Received: 26 May 2021 | Accepted: 10 September 2021 | Accepted article online: 14 October 2021

DOI: 10.1002/pmic.202100058

Proteomics
Proteomics and Systems Biology

TECHNICAL BRIEF

Nanopore sensing of γ-cyclodextrin induced host-guest interaction to reverse the binding of perfluorooctanoic acid to human serum albumin

Xiaojun Wei[1,2] | **Qian Wang**[3] | **Chang Liu**[1,2]

[1] Biomedical Engineering Program, University of South Carolina, Columbia, South Carolina, USA

[2] Department of Chemical Engineering, University of South Carolina, Columbia, South Carolina, USA

[3] Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina, USA

Correspondence
Chang Liu, Biomedical Engineering Program, University of South Carolina, Columbia, SC 29208, USA.
Email: changliu@cec.sc.edu

Funding information
National Institute of Allergy and Infectious Diseases (NIAID), Grant/Award Number: K22AI136686; National Institute of General Medical Sciences (NIGMS), Grant/Award Number: P20GM103499; National Science Foundation (NSF), Grant/Award Number: 2047503

Abstract

Perfluorooctanoic acid (PFOA) has been one of the most common perfluorochemicals, which are globally pervasive contaminants that are persistent, bioaccumulative, toxic, and have adverse impacts on human health. The highest concentration of PFOA occurs in the blood, where it strongly binds to human serum albumins (HSA). Thus, a method to reverse the HSA-PFOA binding is critical to help facilitate the faster elimination of PFOA from the body to minimize its toxicological effects. Inspired by the remediation effect of cyclodextrin (CD) to PFOA through host-guest interactions, herein, by elucidating inter-molecular interactions using a nanopore sensor, we demonstrated in vitro reversal of the binding of PFOA to HSA using γ-cyclodextrin (γ-CD). The competition behavior for the complexation of PFOA between HSA and γ-CD was discussed in combination with in situ nanopore current recording and nuclear magnetic resonance (NMR) characterization. The present work not only demonstrates the potential therapeutic application of γ-CD for PFOA removal from human blood, but also provides an emerging method for investigating interactions between organic compounds and proteins.

KEYWORDS
human serum albumin, nanopore, nuclear magnetic resonance, perfluorooctanoic acid, reverse binding, γ-Cyclodextrin

1 | INTRODUCTION

Perfluorooctanoic acid (PFOA), as one of the most popular ground and surface water contaminants in the fluorinated alkyl substances family, has emerged as an environmental and health crisis in many communities [1]. Exposure to PFOA is associated with negative ecological and human health effects including elevated cholesterol levels [2], liver damage [3], cancer [4], and others [5].

In general, PFOA do not preferentially accumulate in lipids and fatty tissue like other persistent organic pollutants, but rather in body organs with high protein content such as the liver, kidney, and brain, and so on [6]. The highest concentration of PFOA occurs in the blood, where it binds to serum proteins [7]. The results of both field studies and laboratory experiments have suggested that the interactions of PFOA with proteins, particularly organic anion transporters, influence its patterns of bioaccumulation and toxicity [8,9]. Among them, human serum albumin (HSA) has been identified as a major transporter of PFOA in the blood, which is the most abundant protein in human blood with concentrations ranging from 35 to 50 g/L [10]. Additionally, the strong binding between PFOA and HSA has been reported to occur through multiple sites (up to 13) [7], indicating an urgent challenge to reverse this binding to minimize the toxicological effects of PFOA.

Cyclodextrins (CDs) have previously been proposed as a remediation strategy for environmental pollutants, including fluorinated alkyl substances [11, 12]. Acting as cyclic sugar oligomers composed of glucose monomers, the CDs not only have excellent biocompatibility but also the capability of encapsulating a variety of hydrophobic molecules through host-guest interactions due to its hydrophobic inner

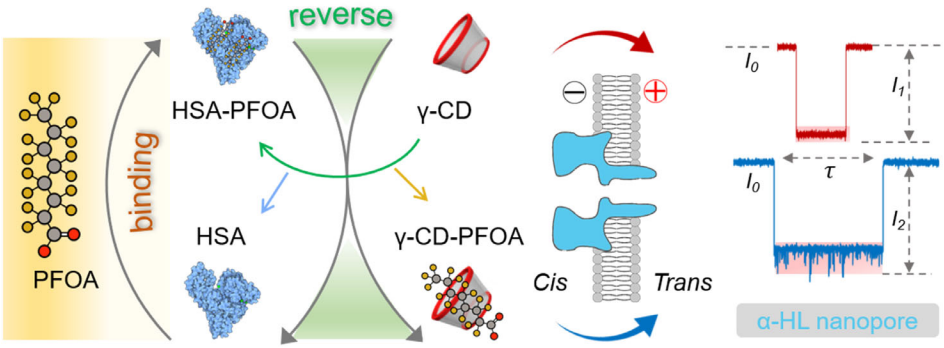

FIGURE 1 Schematic illustration of nanopore sensing for γ-CD induced host-guest interaction to reverse binding of PFOA to HSA

cavity [13]. These features make CDs one of the best candidates for hydrophobic drug delivery [14] and surfactant removal [13, 15]. For example, β-CD can encapsulate PFOA strongly in a host-guest complex without being disturbed by changes in solution [16]. The competition behavior for the complexation of PFOA between HSA and β-CD have been probed employing 19F nuclear magnetic resonance (NMR), circular dichroism, and fluorescence spectroscopies [17], which have been extensively exploited and are routine methods for investigating and determining the interaction between different molecules.

Recently, due to their label-free analytical capability and single-molecule level sensitivity, nanopores have been developed as alternative analytical tools for single molecules and their interactions [18–20], which could provide crucial information from observation and analysis of ionic current modulations caused by the interactions between target analytes and fluidic pores [21–23]. In addition, because CDs fit well inside most nanopores and present a hydrophobic cavity suitable for binding organic analytes [24, 25], they have also been involved in nanopore analysis and are widely used as adapters for detecting organic molecules [26, 27].

Inspired by the host-guest recognition of CDs, herein, we investigated the interactions between PFOA, HSA, and γ-CD by employing α-hemolysin (α-HL) nanopore sensing platform to elucidate the potential of γ-CD for reversing the binding of PFOA to HSA (Figure 1). In this proof-of-concept study, γ-CD was introduced into a solution of HSA-PFOA, and the γ-CD-PFOA host-guest complex was formed in the aqueous solution due to their high complexation stability [12]. Analysis using an α-HL nanopore showed that a snatching process of PFOA by γ-CD from HSA-PFOA complex can be monitored at the single-molecule level in situ through different blockage events generated by γ-CD and γ-CD-PFOA. Furthermore, concentration-dependent ^{19}F NMR verified the reverse of HSA-PFOA binding by γ-CD. This work demonstrates an effective approach for analyzing interactions between protein/organic molecules in an aqueous solution.

2 | RESULTS AND DISCUSSION

In a typical experiment, the tail of the mushroom-shaped α-HL nanopore is inserted into the lipid bilayer that separates *cis* and *trans* compartments in an electrolyte solution. An external positive voltage (100 mV) is applied to the *trans* side of the bilayer while the *cis* side is electrically grounded to produce an ion flux current as the baseline (Figure S1). Upon introduction of samples to the *cis* side, all samples enter the nanochannel through the head of α-HL, causing current blockade events which are then recorded and analyzed (Figure 1) [20]. In the first set of experiments, five different side-by-side groups of molecules/complexes including γ-CD, HSA-γ-CD, PFOA-γ-CD, HSA-PFOA, and HSA-PFOA-γ-CD with the same γ-CD concentration were prepared by dissolving and mixing in ultrapure water. The concentration of PFOA is the same with γ-CD and the concentration of HSA was 40 μM in all cases. It merits mentioning that for the sample preparation of the HSA-PFOA-γ-CD complex, γ-CD was added after an 1 hincubation of HSA and PFOA in an aqueous solution with shaking, and the final mixture was incubated for an additional 12 h with shaking. All above samples produced typical current blockade events upon addition to the *cis* side of the bilayer at the same concentration, respectively (Figure 2A). In comparison with the current blockade events produced by γ-CD, there is no obvious change in the signal of HSA-γ-CD. This result indicates that the introduction of HSA has less effect on the interaction between γ-CD and the nanopore, which can be attributed to the mismatched sizes of HSA (~80 Å) [28] and α-HL (~13 Å) [29] and the weak interaction between HSA and γ-CD with a cavity diameter of ~ 8.6 Å. [2, 30] When PFOA (13 Å × 6.5 Å × 6.5 Å) [31] was introduced, clear differences were observed in signals of PFOA-γ-CD and HSA-PFOA-γ-CD complexes, which included a new type of signal characterized by enhanced current blockade and extended dwell time comparing to γ-CD, HSA-γ-CD. This signature signal can only be detected from the complex of PFOA and γ-CD, which have been confirmed to have strong binding affinity with each other [12]. Furthermore, similar signature signals were observed upon the addition of γ-CD into HSA-PFOA complexes, indicating a possibility that γ-CD could snatch bound PFOA molecules from HSA-PFOA. To rule out the possible PFOA effects on the above signature events, individual PFOA molecules with the same concentration were also analyzed by the α-aHL nanopore. Unfortunately, as a surface-active substance, PFOA strongly damages the lipid membrane that supports the nanopore protein, making it impossible to observe and record signals (Figure S2A). Although this situation was improved by reducing the concentration of PFOA, the obtained baseline and signals were still unstable (Figure S2B). On the other hand, PFOA-γ-CD and HSA-PFOA-γ-CD complexes showed no obvious

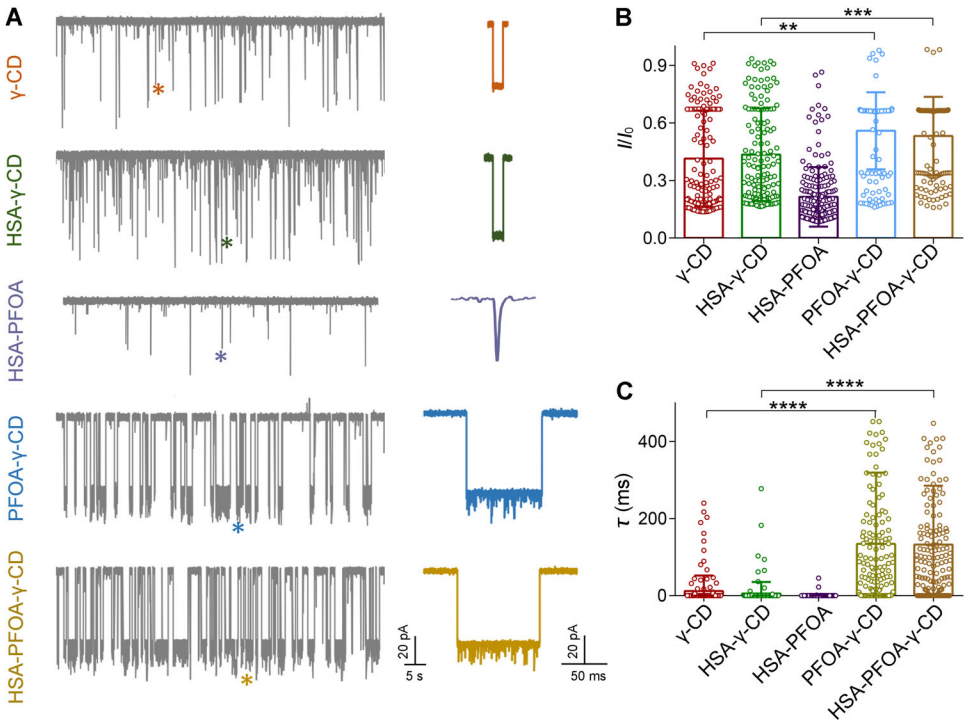

FIGURE 2 Single-molecule analysis of interactions between γ-CD, HSA and PFOA molecules with an α-HL nanopore. (A) Representative current traces of translocations of different complexes through a nanopore, together with expanded views of typical events marked with stars. (B-C) Box plots of current blockade (I/I_0) and dwell time (τ) for different molecules/complexes, respectively, and two-tailed unpaired Student *t*-test between different groups (**: $0.001 < p < 0.01$; ***: $0.0001 < p < 0.001$; and ****: $p < 0.0001$). Each plot contains ≥ 150 blockade events. All data was obtained in the buffer of 3 M KCl, 10 mM Tris-HCl, pH 8.0 in both *cis* and *trans* sides with a transmembrane potential of 100 mV

damaging effect on the lipid membrane and signals. This is because γ-CD can encapsulate PFOA molecules into its hydrophobic cavity, and excess HSA can bind free PFOA molecules through multiple sites (Figure 2A). This observation further confirms the binding and snatching of PFOA by γ-CD described in previous experiments.

To quantitatively profile the differences mentioned above, two parameters including current blockade (I/I_0, I and I_0 are block and open currents, respectively) and blockade duration (τ, dwell time, that represents the effective interaction time between the pore and the analyte) were further quantified by statistical analysis of ≥150 events and characterized with the mean distribution values in box plots (Figure 2B and C). Signals of γ-CD and HSA-γ-CD have similar I/I_0 (0.41 ± 0.02 *vs.* 0.43 ± 0.02) and comparable dwell time (12.1 ± 3.2 *vs.* 5.8 ± 2.3 ms). The slight dwell time decrease of HSA-γ-CD in comparison with γ-CD can be attributed to the false signals caused by the collision of HSAs onto the nanopore entrance and returning to the *cis* side without translocation [32]. Both parameters were increased significantly in the cases of PFOA-γ-CD and HSA-PFOA-γ-CD. The values of I/I_0 were increased to 0.56 ± 0.02 and 0.53 ± 0.02, with an increase ratio of 36% and 23%, respectively. For dwell time, the increase ratio was more obvious upon introducing PFOA to γ-CD and HSA-γ-CD, that is, 134.6 ± 14.8 *vs.* 12.1 ± 3.2 ms and 132.6 ± 12.2 *vs.* 5.8 ± 2.3 ms, indicating a prolonged retention of PFOA-γ-CD host-guest complexes in the nanopore. In addition, similar PFOA-γ-CD host-guest signature events observed for the HSA-PFOA-γ-CD complexes indicate that γ-CD was able to reverse the binding of PFOA to HSA, and thus may attenuate the toxicity of PFOA. These results further inspired us to profile this reversal process over time by sensing the signature signals of PFOA-γ-CD host-guest complexes using a nanopore.

To this end, HSA, PFOA, and γ-CD were sequentially added to the *cis* side of the nanopore while translocation signals were recorded simultaneously. As shown in Figure 3A, low frequency false signals caused by HSA bumping the nanopore can be detected at first. Upon introduction of PFOA into the solution, more signals with short current blockade were observed which may be attributed to the interference of PFOA to the lipid membrane. The binding process of HSA to PFOA was undetectable by our current strategy due to incomparable sizes of HSA and nanopore and indistinguishable signals. Nevertheless, numerous previous studies using NMR or mass spectrometry methods in combination with molecular dynamics simulation have shown that HSA possesses many PFOA binding sites (n = 6–9) with a 0.38 mM binding affinity, indicating that over 90% PFOA molecules would bound to HSA if they present at the same concentration [33, 34]. This complexation was gradually weakened over time after adding an equal concentration of γ-CD in situ into the *cis* side of the nanopore, which was determined by the increasing frequency of signature signals of PFOA-γ-CD host-guest complexes (indicate by red stars in Figure 3A). We obtained the number of PFOA-γ-CD complex signals for a 5 min time interval at each different time points as the interaction time of γ-CD and HSA-PFOA was gradually increased from 0–60 min. The estimated signal

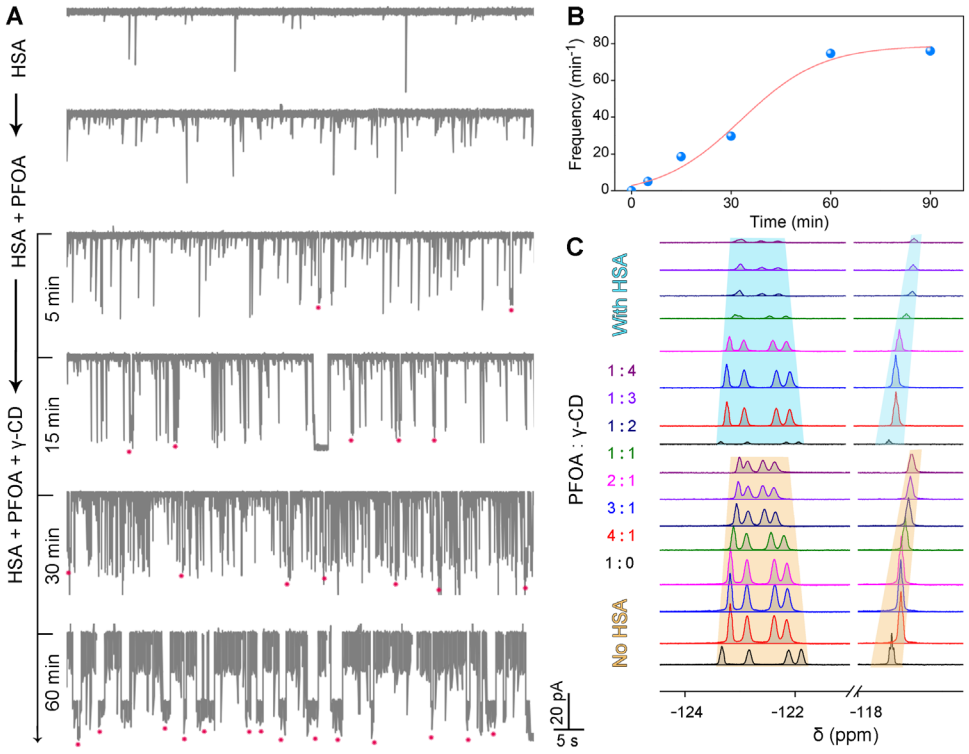

FIGURE 3 In situ nanopore sensing of interactions between HSA, PFOA, and γ-CD molecules. After a single α-HL nanopore was established in the working buffer, HSA, PFOA, and γ-CD, were sequentially added to the *cis* compartment. (A) Representative current trace of translocation signals obtained at different time. Red stars indicate the signature events generated by translocations of PFOA-γ-CD complex. (B) Events frequency of PFOA-γ-CD as a function of time recorded upon the addition of γ-CD into the HSA-PFOA complex solution. All data was obtained in the buffer of 3 M KCl, 10 mM Tris-HCl, pH 8.0 in both *cis* and *trans* sides with a transmembrane potential of 100 mV. (C) ^{19}F NMR spectra of PFOA with various amount of γ-CD in presence and absence of HSA

frequency of PFOA-γ-CD increased from 0 s^{-1} to 74.6 s^{-1}, and gradually reached a steady value (~76 s^{-1}) when extended the interaction time to 90 min, indicating equilibrium of PFOA binding by γ-CD (Figure 3B).

To further verify the ability of γ-CD to reverse the binding of PFOA to HSA, ^{19}F NMR spectroscopy was used to investigate the chemical shift of each fluorine for PFOA-γ-CD host-guest complexes of various molar ratio formed in presence and absence of HSA in aqueous solution. For competition experiments, if the first guest molecule has a stronger association constant with the host molecule than the second guest molecule, the NMR spectrum of the mixture should resemble the spectra of the first guest and the host molecules alone [35]. Based on this theory, results shown in Figure 3C firmly support the above-mentioned speculation: in absence of HSA, fluorine peaks in the yellow shadow showed increasing chemical shifts with increasing concentration of γ-CD. The same trend can also be observed for samples with HSA in the blue shadow, although peaks were broadened and weakened by HSA. This observation further confirms our nanopore results that an equimolar concentration of γ-CD to PFOA can weaken the PFOA binding to HSA, and that a higher amount of γ-CD can further facilitate this process.

Previous studies have probed β-CD inhibition and reverse of HSA-PFOA binding using NMR, circular dichroism, and fluorescence spectroscopies [17]. In this study, we investigated γ-CD mediated inhibition and reverse of HSA-PFOA binding with nanopore sensing and confirmed with NMR. According to the previous reports,[12] calculated association constants indicate a weaker affinity of PFOA-γ-CD complex than PFOA-β-CD complex at 1:1 molar ratio ($8.8 \pm 1.4 \times 10^2$ M^{-1} *vs.* $5.0 \pm 0.1 \times 10^5$ M^{-1}). However, our results shown here indicate that the introduction of γ-CD can still effectively weaken and reverse the PFOA binding to HSA.

3 | CONCLUSION

We have demonstrated the α-HL nanopore sensor for rapid and label-free analysis of interactions between HSA, PFOA, and γ-CD at the single-molecule level. By using the unique signature event produced by PFOA-γ-CD host-guest complex, we elucidated the in situ reversal of HSA-PFOA binding by γ-CD in real-time, and confirmed this process with NMR characterization. Although the present study was not conducted in a physiological condition, the results still demonstrated the possibility of inhibiting and reversing PFOA binding to HSA using γ-CD. The present nanopore sensor also offers an effective approach for analyzing interactions between various proteins and organic molecules.

ACKNOWLEDGMENT

C. Liu acknowledges supports from: Biomedical Engineering Program and Department of Chemical Engineering, University of South Carolina; the National Institute of Allergy and Infectious Diseases (NIAID) award K22AI136686; the South Carolina IDeA Networks of Biomedical Research Excellence Developmental Research Project by the National Institute of General Medical Sciences (NIGMS) award P20GM103499, and the National Science Foundation (NSF) CAREER Award 2047503.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors declare that the data supporting the findings of this study is available within the article and its Supporting Information (SI) files or from the corresponding authors upon reasonable request.

ORCID

Xiaojun Wei https://orcid.org/0000-0002-6229-6228
Qian Wang https://orcid.org/0000-0002-2149-384X
Chang Liu https://orcid.org/0000-0001-8097-9631

REFERENCES

1. Xiao, L. L., Ling, Y. H., Alsbaiee, A., Li, C. J., Helbling, D. E., & Dichtel, W. R.. (2017). beta-cyclodextrin polymer network sequesters perfluorooctanoic acid at environmentally relevant concentrations. *Journal of the American Chemical Society*, *139*(23), 7689–7692. https://doi.org/10.1021/jacs.7b02381
2. Forsthuber, M., Kaiser, A. M., Granitzer, S., Hassl, I., Hengstschlager, M., Stangl, H., & Gundacker, C.. (2020). Albumin is the major carrier protein for PFOS, PFOA, PFHxS, PFNA and PFDA in human plasma. *Environment International*, *137*, 105324. https://doi.org/10.1016/j.envint.2019.105324
3. Gallo, V., Leonardi, G., Genser, B., Lopez-Espinosa, M.-J., Frisbee, S. J., Karlsson, L., Ducatman, A. M., & Fletcher, T.. (2012). Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environmental Health Perspectives*, *120*(5), 655–660. https://doi.org/10.1289/ehp.1104436
4. Barry, V., Winquist, A., & Steenland, K.. (2013). Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environmental Health Perspectives*, *121*(11-12), 1313–1318. https://doi.org/10.1289/ehp.1306615
5. Gorrochategui, E., Perez-Albaladejo, E., Casas, J., Lacorte, S., & Porte, C.. (2014). Perfluorinated chemicals: Differential toxicity, inhibition of aromatase activity and alteration of cellular lipids in human placental cells. *Toxicology and Applied Pharmacology*, *277*(2), 124–130. https://doi.org/10.1016/j.taap.2014.03.012
6. Verreault, J., Houde, M., Gabrielsen, G. W., Berger, U., Haukas, M., Letcher, R. J., & Muir, D. C. G.. (2005). Perfluorinated alkyl substances in plasma, liver, brain, and eggs of glaucous gulls (Larus hyperboreus) from the Norwegian Arctic. *Environmental Science & Technology*, *39*(19), 7439–7445. https://doi.org/10.1021/es051097y
7. MacManus-Spencer, L. A., Tse, M. L., Hebert, P. C., Bischel, H. N., & Luthy, R. G.. (2010). Binding of Perfluorocarboxylates to Serum Albumin: A comparison of analytical methods. *Analytical Chemistry*, *82*(3), 974–981. https://doi.org/10.1021/ac902238u
8. Hebert, P. C., & MacManus-Spencer, L. A.. (2010). Development of a fluorescence model for the binding of medium- to long-chain perfluoroalkyl acids to human serum albumin through a mechanistic evaluation of spectroscopic evidence. *Analytical Chemistry*, *82*(15), 6463–6471. https://doi.org/10.1021/ac100721e
9. Higgins, C. P., McLeod, P. B., Macmanus-Spencer, L. A., & Luthy, R. G.. (2007). Bioaccumulation of perfluorochemicals in sediments by the aquatic oligochaete Lumbriculds variegatus. *Environmental Science & Technology*, *41*(13), 4600–4606. https://doi.org/10.1021/es062792o
10. Peters, T.. (1985). Serum-albumin. *Advances in Protein Chemistry*, *37*, 161–245. https://doi.org/10.1016/s0065-3233(08)60065-0
11. Karoyo, A. H., & Wilson, L. D.. (2016). Investigation of the adsorption processes of fluorocarbon and hydrocarbon anions at the solid-solution interface of macromolecular imprinted polymer materials. *Journal of Physical Chemistry C*, *120*(12), 6553–6568. https://doi.org/10.1021/acs.jpcc.5b12246
12. Weiss-Errico, M. J., Ghiviriga, I., & O'Shea, K. E.. (2017). F-19 NMR characterization of the encapsulation of emerging perfluoroethercarboxylic acids by cyclodextrins. *Journal of Physical Chemistry B*, *121*(35), 8359–8366. https://doi.org/10.1021/acs.jpcb.7b05901
13. Barbosa, P. F. P., Cumba, L. R., Andrade, R. D. A., & do Carmo, D. R.. (2019). Chemical modifications of cyclodextrin and chitosan for biological and environmental applications: Metals and organic pollutants adsorption and removal. *Journal of Polymers and the Environment*, *27*(6), 1352–1366. https://doi.org/10.1007/s10924-019-01434-x
14. Liu, J., Ding, X., Fu, Y. P., Xiang, C., Yuan, Y., Zhang, Y. M., & Yu, P.. (2021). Cyclodextrins based delivery systems for macro biomolecules. *European Journal of Medicinal Chemistry*, *212*, 1–23. https://doi.org/10.1016/j.ejmech.2020.113105
15. Kundu, S., Manor, N. K., & Radian, A.. (2020). Iron-montmorillonite-cyclodextrin composites as recyclable sorbent catalysts for the adsorption and surface oxidation of organic pollutants. *Acs Applied Materials & Interfaces*, *12*(47), 52873–52887. https://doi.org/10.1021/acsami.0c17510
16. Weiss-Errico, M. J., & O'Shea, K. E.. (2017). Detailed NMR investigation of cyclodextrin-perfluorinated surfactant interactions in aqueous media. *Journal of Hazardous Materials*, *329*, 57–65. https://doi.org/10.1016/j.jhazmat.2017.01.017
17. Weiss-Errico, M. J., Miksovska, J., & O'Shea, K. E.. (2018). beta-cyclodextrin reverses binding of perfluorooctanoic acid to human serum albumin. *Chemical Research in Toxicology*, *31*(4), 277–284. https://doi.org/10.1021/acs.chemrestox.8b00002
18. Zhang, Z., Wang, X., Wei, X., Zheng, S. W., Lenhart, B. J., Xu, P., Li, J., Pan, J., Albrecht, H., & Liu, C.. (2021). Multiplex quantitative detection of SARS-CoV-2 specific IgG and IgM antibodies based on DNA-assisted nanopore sensing. *Biosensors & Bioelectronics*, *181*, 113134. https://doi.org/10.1016/j.bios.2021.113134
19. Lenhart, B., Wei, X., Watson, B., Wang, X., Zhang, Z., Li, C.-Z., Moss, M., & Liu, C.. (2021). In vitro biosensing of β–Amyloid peptide aggregation dynamics using a biological nanopore. *Sensors & Actuators, B: Chemical*, *338*, 129863. https://doi.org/10.1016/j.snb.2021.129863.
20. Wei, X., Ma, D., Zhang, Z., Wang, L. Y., Gray, J. L., Zhang, L., Zhu, T., Wang, X., Lenhart, B. J., Yin, Y., Wang, Q., & Liu, C.. (2020). N-terminal derivatization-assisted identification of individual amino acids using a biological nanopore sensor. *Acs Sensors*, *5*(6), 1707–1716. https://doi.org/10.1021/acssensors.0c00345
21. Robertson, J. W. F., & Reiner, J. E.. (2018). The utility of nanopore technology for protein and peptide sensing. *Proteomics*, *18*(18), 1–14. https://doi.org/10.1002/pmic.201800026
22. Wei, X., Ma, D., Jing, L., Wang, L Y., Wang, X., Zhang, Z., Lenhart, B J., Yin, Y., Wang, Q., Liu, C.. (2020). Enabling nanopore technology for sensing individual amino acids by a derivatization strategy. *Journal of Materials Chemistry B*, *8*(31), 6792–6797. https://doi.org/10.1039/d0tb00895h
23. Wei, X., Zhang, Z., Wang, X., Lenhart, B., Gambarini, R., Gray, J., & Liu, C.. (2020). Insight into the effects of electrochemical factors on host-

guest interaction induced signature events in a biological nanopore. *Nanotechnology and Precision Engineering*, *3*(1), 2–8. https://doi.org/10.1016/j.npe.2019.12.001

24. Li, M. J., Rauf, A., Guo, Y. L., & Kang, X. F.. (2019). Real-time label-free kinetics monitoring of trypsin-catalyzed ester hydrolysis by a nanopore sensor. *Acs Sensors*, *4*(11), 2854–2857. https://doi.org/10.1021/acssensors.9b01783
25. Gu, L. Q., Braha, O., Conlan, S., Cheley, S., & Bayley, H.. (1999). Stochastic sensing of organic analytes by a pore-forming protein containing a molecular adapter. *Nature*, *398*(6729), 686–690. https://doi.org/10.1038/19491
26. Meng, F. N., Yao, X. Y., Zhang, J. J., Ying, Y. L., & Tian, H.. (2016). Single molecule analysis of self-assembly supramolecular oligomers in solution. *Acs Sensors*, *1*(12), 1398–1402. https://doi.org/10.1021/acssensors.6b00575
27. Meng, F. N., Yao, X. Y., Ying, Y. L., Zhang, J. J., Tian, H., & Long, Y. T.. (2015). Single-molecule analysis of the self-assembly process facilitated by host-guest interactions. *Chemical Communications*, *51*(7), 1202–1205. https://doi.org/10.1039/c4cc07919a
28. Khorolskyi, O. V., & Malomuzh, N. P.. (2020). Macromolecular sizes of serum albumins in its aqueous solutions. *Aims Biophysics*, *7*(4), 219–235. https://doi.org/10.3934/biophy.2020017
29. Lenhart, B., Wei, X., Zhang, Z., Wang, X., Wang, Q., & Liu, C.. (2020). Nanopore fabrication and application as biosensors in neurodegenerative diseases. *Critical Reviews in Biomedical Engineering*, *48*(1), 29–62. https://doi.org/10.1615/CritRevBiomedEng.2020033151
30. Pinjari, R. V., Khedkar, J. K., & Gejji, S. P.. (2010). Cavity diameter and height of cyclodextrins and cucurbit [n] urils from the molecular electrostatic potential topography. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *66*(3-4), 371–380. https://doi.org/10.1007/s10847-009-9657-z.
31. Van Den Bergh, M., Krajnc, Až, Voorspoels, S., Tavares, S. R., Mullens, S., Beurroies, I., Maurin, G., Mali, G., & De Vos, D E.. (2020). Highly selective removal of perfluorinated contaminants by adsorption on all-silica zeolite beta. *Angewandte Chemie*, *132*(33), 14190–14194.
32. Wang, Y., Zheng, D., Tan, Q., Wang, M. X., & Gu, L-Q.. (2011). Nanopore-based detection of circulating microRNAs in lung cancer patients. *Nature Nanotechnology*, *6*(10), 668–674. https://doi.org/10.1038/nnano.2011.147
33. Han, X., Snow, T. A., Kemper, R. A., & Jepson, G. W.. (2003). Binding of perfluorooctanoic acid to rat and human plasma proteins. *Chemical Research in Toxicology*, *16*(6), 775–781. https://doi.org/10.1021/tx034005w
34. Salvalaglio, M., Muscionico, I., & Cavallotti, C.. (2010). Determination of energies and sites of binding of PFOA and PFOS to human serum albumin. *Journal of Physical Chemistry B*, *114*(46), 14860–14874. https://doi.org/10.1021/jp106584b
35. Ramos Cabrer, P., Alvarez-Parrilla, E., Meijide, F., Seijas, J. A., Rodríguez Núñez, E., & Vázquez Tato, J.. (1999). Complexation of sodium cholate and sodium deoxycholate by β-cyclodextrin and derivatives. *Langmuir*, *15*(17), 5489–5495. https://doi.org/10.1021/la9817359

SUPPORTING INFORMATION

Additional supporting information may be found online https://doi.org/10.1002/pmic.202100058 in the Supporting Information section at the end of the article.

How to cite this article: Wei, X., Wang, Q., & Liu, C. (2021). Nanopore sensing of γ-cyclodextrin induced host-guest interaction to reverse the binding of perfluorooctanoic acid to human serum albumin. *Proteomics*, e2100058. https://doi.org/10.1002/pmic.202100058