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Mapping of lanthanide-tagged proteins on western blot paper using microextraction-inductively coupled plasma-mass spectrometry†

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A microextraction (ME) sampling system, paired with inductively coupled plasma-mass spectrometry (ICP-MS), was employed to spatially analyze proteins tagged with lanthanum (La), gadolinium (Gd), or terbium (Tb) on the surface of western blot paper. The proteins were covalently tagged, separated *via* gel electrophoresis, and transferred to western blot paper for analysis by ME-ICP-MS. The ME-ICP-MS method enables the direct sampling of the tagged species on the western blot paper, without any sample preparation. Traditionally, the tagged analyte would need to be stained, excised, and digested to be analyzed by ICP-MS for its elemental and isotopic characterization. Preliminary detection limits for the ME-ICP-MS method applied to western blot paper were established to be 564, 54, and 2.5 fg for La, Gd, and Tb, respectively. The developed ME-ICP-MS method was compared to laser ablation (LA) ICP-MS, another direct solid sampling technique; it was readily determined that ME-ICP-MS can effectively map the elemental constituents on the western blot paper with comparable analysis time and measurement sensitivity. The analysis time per 2 × 4 mm extraction is ~1 minute; if protein spots are directly targeted (rather than systematically mapping the entire blot paper), the analysis time per protein spot is ~1 min. This developed method proved to be fast, effective, and accessible for correlating protein molecular weight with the detection of the inorganic tagant. The ME-ICP-MS approach could be widely applicable in research areas that involve metal-tagged protein bioconjugates, such as in the development of diagnostic and therapeutic agents and other biochemical probes.

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Introduction

Protein bioconjugates, with chelated metal ions, are valuable biochemical tools used in numerous applications, including: probes for luminescence imaging,¹ mass spectrometry,² nuclear magnetic resonance,³ electron transfer,⁴ and importantly, diagnostic and therapeutic applications.⁵ In experimental protein research, gel electrophoresis and western blot analysis are commonly used to separate and identify proteins. Western blot techniques enable the identification of specific proteins by using primary and secondary antibodies to bind, visualize, and quantify proteins of interest.⁶ Labeling of target proteins on

western blot membranes with primary and secondary antibodies requires multiple incubation and washing steps thus requiring increased time before analysis and materials costs. Moreover, treated western blot membranes can confirm the size and identity of target proteins but provide little to no chemical or elemental information about the material in the membrane.

Traditionally, quantification of proteins in thin tissue sections, gels, western blots, and similar samples require excising and digesting a section of interest prior to analysis by mass spectrometry.^{7–9} An alternative method would be to directly sample the separated species and bypass the laborious excision and digestion steps. One such direct sampling technique, if elemental/isotopic analysis is warranted, is laser ablation (LA)-inductively coupled plasma-mass spectrometry (ICP-MS). LA-ICP-MS has been previously demonstrated, and routinely employed, for the mapping of metals and metalloids in thin tissue samples,¹⁰ and for the mapping of protein bound metals in gels and gel blots.^{11,12} LA-ICP-MS offers a direct sampling approach with high spatial resolution and low limits of detection.¹⁰ Besides LA-ICP-MS, limited approaches have been developed for direct interrogation of chemical and elemental components linked to proteins in western blot membranes.

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The present work adopts a microextraction system coupled to a quadrupole-based ICP-MS, to directly sample the surface of western blot paper. This direct sample technique allows for the ability to isotopically map the surface for selected protein-metal samples. Microextraction self-sealing techniques, coupled to mass spectrometers (with a soft ionization source), were originally invented for the analysis biomolecules on TLC plates, or in thin tissue samples.^{8,13} More recently, the microextraction sampling technique was modified for inorganic measurements, by coupling to ICP-MS, to extract deposits^{14–16} and particles^{17–19} from cotton swipes, and even urine from filter paper.²⁰ The approach presented here describes the successful first application of ME to directly detect metal-tagged proteins in western blot paper substrate using large area mapping (50 × 60 mm). Implications of this work can be expanded to biologically relevant fields that require accurate, fast, and low-cost (compared to LA) analysis methods for metal-tagged proteins.

Experimental

Reagents and standards

The chelating agent used for the metal-tagging of proteins (2,2',2'',2'''-(2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl) tetraacetic acid (*p*-SCN-Bn-DOTA) was obtained from MacroCyclics (Plano, TX USA) and used without further purification. The proteins selected for use were lysozyme (LYS), immunoglobulin G (IgG), and myoglobin (Mb) due to their common use in protein research, relatively low cost, and diverse molecular weights. LYS from chicken egg white, Mb from equine skeletal muscle 95–100%, and IgG from Human Serum were obtained from Sigma Life Science (from Sigma-Aldrich) without further purification. For protein separation by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), 4–15% Mini-PROTEAN TGX Precast Protein Gels and Precision Plus Protein Kaleidoscope Ladder from Bio-Rad were used. The metals selected to tag the three proteins were La, Gd, and Tb due to their known coordination chemistry with DOTA-based chelators and their applications as protein bioconjugates as radionuclide surrogates and imaging isotopes. Lanthanum(III) nitrate hexahydrate (La(III)(NO₃)₃·6H₂O) and gadolinium(III) nitrate hexahydrate (Gd(III)(NO₃)₃·6H₂O) were obtained from ThermoFisher and used without further purification. Terbium(III) chloride hexahydrate (Tb(III)(Cl₃)₃·6H₂O) was obtained from Acros and used without further purification.

Metalation of chelator and covalent tagging to protein

Stock solutions of lanthanides were prepared by dissolving each salt (10.1 mg La(III)(NO₃)₃·6H₂O; 5.6 mg Gd(III)(NO₃)₃·6H₂O; 7.2 mg Tb(III)(Cl₃)₃·6H₂O) in deionized H₂O, from a Nanopure water purification system, to afford 3.0 mL at 7.8 mM, 4.1 mM, and 6.4 mM, respectively. *p*-SCN-Bn-DOTA stock solution was prepared weighing 2.3 mg and dissolving into 1:1 (v/v) H₂O/MeOH solution to give 1.7 mL for a final concentration of 2.0 mM. The reaction mixtures contained 0.029 mL (La), 0.054 mL (Gd), and 0.035 mL (Tb) of each metal stock solution

and 0.125 mL of *p*-SCN-Bn-DOTA, then diluted to a final volume of 0.250 mL to afford reaction mixtures with 0.9 mM lanthanide to 1 mM *p*-SCN-Bn-DOTA). Reactions were performed at 40 °C for 1 h. Reaction were monitored by electrospray ionization – MS to confirm metalation (Fig. S1†).

Protein stock solutions of LYS and Mb were prepared by dissolving 15.5 mg LYS, and 14.0 mg Mb to afford 0.75 mM stocks using 1.45 mL and 1.10 mL deionized water, respectively. Commercial Human IgG stock (37.85 mM) was used as is. Metal-tagging of the protein was achieved by covalent labeling of lysine (Lys) residues; *p*-SCN-Bn-DOTA(M³⁺) (where M³⁺ represents 0.9 mM total of La, Gd, and Tb). 44.4 μL, 44.4 μL, and 22.2 μL, respectively, of *p*-SCN-Bn-DOTA(M³⁺) solutions were reacted with 5.3 μL LYS, 5.3 μL Mb, and 55 μL IgG protein stock solutions (1:10 protein:metal chelator equivalents) in sodium carbonate buffer (0.1 M, pH 9.2), for a total reaction volume of 0.100 mL. Bioconjugation reactions were performed for 1 h at room temperature.

SDS-PAGE and western blot analysis

SDS-PAGE and western blot samples were prepared to give approximately 5 μM protein in each well using Laemmli buffer with 5% β-mercaptoethanol. Samples were boiled for 5 min and loaded onto a 4–15% mini-protean gel with protein ladder. The gel was run at 80 V for 30 min, and 180 V for 30–45 min. Gels and sponges were then soaked in western blot transfer buffer (Tris 24 mM, glycine 192 mM, 20% methanol). Polyvinylidene fluoride (PVDF) membrane was soaked in methanol and western blot transfer buffer. Electrotransfer was run for 20 min at 15 V using the Bio-Rad semi-dry transfer apparatus, and the membrane was subsequently stained with swift membrane stain for visual detection of transferred proteins.

Microextraction ICP-MS

A modified (described previously)¹⁹ Advion Plate Express (Advion, Ithaca, NY), fitted with a ProScan Motorized XY Stage (Prior Scientific, Rockland, MA) and a custom probe head, was used to extract analytes from the western blot paper and deliver them to an ICP-MS (iCAP TQ, Thermo Scientific, Bremen, Germany). The experimental set up is depicted in Fig. 1. The custom probe head (Fig. S2†) has a beveled tip which limits contact with the sample to the extraction zone, facilitating systematic mapping. When engaged, the probe head descends with a force of 300 N, forming a seal on the surface of the blot paper. The extraction time is 30 s with a 45 s data collection window. The extracting solvent (5% HNO₃) is delivered by an isocratic pump (Advion, Ithaca, NY) at 100 μL min⁻¹. A six-port valve is used to direct the solution to the extraction probe, and/or to the ICP-MS nebulizer housed within a quartz cyclonic spray chamber. The ICP-MS is operated in time resolved analysis mode and the entire measurement window is integrated to give the signal intensity. Here, ¹³⁹La, ¹⁵⁸Gd, and ¹⁵⁹Tb were monitored with 100 ms dwell times. Respective transient signals were processed *via* peak integration through the Qtegra software. Elemental maps generated *via* ME-ICP-MS analysis



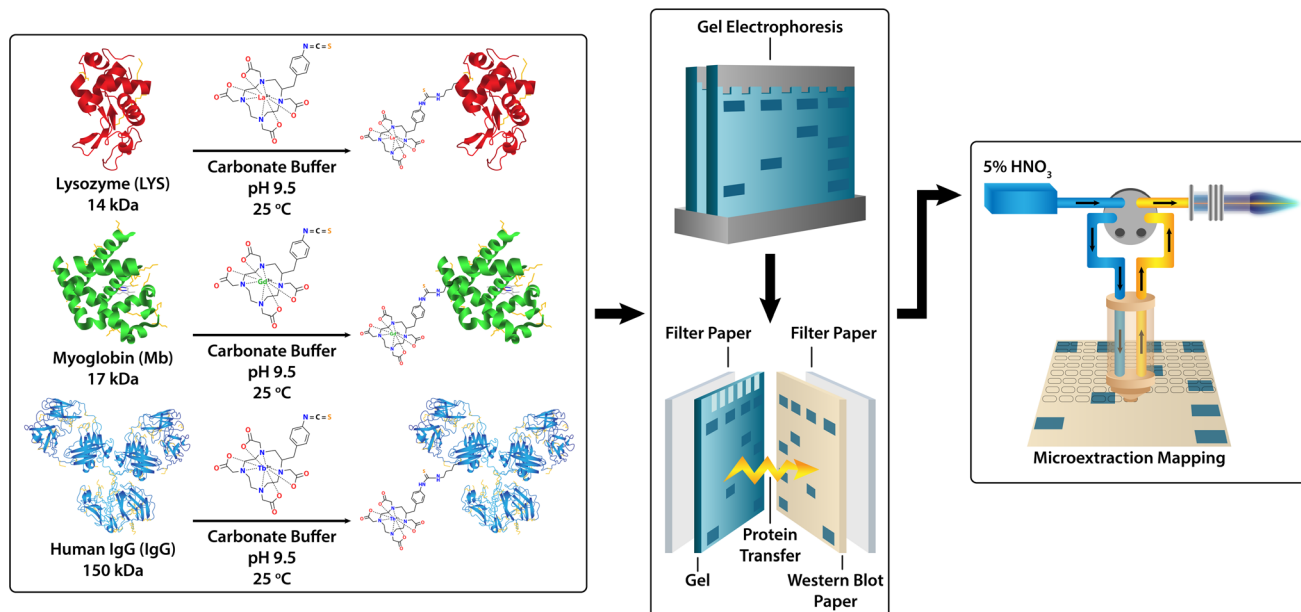


Fig. 1 Experimental set-up depicting protein tagging process and gel electrophoresis separation. The separated proteins are then transferred to western blot paper for subsequent analysis *via* ME-ICP-MS mapping.

were constructed through an in-house Python code previously described for ME-ICP-MS mapping.¹⁹

Laser ablation ICP-MS

Duplicated western blot samples were also mapped *via* laser ablation inductively coupled plasma-mass spectrometry (LA-ICP-MS) with an imageGEO 193 nm excimer laser (Elemental Scientific Lasers, Bozeman, MT, USA). The paper was secured onto a sampling tray using double sided tape and loaded into a sampling chamber (TwoVol3 cell) which was then purged at 1000 mL min^{-1} with helium (UHP, 99.94%, Airgas, Radnor, PA, USA). The mapping conditions included $150 \mu\text{m}$ circular ablation spots, with $10 \mu\text{m}$ steps, and the line scan raster spacings were $175 \mu\text{m}$ ($25 \mu\text{m}$ between each line). Laser fluence was $\sim 5 \text{ J cm}^{-2}$ and the laser was run with a repetition rate of 200 Hz, and the sample was rastered at $2000 \mu\text{m s}^{-1}$. During ablation, helium was also used as the carrier gas, at 900 mL min^{-1} to transport the material into an iCAP TQ ICP-MS (Thermo Scientific, Bremen, Germany). Ablated sample was carried in helium through Tygon tubing into a dual concentric injector – DCI2 (Elemental Scientific Lasers, Bozeman, MT, USA) into the plasma. Dwell times of 33 ms were used for each selected isotope (^{139}La , ^{157}Gd , and ^{159}Tb). Total acquisition time of the western blot paper ($79 \text{ mm} \times 53 \text{ mm}$) was approximately 4 hours. LA-ICP-MS-generated data was processed through the iolite v4 software.²¹

Results and discussion

Assessment of extraction profiles and measurement sensitivity

Multi-element (La, Gd, and Tb) standards were prepared at 0.1, 1, 5, 10 and 20 ng mL^{-1} by gravimetric dilution with 2% HNO_3 ,

and deposited at $1 \mu\text{L}$ volumes (to minimize spreading within the $2 \times 4 \text{ mm}$ extraction area), and allowed to dry. The ME-ICP-MS method was then used to analyze the deposited standards. Fig. 2a depicts a representative microextraction transient of the measurement equating to 5 pg of La, Gd, and Tb, on western blot paper. After an uptake delay, the microextraction transient shows a characteristic trend of a high elution peak followed by a plateau of the signal. This transient nature is similar to what has been previously demonstrated for the extraction of uranium¹⁴ and plutonium¹⁵ deposits. Typically, extraction transients are short (10–30 s) and can be elongated with higher loading of material or longer dissolution/extraction times. The plateau demonstrated here is likely due to less efficient extraction from the blot paper. Future studies will be dedicated to improving this extraction efficiency, but for the intents of the work presented here, the ability to extract pg-levels of lanthanides is appropriate.

Multiple extractions performed in succession on the same location indicate that $\geq 95\%$ of analyte is sequestered on the first extraction. The analysis ($n = 3$) of varying deposits (0.1–20 pg) of lanthanides can be seen in Fig. 2b. The signal from each extraction was integrated over the entire data collection window and blank subtracted from blank extractions of the western blot paper. Running extraction blanks between extractions is analogous to washing the sampling probe for traditional solution-based ICP-MS. This approach has been previously described for ME-ICP-MS.¹⁹ The R^2 values for the calibration curve were 0.975, 0.996, and 0.995 for La, Gd, and Tb, respectively. This calibration curve demonstrates the linearity between analyte deposited on western blot paper and signal response. Preliminary limits of detection (LOD) based on this measurement were determined to be 564, 54, and 2.5 fg for La, Gd, and Tb, respectively. La had a higher background signal than Gd or



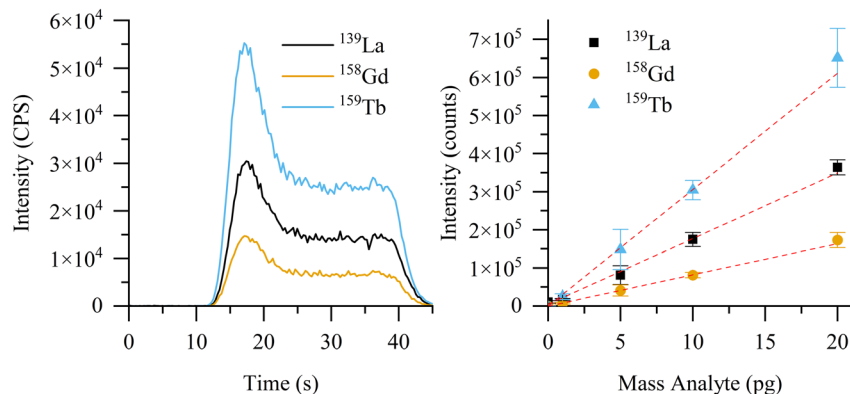


Fig. 2 (a) Example transient of an extraction of western blot paper that was loaded with 5 pg of La, Gd and Tb. (b) A calibration curve generated by drop casting various masses of La, Gd and Tb onto western blot paper. Error bars represent standard deviation of triplicate measurements.

Tb, leading to its higher LOD. These detection limits are determined by using a traditional 3 sigma approach which incorporates the analysis of blank extractions ($n = 10$), performed at the start of analysis, and the response factor from the calibration curve. These initial detection limits are well within reasonable predicted concentration of value for gel electrophoresis/western blot-based separations.

Mapping of gel separated lanthanide functionalized proteins

Lanthanide-tagged proteins were separated using gel electrophoresis and then transferred to western blot paper. This blot paper was then fully analyzed using ME-ICP-MS, and the generated isotopic map with western blot lanes labeled is presented in Fig. 3a. Here, three lanthanide tagged proteins, Tb-IgG, Gd-Mb, and the La-LYS were loaded both separately and combined. The mapping of the metals matches well with the visualization of stained western blot paper (Fig. S3†). For the ME-ICP-MS mapping, the stage was rastered such that extractions could be made in steps of 3 mm in the vertical direction

and 6 mm in the horizontal direction. This resulted in small gaps between extractions which prevented tearing of the western blot paper. The photograph of the post-extracted map is seen in the background of Fig. 3a. Maps were generated systematically row by row; vertical rows (3 mm movements) were completed, followed by a horizontal move (6 mm), and repeated. This mapping approach subsequently led to analyte being detected between multiple lanes (vertical rows) in some cases. For example, Gd was detected in extraction lanes 6 and 7 around 15 kD.

The resolution, of the microextraction system used in this experiment, is limited by the probe head dimensions ($\sim 2 \times 4$ mm); however, individual lanes of the blot were easily resolved. In lane 2, with all three tagants, ME-ICP-MS was able to spatially resolve the heavy and light Tb-IgG chains (50 and 25 kD) from the other complexes. On the other hand, the signal from Gd-Mb (17 kD) and La-LYS (14 kD) overlapped; both are detected in the extractions just above and below 15 kD. However, Gd signal was higher intensity in the extraction just above 15 kD, and La signal was higher intensity just below 15 kD.

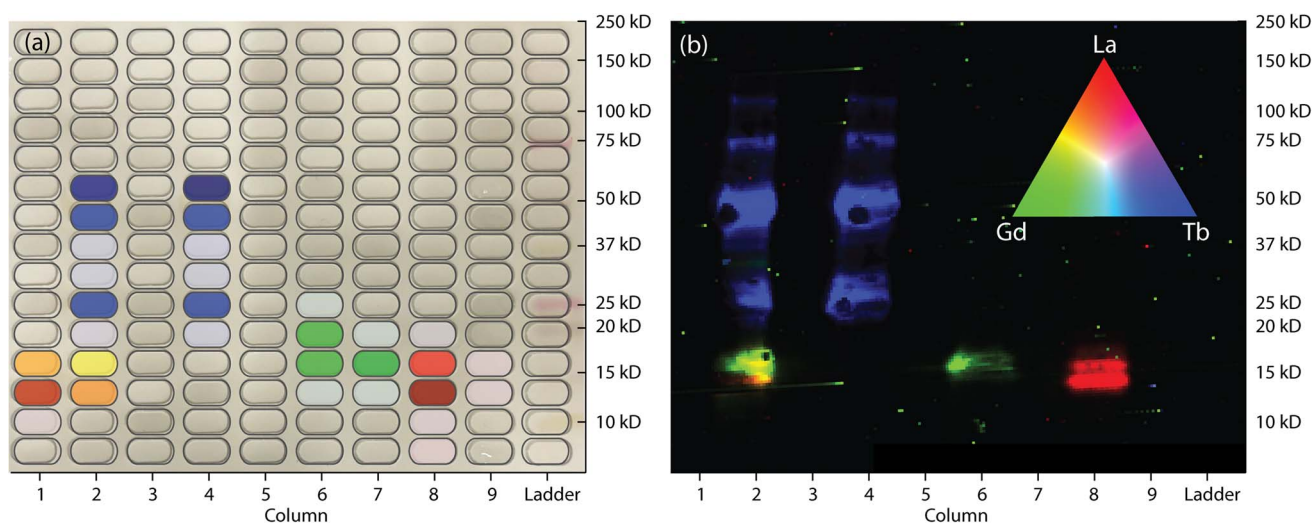


Fig. 3 Analyte maps of the western blot paper generated by (a) ME-ICP-MS and (b) LA-ICP-MS. Samples lanes are the same for maps A and B and correspond to: lane 8 (LYS-La); lane 6 (Mb-Gd); lane 4 (IgG-Tb), lane 2 (all samples combined).



An estimate calculation of total analyte extracted using the intensity and the calibration curve previously shown (Fig. 1b) indicated 347, 379, and 61 pg of La, Gd, and Tb, respectively. This is less than the amount initially placed in the sample wells of the gel (13.8, 15.8, and 15.8 ng respectively). Proteins may not have been exhaustively metal-tagged, and the separation transfer of the tagged proteins to western blot was never validated to ensure complete transfer. While this decrease is expected, it should be explored further in future studies.

A more traditional solid sampling technique for inorganic analysis, LA-ICP-MS, was also used to compare locations of lanthanide-tagged proteins. The resultant elemental map generated from the LA-ICP-MS data is seen in Fig. 3b. The maps obtained by both techniques matched well with regards to protein location. Comparison of the two maps shows similar interpretations of the gel and western blot results as well. The element-tagged protein mixture is clearly seen in lane 2 *via* the yellow color generated from the red-green-blue map from the La, Gd, and Tb, respectively. The Tb-tagged IgG is separated into multiple bands (structures with different molecular weights) due to incomplete reduction of the disulfide bonds connecting the IgG subunits. While there was slight signal spreading seen in the ME-ICP-MS map (lane 1 and 7), clear separations are seen from both LA-ICP-MS and ME-ICP-MS. Total analysis time was also similar for both methods; the total analysis time for the ME-ICP-MS map was 3 h 23 min, while the LA-ICP-MS map was 3 h 8 min. It should be noted that the analysis time for LA-ICP-MS does not include purging sample chamber, ramping up carrier gas, and tuning for laser ablation conditions, which generally encompasses 30 min in our laboratory. Lastly, to compare measurement responses, the integrated counts within the Gd and La band were compared between the ME-ICP-MS and LA-ICP-MS techniques. For ME-ICP-MS, the Gd and La band had 4.2×10^6 and 6.5×10^6 counts for their respective bands while LA-ICP-MS yielded 5.5×10^7 and 2.5×10^9 counts for their respective bands. As a first look into detection limit comparison, it appears that ME-ICP-MS is slightly less sensitive than LA-ICP-MS approach, but other caveats should be considered regarding these were on separate SDS-PAGE and western blot samples. Future studies should explore this with more vigor.

In summary ME-ICP-MS performed comparably to LA-ICP-MS, an established method, for elemental mapping of western blot paper. Advantages over LA-ICP-MS include potentially eliminating the need to clean the ablation cell between samples, as ablated debris can readily accumulate from the blot paper substrate. Additionally, the thermal load from the laser to the sample can lead to disrupting the shape and stability of the sample being adhered to a sample surface. The ME-ICP-MS approach is also beneficial as it is more readily implementable into in-field laboratories due to its size, utility requirements, and instrument interface.

Conclusion

This work demonstrates the ability of ME-ICP-MS to elementally map metal functionalized protein distributions on western blot

paper. Preliminary detection limits were established for lanthanides of La, Gd, and Tb to be 564, 54, and 2.5 fg, respectively. Overall, this work achieved the goal of mapping a western blot paper using ME-ICP-MS, and future work will focus on expanding functionality including improved element quantification by using internal standards, quality controls, and isotopic dilution mass spectrometry. Given the increasing utility of protein-tagged metal bioconjugates and ubiquity of western blot analysis, the method described here offers wide applicability to identify and characterize bioconjugates with incorporated metals. Moreover, the direct measurement, requiring minimal sample preparation, and rapid analysis lends itself for a useful approach in a point-of-care-based laboratory as it truly is a simplistic approach for elemental and isotopic determination of western blot samples compared to LA-ICP-MS or, more commonly sample excision and digestion.

Data availability

The authors are happy to provide data upon request.

Conflicts of interest

There are no conflicts of interest to declare.

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