Design and Synthesis of Target-Responsive Hydrogel for Portable Visual Quantitative Detection of Uranium with a Microfluidic Distance-Based Readout Device

*Yishun Huang^a, Luting Fang^a, Zhi Zhu^a, Yanli Ma^a, Leiji Zhou^a, Xi Chen^b,
Dunming Xu^b, Chaoyong Yang^{a*}*

a: MOE Key Laboratory of Spectrochemical Analysis & Instrumentation, Collaborative Innovation Center of Chemistry for Energy Materials, Key Laboratory for Chemical Biology of Fujian Province, State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University Xiamen 361005 (China)

b: Xiamen Entry-Exit Inspection and Quarantine Bureau, Xiamen 361026, China

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* To whom correspondence should be addressed. Tel: (+86) 592-218-7601, E-mail:

cyyang@xmu.edu.cn

Abstract

Due to uranium's increasing exploitation in nuclear energy and its toxicity to human health, it is of great significance to detect uranium contamination. In particular, development of a rapid, sensitive and portable method is important for personal health care for those who frequently come into contact with uranium ore mining or who investigate leaks at nuclear power plants. The most stable form of uranium in water is uranyl ion (UO_2^{2+}). In this work, a UO_2^{2+} responsive smart hydrogel was designed and synthesized for rapid, portable, sensitive detection of UO_2^{2+} . A UO_2^{2+} dependent DNzyme complex composed of substrate strand and enzyme strand was utilized to crosslink DNA-grafted polyacrylamide chains to form a DNA hydrogel. Colorimetric analysis was achieved by encapsulating gold nanoparticles (AuNPs) in the DNzyme-crosslinked hydrogel to indicate the concentration of UO_2^{2+} . Without UO_2^{2+} , the enzyme strand is not active. The presence of UO_2^{2+} in the sample activates the enzyme strand and triggers the cleavage of the substrate strand from the enzyme strand, thereby decreasing the density of crosslinkers and destabilizing the hydrogel, which then releases the encapsulated AuNPs. As low as 100 nM UO_2^{2+} was visually detected by the naked eye. The target-responsive hydrogel was also demonstrated to be applicable in natural water spiked with UO_2^{2+} . Furthermore, to avoid the visual errors caused by naked eye observation, a previously developed volumetric bar-chart chip (V-Chip) was used to quantitatively detect UO_2^{2+} concentrations in water by encapsulating Au-Pt nanoparticles in the hydrogel. The UO_2^{2+} concentrations were visually quantified from the travelling distance of ink-bar on the V-Chip. The method can be used for portable and quantitative detection of uranium in field applications without skilled operators and sophisticated instruments.

Keywords: Uranium, DNA hydrogel, portable detection, DNzyme.

1. Introduction

Uranium is a ubiquitous trace radioactive element that is used as the main fuel in nuclear reactors. With its growth in the nuclear power industry and in nuclear weapons (Domingo 2001a), the worldwide uranium consumption steadily increased. Meanwhile, uranium pollution induced by the mining of uranium ores, the inappropriate disposal of uranium compounds and possible nuclear leakage due to reactor disasters (Gongalsky 2003) become growing concern due to its high radioactivity, toxicity and bioavailability.(Aschner and Jiang 2009; Brugge et al. 2005; Domingo 2001b; Stojanovic et al. 2012). As its toxicity even in low concentrations can severely endanger human health, there is high demand for development of an effective method for sensitive uranium contamination monitoring. Current uranium detection relies mainly on instrumental methods, such as atomic emission spectrometry (AAS) (Jamali et al. 2006), inductively coupled plasma mass spectrometry (ICP-MS),(Wang et al. 2006) X-ray fluorescence (XRF) (Misra et al. 2010), fluorescence spectroscopy (Kushwaha et al. 2012; Sugitani et al. 1980; Yang et al. 2015) and surface-enhanced Raman spectroscopy (SERS) (Ruan et al. 2007). Although these methods offer excellent sensitivity, they require expensive equipment with high running cost and skilled operators.

DNAzymes are artificially evolved oligonucleotides which can be used as sensors for their specific targets (Gong et al. 2015; Lu 2002; Willner et al. 2008). Lu group reported the discovery of a DNAzyme for detection of uranyl (UO_2^{2+}) with ultrahigh sensitivity and selectivity based on the cleavage of substrate strand by enzyme strand upon recognition of UO_2^{2+} (Liu et al. 2007). The sensor was applied in the fluorescent (He and Lu 2011; Wu et al. 2013; Zhang et al. 2015b) and electrochemical detection (Ma et al. 2014; Peled et al. 2015) of UO_2^{2+} after modification with

fluorescent and electrochemical tags, respectively. Colorimetric methods were also developed with gold nanoparticles (AuNPs) (Lee et al. 2008). While the DNAzyme based sensors are cost-effective and readily fabricated, they are still not suitable for routine analysis in the field without sophisticated instruments. Therefore, it is desirable to develop a method to detect uranium in a speedy, inexpensive and portable way for field uranium contamination monitoring.

As a platform for portable detection, stimulus-responsive hydrogels utilize a synthetic polymer as scaffold and functional DNA as crosslinker (Guo et al. 2013; Lin et al. 2011; Yang et al. 2011; Yan et al. 2013; Zhu et al. 2010). The platform exhibits significant advantages for sensitive, selective, cost-effective and portable detection (Yan et al. 2013; Zhu et al. 2010). In this work, we designed and synthesized a uranyl ion responsive hydrogel using a UO_2^{2+} dependent DNAzyme and its substrate strand to crosslink DNA-grafted polyacrylamides for rapid, sensitive, and portable detection of UO_2^{2+} . The activation of DNAzyme by UO_2^{2+} enables the cleavage of the substrate sequence, which subsequently destabilizes the hydrogel, which releases the initially encapsulated AuNPs for colorimetric detection. Lake water was used to verify that the UO_2^{2+} responsive hydrogel is applicable in real water samples. The detection of UO_2^{2+} in lake water was also carried out with a previously developed V-chip system (volumetric bar chart chip) (Huang et al. 2014; Zhu et al. 2014) by encapsulating Au-Pt nanoparticles (Au@AuPtNPs) in the hydrogel. The limit of detection reached 37 nM, which is lower than the EPA (United States Environmental Protection Agency) limit for uranium in drinking water, establishing a speedy, inexpensive, portable, and quantitative detection method for in-field detection of UO_2^{2+} .

2. Experimental

2.1. Materials and reagents

All reagents for DNA synthesis (including A-TOM-CE phosphoramidite) were purchased from Glen Research (Sterling, VA, USA). Uranyl (VI) acetate was purchased from SPI supplies (Westchester, PA, USA). Acetate acid, 2-(N-morpholino) ethanesulfonic acid (MES), sodium chloride and acetonitrile were purchased from J&K Scientific (Shanghai, China). Acrylamide, ammonium persulfate (APS), and tetramethylethylenediamine (TEMED) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Other reagents were purchased from Sinopharm Chemical Reagents (Shanghai, China).

2.2. Acrydite phosphoramidite synthesis

Methacrylic acid (440 mg, 5 mmol), dicyclohexylcarbodiimide (DCC, 1356 mg, 6 mmol), N-hydroxybenzotriazole (HOBT, 59.5 mg, 0.5 mmol) and 6-amino-1-hexanol (585 mg, 5 mmol) were dissolved in 4 mL N,N-dimethylformamide (DMF) and incubated overnight while stirring under an N₂ atmosphere. After removing the precipitate of dicyclohexylurea (DCU) by filtration, water/acetic ether mixed liquor were used to remove residual DMF, and extraction of the product by acetic ether. The organic extract was dried over anhydrous magnesium sulfate and purified by column chromatography. The product (213 mg, 1.15 mmol) was dissolved in dichloromethane (DCM) and cooled to 0 °C. After dropwise addition of 0.55 ml N,N-diisopropylethylamine (DIPEA) and 0.28 ml 2-cyanoethyl N,N-diisopropylchlorophosphoramidite (P-(N-iPr₂)₂(OCH₂CH₂CN)), the mixture was incubated at 0 °C in the dark for 4 hr. The product was obtained by column chromatography and dried to a colorless oil. ³¹P NMR (400 MHz, CDCl₃): 147 (s, 1P).

2.3. Modified DNA synthesis

All DNAs used in the work were synthesized on a Polygen GmbH 12-Column DNA Synthesizer. DNA sequences used for this work are shown in **Fig. 1** and Table S1. Strands A1 and strand A2 were acrydite-modified DNAs. Common DNAs (except for acrydite DNAs) were deprotected by ammonia/methylamine (v/v=1/1) solution at 65 °C for 20 min after synthesis. They were purified by high-performance liquid chromatography (HPLC) using a reversed-phase C18 column. Two solutions with varying polarities were used for gradient elution: 0.1 M triethylamine acetate (pH 7.0) and HPLC-grade acetonitrile. Due to the lack of a hydrophobic group (4,4'-dimethoxytriphenylmethyl group) in acrydite-modified DNA, the elution gradient differed. Non-modified DNAs were eluted with a gradient of acetonitrile from 10 to 65 percent with times from 4 min to 35 min. Acrydite-modified DNAs were eluted in a gradient of acetonitrile varying from 12 to 27 percent with the time from 4 min to 55 min. After vacuum removal of the solvent, the primitive non-modified DNA was detritylized by 80% (v/v) acetate acid. Acrydite-modified DNA did not require detritylization, and was desalted 3 times with a 3k NMWL (nominal molecular weight limit) Millipore ultracentrifugal filter. Substrate strand modified in the middle with A-TOM-phosphoramidite was purified as follows. The abovementioned steps before detritylation were performed the same as non-modified DNA. After that, the protecting 2'-O-triisopropylsilyloxymethyl (TOM) group was removed by addition of 125 µL triethylamine trihydrofluoride in 100 µL DMSO for 3 hr at 65 °C. Then, 25 µL 3M sodium acetate and 1 mL butyl alcohol were used to precipitate DNA at -20 °C after 30 min incubation. All product DNA was desalted 3 times by a 3k NMWL (nominal molecular weight limit) Millipore ultracentrifugal filter and dissolved by RNase free water. The concentration was quantified by the absorbance at

260 nm, and the stock solution was stored at -20 °C for future use.

2.4. Preparation of DNA-grafted polyacrylamide chains

Stock solutions of strand A1 and A2 grafted polyacrylamide chains were prepared in final concentration of 0.5 mM separately in PCR tubes. The tubes contained 4% acrylamide in total volume of 40 μ L. After degassing by air pump for 10 min, 0.56 μ L freshly prepared 10% (m/v) APS and 1.12 μ L TEMED (5%, v/v) solution were added to the abovementioned tubes. Immediately after the mixing of APS and TEMED, the tubes were vacuumed by an air pump in a vacuum desiccator for another 15 min at 37 °C to copolymerize the acrydite DNA and acrylamide, yielding DNA-grafted chains pA1 and pA2. Ultracentrifugal filtration with 100 k NMWL removed the unpolymerized strands.

2.5. Modification of nanoparticles

The synthesis of nanoparticles is described in the supporting information. The unprotected nanoparticles are not suitable for encapsulation in the hydrogel due to the high concentration of salt, which would induce nanoparticle aggregation. Therefore, AuNPs were protected by thiol–polyethylene glycol (PEG-SH, MW 5000). Briefly, 2.5 nM AuNPs were incubated with 1 μ M PEG-SH at 37 °C for 30 min. After centrifuging and redispersing 3 times, RNase-free water was used to dilute AuNPs to 150 nM. Au@AuPtNPs were neutralized in 10 mM phosphate buffer first. After the addition of 0.01% Tween 20, 1 μ M PEG-SH and 2 μ M T15-SH (3' thiol polyThymine) were added and vortexed vigorously. Finally, 100 mM MgCl₂ were used to age Au@AuPtNPs for 30 min at 37 °C. The same centrifuging and redispersing steps were implemented and the final stock concentration of Au@AuPtNP was 100 nM.

2.6. Preparation of UO₂²⁺ responsive hydrogel.

To prepare the hydrogel, pA1: pA2: substrate strand: enzyme strand were mixed in a molar ratio of 100 μ M: 100 μ M: 50 μ M: 100 μ M. The 30 nM AuNPs or 10 nM Au@AuPtNPs were encapsulated in the formed hydrogel. The mixture was alternately vortexed vigorously and incubated at 65 °C for 1 min three times to generate a homogenous hydrogel. Finally, the hydrogel

was slowly cooled to room temperature. The total volume of hydrogel was 10 μL . The reaction buffer was 50 mM MES buffer (pH 5.5, containing 250 mM NaCl).

2.7. Detection of UO_2^{2+} by colorimetric assay

The AuNP-encapsulated hydrogel was formed in the previous step. Fifty μL UO_2^{2+} samples in different concentrations were added to the hydrogel and allowed to incubate at 25 $^\circ\text{C}$ while shaking at 150 rpm for 2 hr. Color changes were observed in the supernatant of the hydrogel indicating the UO_2^{2+} induced collapse of the hydrogel and release of the internal AuNPs. Supernatant absorbance at 520 nm of AuNPs showed the concentration-dependent collapse of hydrogel by UO_2^{2+} .

2.8. V-chip visual detection of UO_2^{2+}

Fifty μL volumes of different concentrations of UO_2^{2+} were loaded onto 10 μL Au@AuPtNP-encapsulated hydrogel. The reaction between UO_2^{2+} and the hydrogel was allowed to proceed for 2 hr at 25 $^\circ\text{C}$ while shaking at 150 rpm. The resultant supernatant with released Au@AuPtNPs was then transferred to the sample position on the V-Chip. After sliding the top layer of the chip, Au@AuPtNPs in the sample were mixed with H_2O_2 to produce O_2 . A large volume of O_2 was generated to push forward the ink bar through the connected vertical channel. The length of the ink bar was used to calculate the concentration of UO_2^{2+} .

3. Results and Discussion

3.1. Working principle of uranyl ion responsive hydrogel

The working principle of the uranyl ion responsive hydrogel is schematically shown in **Fig. 1**. The enzyme strand and substrate strand form a stem-loop complex which is designed to hybridize with two types of DNA polyacrylamide chains to form the DNAzyme hydrogel. AuNPs are encapsulated in the hydrogel during the formation process to indicate the integrity of hydrogel. The hydrogel stays stable until uranyl ion is present in the sample. After activation of the enzyme by uranyl ion, the enzyme strand starts to cleave the substrate strand, inducing the dissociation of the stem-loop structure. Thus the crosslinking ratio of the hydrogel is gradually decreased, and

subsequently the hydrogel is destabilized to release the encapsulated AuNPs. Meanwhile, the uranyl ion binding to the original enzyme and substrate complex will dissociate to bind to another preformed enzyme and substrate complex to facilitate another cycle of cleaving reaction. As a result, a small amount of uranyl ion induces the release of large amounts of AuNPs, which turn the supernatant from colorless to red. Therefore, the concentration of uranyl ion is indicated by the supernatant color change. The AuNPs encapsulated in the hydrogel can also be replaced by enzymes or PtNPs to catalyze the generation of large amounts of signaling molecules for a variety of readout devices, such as a glucometer, distance-based microfluidic chip etc. (Yan et al. 2013; Zhu et al. 2014)

Fig. 1 Working principle of the uranyl ion responsive hydrogel. AuNPs encapsulated in hydrogel are released in the presence of uranyl ion due to the cleavage of the crosslinking substrate strands. The subsequent result can be monitored by naked eye.

3.2. Sequence design and optimization of the hydrogel

The structure of the enzyme and substrate strand complex and construction of hydrogel are

shown in **Fig. 2**. The hydrogel is composed of four strands of DNAs, including polymerized A1 (pA1), polymerized A2 (pA2), enzyme strand (Enz) and substrate strand (Sub). Sequence A1, enzyme strand, and A2 are designed to hybridize to the adjacent sequences on the substrate. To enable a stable hydrogel construction, A1 and A2 were set to 14 nucleotides each to ensure stable hybridization with the full substrate sequence to crosslink pA1 and pA2 for formation of a stable hydrogel. As shown in **Fig. S1C**, the melting temperature (T_m) of Enz/Sub is about 50 °C, thus stable formation of Enz/Sub at room temperature is expected. On the other hand, once the substrate is cleaved by activated enzyme, either of the resulting daughter sequences can dissociate from the enzyme sequences to ensure rapid dissolution of the hydrogel. Unfortunately, the T_m s of full length Enz with two daughter sequences of Sub (Sub1 and Sub2) after the cleavage are 40 °C and 45 °C, respectively (**Fig. S1C**). At this binding strength, it is expected that the DNAzyme can still bind to Sub1 and Sub2 at room temperature, leaving the hydrogel undissolved after target- induced enzymatic cleavage. Therefore, the enzyme sequence was shortened by 1, 2, 3 nucleotides respectively at the 3' end to obtain Enz-1, Enz-2, Enz-3, as shown in **Table S1**. As a result, the T_m s of sub1 with Enz-1, Enz-2, and Enz-3 were significantly decreased to less than 20 °C with Enz-3 having the smallest binding ability to sub1 (**Fig. S1A**). More importantly, all three shortened enzyme sequences retain their activity to cleave the substrate sequence in the presence of UO_2^{2+} (**Fig. S1D**). As a result, Enz-3 was chosen as the enzyme sequence for hydrogel synthesis.

Fig. 2. Design of hydrogel-forming DNA and optimized sequences for the UO_2^{2+} responsive hydrogel. (A) The hydrogel is composed of 4 strands of DNA: pA1, pA2, enzyme strand (Enz) and substrate strand (Sub). (B) The Enz was cut down from original sequence by 1, 2, 3 nucleotides at 3' end of strands to gain Enz-1, Enz-2, Enz-3.

3.3. Sensitive and Selective Colorimetric Detection of UO_2^{2+}

Four types of DNA were added together in the tube to prepare UO_2^{2+} responsive hydrogel. As shown in **Fig. S2**, gold nanoparticles were stably trapped inside the hydrogel, suggesting the successful preparation of stable hydrogel. To test the target sensing behavior of the hydrogel, AuNP-encapsulated hydrogel was reacted with 1 μM UO_2^{2+} . The result showed that in absence of target, no leakage of AuNPs into the supernatant was observed, while steady increase of AuNP absorption from the supernatant was recorded upon addition of target. This experiment clearly proved that the hydrogel was responsive to UO_2^{2+} . Afterwards, the hydrogel was treated with various concentrations of UO_2^{2+} to monitor the target-responsive performance. As shown in **Fig. 3A**, with increasing concentrations of UO_2^{2+} , the volume of hydrogel became smaller, and the color of the supernatant became darker, indicating that the recognition of UO_2^{2+} triggered the cleavage reaction and thus the disruption of the hydrogel. Even with 100 nM UO_2^{2+} , a clear color change can be observed, which is lower than the requirement of EPA (United States Environmental Protection Agency, 130 nM). Further UV-Vis spectroscopy measurement results shown in **Fig. 3B** offer more precise quantitative results. The target-responsive hydrogel can detect UO_2^{2+} from 0 - 800 nM. The linear range is between 0 – 200 nM with the limit of detection (LOD) of 14 nM based on the 3σ rule.

Fig. 3 (A) Sensitivity of hydrogel for UO_2^{2+} detection. UO_2^{2+} in the samples induces the decomposition of hydrogel to release the encapsulated AuNPs. The results can be observed by the naked eye. (B) Absorbance at 520 nm of supernatant corresponding to A. The linear range is observed between 0 and 200 nM.

Taking advantage of the high selectivity of the UO_2^{2+} DNAzyme, our UO_2^{2+} responsive hydrogel displayed good selectivity against other cations. As shown in **Fig. 4A**, in the presence of other common cations with even 100-fold higher concentration than that of UO_2^{2+} , the uranyl ion responsive hydrogel did not show any color change in the supernatant, proving that the presence of other cations does not contribute to the output signal. Corresponding UV-Vis data in **Fig. 4B** clearly demonstrated that uranyl ion hydrogel did not react with cations other than UO_2^{2+} . The results confirmed the fidelity of the uranyl ion hydrogel in selective detection of UO_2^{2+} .

Fig. 4 Selectivity of uranyl ion hydrogel. (A) Response of hydrogel to 100 μ M cations and 1 μ M UO_2^{2+} . (B) The corresponding supernatant absorbance at 520 nm.

3.4. Trace UO_2^{2+} detection in lake samples with the hydrogel.

Natural water can be contaminated with uranium due to poorly controlled mining and processing or leakage from nuclear power plants. The uranyl ion responsive hydrogel was applied to detect trace UO_2^{2+} in natural lake water which was used as a complex matrix. Lake water not polluted by uranium was sampled from Furong Lake on Xiamen University campus by simply filtering with 0.25 μ m filter. Different concentrations of UO_2^{2+} were spiked into the lake sample. As shown in **Fig. 5**, similar to the results with buffer only as the matrix, the supernatant colors gradually turned deeper as the concentration of UO_2^{2+} increased. UV-Vis measurements of the supernatant solution showed that the linear range for UO_2^{2+} is between 0 to 300 nM, with LOD of 20 nM.

Fig. 5 Sensitive detection of UO_2^{2+} in spiked lake water. (A) Different concentrations of UO_2^{2+} were spiked in natural lake water to react with the AuNP encapsulated hydrogel. (B) The corresponding supernatant absorbance of AuNPs at 520 nm.

3.5. Hydrogel coupled with V-Chip for Quantitative Detection of UO_2^{2+}

Colorimetric detection was limited to semi-quantitation due to the color intensity limitations of the naked eye. Translating the target recognition to visual length signal is a good alternative for a portable quantitative method. The lengths are in accordance with target concentration due to the specificity of the reaction achieved by molecular recognition. The V-Chip (volumetric bar chart

chip) has been proven to be a good visual distance-based detection apparatus for sensitive detection of cocaine, lead ion, etc. (Huang et al. 2014; Zhu et al. 2014). The working principle of V-Chip has been described previously (Huang et al. 2014; Zhu et al. 2014). Briefly, as shown in **Fig. S3**, the V-Chip is composed of two glass slides, top layer and bottom layer separately. Each slide is patterned with different disconnected channels. The patterns are designed so that when assembling the two glasses, the disconnected channels are connected into a thoroughly horizontal or vertical connected channel. The choices are controlled by the relative positions between two glass slides.

We further exploited this device to realize quantitative detection of UO_2^{2+} by ink bar length. When the horizontal direction was connected, the chip was loaded with sample, H_2O_2 and dye in different chambers located at different positions of the chip. Samples were obtained from the hydrogel supernatant following the reaction of the Au@AuPtNP-encapsulated hydrogel with different concentrations of UO_2^{2+} . Immediately after sliding of the top layer, the sample chamber of the top layer was brought to the H_2O_2 chamber of the bottom layer to trigger the enzymatic decomposition of H_2O_2 to generate O_2 by Au@AuPtNPs. Meanwhile the sliding changed the horizontal connecting channels into vertical connecting channels and thus the resultant O_2 pushed the ink bar via the vertical connecting channels. By reading the increase in ink bar length, the UO_2^{2+} concentration was visually determined. The concentrations of UO_2^{2+} spiked in lake water were measured in V-chip as shown in **Fig. 6**. The UO_2^{2+} concentration was linearly correlated to the ink bar length in the range of 0-600 nM. The detection limit of 37 nM based to the 3σ rule was comparable to that of the previously reported colorimetric method.(Lee et al. 2008; Zhang et al. 2015a) The results of V chip detection were also verified by the traditional ICP-MS method to

confirm the accuracy. The agreement between V chip results and ICP-MS results proved the utility of our portable V chip method for accurate and sensitive detection of UO_2^{2+} (Table S2).

Fig. 6. Sensitive and portable detection of UO_2^{2+} on a V-Chip. (A) Different concentrations of UO_2^{2+} spiked in lake water induce different lengths of the ink bars. (B) The linear range by V-chip was 0-600 nM with the LOD of 37 nM.

4. Conclusions

In conclusion, a UO_2^{2+} responsive hydrogel was constructed utilizing a DNAzyme-substrate complex structure as crosslinker to hybridize with DNA-grafted polyacrylamide chains. The presence of UO_2^{2+} activates the DNAzyme's activity to cleave the substrate strand, and the breakage of the substrate strand and dissociation of the enzyme strand lead to the collapse of hydrogel. The hydrogel encapsulating AuNPs allows colorimetric detection of UO_2^{2+} concentrations as low as 100 nM by naked eye portably and selectively. To overcome the lack of accuracy by colorimetric assay, a distance-based V-chip detecting apparatus was incorporated with the hydrogel sensing system for portable and quantitative detection of UO_2^{2+} in lake water sample with a detection limit of 37 nM, which is lower than the EPA limit (130 nM). This result

was consistent with that by the traditional ICP-MS method. The target responsive hydrogel incorporating V-chip system offers a promising platform to detect UO_2^{2+} in a sensitive, specific, portable, user-friendly, and quantitative manner for monitoring uranium contamination in field work.

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