false positives). However, since no single protein biomarker provides sufficient specificity, the right combination (e.g., 5-plex?) may do so in the future. Therefore, enabling a multiprotein detection modality is likely to be crucial, especially for a POC diagnostic application. EC sensors seem technologically apt for (simultaneous) multiple protein mTBI biomarker target detection - in 26 publications authors report data on multiprotein detection within a single assay (MuxT). However, very limited information is provided in terms of multi-analyte panels (comprising various protein mixtures in complex matrix representing physiological situations) used to challenge sensor performances.

- **Sample Volume**
  - In many referenced publications sample volumes of 50 µL and less were used, which – being a design constraint in the context of mTBI POC diagnostic applications – is compatible with EC sensing.

- **Time-to-results**
  - Most of the reported EC sensor measurement times exceed acceptable time-to-results (< 15 min) requirements for POC diagnostic applications. It is conceivable that in the future, optimized assay and shortened incubation conditions will still be compatible with good assay performance, but this requires likely a significant R&D effort.

- **Manufacturability and Costs of Goods Produced (COGP)**
  - As pointed out in Figure 8, the small sample and reagent consumption anticipated as well as the low costs of the materials and fabrication make EC sensors attractive candidates for a future POC device for mTBI diagnostics. The main challenges, however, may be the difficulties and costs associated with electrode-bioreceptor functionalization (for multiple mTBI protein target analytes) and limited sensor stability and thus short shelf-life.
The process of non-specific binding (NSB) is a complex phenomenon that is extremely sensitive to the properties of both the sensing surface (e.g., heterogeneity, topography, functional groups, surface potential) and the protein(s) to be adsorbed (e.g., size, chemical and 3D structure, charges, apolar properties), as well as the sample media. The interaction between the surface and the protein defines its conformation and is strongly affected by the ionic strength and the pH value of the sample, specifically by the composition of the solution adjacent to the electrode. Integration of antifouling materials reducing NSB is crucial in order to enable reliable detection in a complex matrix and is typically achieved via one or more of the following mechanisms: (i) formation of a hydration layer, i.e. increasing the hydrophilicity of the sensing surface resulting in decreased adhesion of biofoulant; (ii) steric repulsion, e.g. via integration of polymers sterically preventing the foulants from reaching the electrode surface; (iii) electrostatic repulsion via attachment of molecules with anionic and/or cationic moieties (e.g. zwitterionic materials); (iv) optimized surface topography (altering the surface roughness on nanoscale level). Among most commonly applied strategies is the immobilization of ‘blocking’ proteins, e.g. avidin, streptavidin, neutravidin, casein or (most frequently) bovine serum albumin (BSA). This and other methods based on physical adsorption provide a relatively inexpensive and fast solution, however possess a few disadvantages, such as non-uniformity of the adsorbed layer and reversibility of the adsorption process. The latter is governed by the weak intermolecular interactions and is sensitive towards the experimental conditions (solvent polarity, ionic strength, temperature, pH). Furthermore, most protein blockers have a high lot-to-lot variability and cross-reactivity, alter original surface properties, and, as some studies have reported, e.g. a BSA layer does not always efficiently prevent protein adsorption. An NSB suppressing layer can be obtained or optimized using some other physical approaches to surface modification or combinations thereof: mechanical coatings (polymer films), integration of nanoporous structures (e.g. carbon nanotubes, graphene-based materials, metallic nanoparticles) and/or superhydrophobic surfaces. Chemical approaches present a more robust antifouling strategy for EC biosensing in comparison to physical approaches discussed above and are often accomplished via formation of SAMs containing antifouling moieties such as polyethylene glycol (PEG), oligo(ethylene glycol), zwitterionic peptide-based molecules or polymers. Furthermore, the thiolated alcohol compounds, such as e.g. 6-mercaptohexanol or 11-mercaptoundecanol, are often applied to gold surfaces in order to ‘block’ empty spots and stabilize the SAM conformation. However, the relatively poor stability of SAMs, narrow choice of transducer substrates (mainly applied to gold, less frequently to silver, copper and platinum) and grafting molecule types (mainly thiolated compounds) limit the application of SAMs for NSB reduction in EC sensing. As an alternative to SAMs, polymer brushes can be tethered on substrates using different grafting methods. Unlike SAMs, this strategy is not limited to gold surfaces and has been applied to numerous substrates such as carbon, ITO, graphene etc. A typical example would be electrodeposition of PEDOT or PANI films, with or without additional doping with PEG (or grafting of PEG) on a carbon- or graphite-based substrate. While grafting of non-conductive antifouling reagents with the long chains (such as PEG) directly onto transducer surface often results in the loss of sensitivity due high impedance of the polymeric layer, incorporation of PEG with conductive soft polymers such as PEDOT and PANI is one way to resolve this issue. However, in many cases CP layers have been shown to suffer from low mechanical and complex media stability. In another promising strategy the polymeric brushes are formed via reduction of diazonium salts providing a rapid single-step approach to polymeric brush immobilization. This approach ensures a low energy barrier for the injection of electrons at the contact between the metal and organic molecule, along with the improved stability due to covalent character of the formed bond. Despite the large number of strategies suggested in the literature for NSB reduction, hardly any of them are sufficient to completely overcome this problem in view of POC diagnostic applications in biological matrices. Further efforts are needed in this field in order to establish an effective combination of antifouling materials with surface modification strategies and to better understand the synergetic effect of the complex media and the antifouling probes on the properties of the biorecognition element.
ABBREVIATIONS for SI

µPAD: microfluidic paper-based analytical device; 1-NPP: 1-naphthyl phosphate; 11-FcC: 11-ferrocenyl-undecanethiol; 3D-GRS: porous three-dimensional graphene-starch architecture; 3DM: three dimensionally macroporous; 3D-SiPCC: three dimensional silica close-packed colloidal crystal; 3-ICT: (3-isocyanatopropyl)triethoxysilane; 4-ATP: 4-aminothiophenol; 4-MBA: 4-mercaptobenzoic acid; 9-MN: 9-mercaptopo-nonanol; AA: ascorbic acid; AAP: ascorbic acid 2-phosphate; Ab: antibody; AB: acetylene black; ACN: acetonitrile; ACP: acid phosphatase; AEDP: monomer, 2-acrylamidoethyl dihydrogen phosphate; AIBN: 2,2′-azobis(2-methylpropionitrile); AJPE: aerosol jet printed electrode; AM: acrylamide; AMCs: TiO2 (anatase) mesocages, here: Ru(bpy)32+@AMCs composite for dual response [DVP and ECL, Ru(bpy)32+: ruthenium (II) tris(bipyridine)]; ALP: alkaline phosphatase; amFc: aminoferrocene; APMA: 4-aminophenylmercuric acetate; Ap: (oligo)cationic aptamer for the target (T); APTES: 3-aminopropyl triethoxysilane; APTMS: 3-aminopropyl trimethoxy silane; AQ: anthraquinone; ASV: anodic stripping voltammetry; Au@Pd-P(BBY): core/shell Au nanoparticles @Pd nanoclusters-poly(bismarck brown Y); AuNA: gold nanoparticle; AuNPs: gold nanoparticles; AuNs: gold nanostars; AuPt NAS: hierarchical AuPt nanoassemblies; Av: avidin; Bis: bovine implant serum; BNP: B-type natriuretic peptide; BSA: bovine serum albumin; C6H4NBFe: 1-butylpyridine tetrafluoroborate; CB7: cucurbit[7] uril; CBMA: 2-[carboxy,N,N-dimethyl-(2’-methacryloyloxyethyl)amethanamine inner salt], zwitterionic monomer; CBP: constant bias potential; CD-GS: 4,4′-cyclohexylenedimethane-graphene sheets; CDI: carbonyldimidazol; CDP-choline: cytidine diphosphate-choline (cytidine 5′-diphosphocholine sodium salt dihydrate); CGR: carbonyl graphene; CMA: 4-carboxyethyl aryl diazonium; CMS: cysteine-modified epoxide; CNTS: carbon nanotubes; COF: covalent organic framework; CP: conductive polymer; CPA: constant potential amperometry; CPE: carbon paste electrode; CPT: 5-carboxy-1-panthenol; CP (PPE): mixed layers of 4-carboxyphenyl and 4-aminophenyl phosphorylcholine; CS: chitosan; CSV: cathodic stripping voltammetry; CT(PEG)2: carboxy-PEG12-thiol; CTIL: carboxyl-terminated liquid; CuPt: copper phthalocyanine-3,4,4′,4″-tetrasulfonic acid tetrasodium salt (as dopant counterion); Cy c: ferric cytochrome c; DAB: diaminobenzene; DG: dual gated (transistors); DG-ISFET: dual gated ion-sensitive field effect transistor; dil.: diluted; DMA: monomer, dimethylacrylamide; DMAP: 4-(dimethylamino)pyridine; DN: 1,5-diaminonaphthalene; dNTPs: deoxyribonucleoside triphosphate; DPASV: differential pulse anodic stripping voltammetry; DPI: dual probe immunosensor; DPMBr: 1,3-di(3-N-pyryl-propyl)imidazolium bromide; DP: differential pulse; DTSP: 3,3′-dithiobis(succinimidyl propionate); DPU: differential pulse voltammetry; EC: electrochemical; EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EDTA: ethylene diamine tetraacetic acid disodium salt; EG, COOH: (11-mercaptopoundecyl)hexaethylene glycol) acetic acid terminated; EGDMMA: ethylene glycol dimethylacrylate; ELISA: enzyme-linked immunosorbent assay; Eo: ex: exunction level; FBS: fetal bovine serum; Fe: ferrocene; Fe-Cu-Au@Pd-P(BBY): ferrocene grafted Au@Pd-P(BBY); FED: field-effect based detection (voltage controlled current amplification); FN: fibronectin; FRGG: p-Nitrobenzene diazonium tetrafluoroborate (Fast Black GGI salt); fUb: free ubiquitin; GA: glutaraldehyde; GC: glassy carbon electrode; GNs: gold nanorods; GOx: glucose oxidase; GOx-LS: glucose oxidase loaded liposomes; GRONRs: graphene oxide nanoribbons; H-Er: elution; ELISA: enzyme-linked immunosorbent assay; Hem: hemin; His: histidine; HME: histidine-modified epoxide; HP: human plasma; hDNA: hairpin DNA; HP: horseradish peroxidase; HS: human serum; HT: hexanethiol; HQ: hydroquinone; hSAM: homogenous ordered self-assembled monolayer; IDE: interdigitated electrode; IL: ionic liquid; ITO: indium tin oxide; K-GS: K-modified graphene; LP-NHS: N-hydroxysuccinimide ester; LSASV: linear sweep ASV; M: N-methacroyl-lysine; MBS: magnetic beads; MBT: 4-mercaptopentanol; MCH: mercaptohexanol; MIDEA: microdisc electrode array; MeB: methylene blue; MeCN: acetonitrile; MECs: macroelectrode with a comb structure; mpCeO2: mesoporous-hollow ceria nanophosphates; MHDMA: mercaptohexadecanoic acid; microel.: microelectrode(s); microfab.: microfabricated MOF(s); metal-organic framework type c (particle size 300 nm); MOF: metal-organic framework; MPA: 3-mercaptopropionic acid; MCP: porous carbon matrix; MPOH: 3-mercaptopropanol; mSAM: mixed self-assembled monolayer; mTub: multibiquitin chains; MUA: 11-Mercaptoundecanecacid; MuxT: multiple protein biomarker targets detected within the same immunoassay; MVIMBF: 1-(3-mercapto-propyl)-3-vinyl-imidazolium tetrafluoroborate ionic liquid; MWCNts: multivalye carbon nanotubes; N: N-acetylcysteamine; NBS: Nile blue A; NCBs: nanocubes; NCs: nanocrystals; NGR: nitrogen-doped graphene; NHS: N-hydroxysuccinimide; NIPAM: N-Isopropylacrylamide; NiWO4-NS: saw-blade-like NiWO4 nanostructures; NPs: nanoparticles; NSNs: nanoblock spherical nanochip-conductors; NSs: nanospheres; NTCDI: naphthalenetetracarboxylic diimide; NTs: nanotubes; NWs: nanowires; OAMS: octadecahedral anatase TiO2 mesocrystals; OECD: organic electrochemical transistor; OFET: organic field effect transistor; OMCSi-AuNPs: gold nanoparticle incorporated ordered mesoporous carbon-silica; OPD: o-phenylenediamine; OSW: Osteryoung square-wave voltammetry; pABA: p-aminoanbenzoic acid; PAD: microfluidic paper-based device; PAMAM: poly(amidoamine); PAN: polyaniline; PANI-PA: phytic acid-doped polyaniline; PAPP: 4-aminoaryl phosphate; PASE: pyrenebutyluric acid succinimidyl ester; pATP: poly-aminothiophenol; PB: Prussian blue; PBASE: 1-pyrenecarbonylic acid N-hydroxysuccinimide ester; PB-PEDOT-AuNPs: Prussian blue poly(3,4-ethylenedioxythiophene)-AuNPs; PBS: phosphate buffer saline; PC: porous polycarbonate membrane; pCOF: porphyrin covalent organic framework; PDA: polydopamine; PDDANS: polydopamine nanospheres; PEC: photoelectrochemical (detection); PEDOT: poly(3,4-ethylenedioxythiophene); PEI: poly(ethyleneimine); PEG: polyethylene glycol; Peptide: thiolated peptide; pGluA: poly-glutamic acid; PHA: 6-phosphohexonic acid; pHEMA: poly(2-hydroxethyl methacrylate); pMeB: poly(methylene blue); PMMA: poly(methyl methacrylate); PMPC-SP: thiol-terminated poly(2-methacryloyloxyethyl phosphorylcholine); pNE: polynorolepinephine; pNP: p-nitrophenyl phosphate; PPCE: conjugated polypyrrole polymer containing epoxy active side groups; pPG: amine functionalized 1st generation trimethylolpropane tris(poly[propylene glycol]) dendrimers; pPnPD: poly(p-phenylenediamine); pPTNPs: porous platinum nanoparticles; PPy: polypyrrole; PPy-NWs: polypyrrole-nanowires; PPyPAC: polypyrrole electrodes modified by electrodeposition of diazonium salts using 4-aminophenylacetic acid (4APAC); precon.: preconcentration; Protein G AP: protein G labeled with alkaline phosphatase; PS: polystyrene; PS-MA: polystyrene-co-methylacrylic acid; PSS: polystyrene sulfonate; pTMB: poly (3,3′,5,5′-tetramethylbenzidine); PTSA: 1,3,6,8-pyrenetetrasulfonic acid tetrasodium salt; pTTBA: (2,2,5,5-19
