Ultrasensitive point-of-care biochemical sensor based on metal-AIEgen frameworks

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Point-of-care (POC) biochemical sensors have found broad applications in areas ranging from clinical diagnosis to environmental monitoring. However, POC sensors often suffer from poor sensitivity. Here, we synthesized a metal-organic framework, where the ligand is the aggregation-induced emission luminogen (AIEgen), which we call metal-AIEgen frameworks (MAFs), for use in the ultrasensitive POC biochemical sensors. MAFs process a unique luminescent mechanism of structural rigidity-enhanced emission to achieve a high quantum yield (~99.9%). We optimized the MAFs to show $10^3$- to $10^5$-fold enhanced sensitivity for a hydrogel-based POC digital sensor and lateral flow immunoassays (LFIA). MAFs have a high affinity to directly absorb proteins, which can label antibodies for immunoassays. MAFs-based LFIA with enhanced sensitivity shows robust serum detection for POC clinical diagnosis.

INTRODUCTION

Point-of-care (POC) biochemical sensors constitute a great advance for the growing demand for health care, food/water safety, and antibiotic/drug tests (1–7). POC sensors offer convenience and efficiency in both time and cost, but they often sacrifice the required sensitivity. To increase sensitivity, the enzyme/nanozyme-linked amplification (8–12), surface-enhanced Raman scattering (13), Cas endonuclease–mediated assays (14), and spin-enhanced nanodiamond techniques (15) are developed to cooperate with traditional POC sensors. These ultrasensitive improvements typically have to resort to auxiliary operations, reactions, or devices, to compromise the convenience and time/cost-efficiency. POC sensors face the limitation to balance sensitivity and convenience. An ultrasensitive and convenient POC sensor is the desired choice but a great challenge.

Metal-organic frameworks (MOFs), one of the most versatile materials for broad applications in chemistry and biomedicine (16–27), may provide a solution to the problem of sensitivity in POC sensors by fluorescent MOFs. Although lanthanide-based fluorescent MOFs are broadly reported (28–30), they use rare-earth metals that are costly. Fluorophores conjugating with metal ions that are not rare-earth metals constitute strong candidates for fluorescent MOF sensors. Unfortunately, so far, the fluorescent MOF sensors are limited owing to the low quantum yield (QY) and partially because of the lack of systematic investigation of nanoscale synthesis of particles. Existing MOFs are typically not sensitive enough for POC sensors. The low QY is restricted by aggregation-caused quenching (ACQ) and ligand-to-metal charge transfer (31, 32). To de novo design fluorescent MOFs, aggregation-induced emission lumogens (AIEgens) are the ideal ligands (33, 34). Recent studies have explored AIEgen-based MOF to some extent (35–41). Unlike fluorophores undergoing ACQ, AIEgens are brightly emissive in an aggregated state (42, 43). Their luminescent mechanism perfectly fits MOFs, which have metal ions–anchored rigid state to confine the intramolecular rotation/vibration, thus generating strongly fluorescent metal–AIEgen frameworks (MAFs). QY of MAFs is high, even close to 99.9% (33). However, MAFs, as a powerful light-emitting material, have not been valued, especially in the context of POC sensors.

Here, we exploited the mesoporous MAFs to develop sensitive and convenient POC sensors, e.g., hydrogel digital sensors (HDSs) and lateral flow immunoassays (LFIA). The successful integration of MAFs with HDS and LFIA enables fast POC detection of ions and macromolecular clinical biomarkers with $10^2$- to $10^5$-fold enhanced sensitivity. We used 1,1,2,2-tetra(4-carboxylphenyl)ethylene (TCPE, a typical AIEgen) and zirconium chloride to synthesize the bright MAFs and modulated the morphology and particle size to improve their detection properties. Using the blue-emissive mesoporous MAFs (B-MAFs) and commercial red-emissive quantum dots (R-QDs) to integrate with a custom-designed hydrogel complex, we fabricated the white-emissive POC HDS. HDS shows a white-to-red fluorescence color transition signal, which is more readable for naked eyes at a low analyte concentration and quantitative digital detection using smartphone-based red-green-blue (RGB) analysis. Using MAFs for LFIA, we found a high affinity between MAFs and antibodies (Ab). Without stabilizing polymers or covalent linking agents, MAFs can directly absorb Abs to form fluorescent labeling particles. MAFs-based LFIA shows excellent sensitivity, selectivity, and reliability for real clinical diagnosis.

RESULTS

For POC detection using HDS, we designed a cross-linked polyvinylpyrrolidone (PVP) hydrogel to support the analyte-triggered reaction. By introducing the B-MAFs and R-QDs, we developed the white-emissive MAFs@QDs-PVP hydrogel complex (Fig. 1). After freeze-drying, the MAFs@QDs-PVP hydrogel complex becomes spongy-like HDS, which is highly stable and storable. Once an analyte solution is added, the solid sensor absorbs water fast, swells, and turns transparent. Using the white-to-red fluorescence color transition
signal, we realized fast and sensitive POC detection with naked eyes and quantitative digital RGB analysis within a few minutes. This quantitative HDS strategy can be versatile by replacing MAFs with any other stimuli-responsive MOFs or other materials.

We synthesized different MAFs by heating a mixture of TCPE and ZrCl₄ in the presence of different regulators [N,N’-dimethylformamide (DMF), 90°C; Fig. 2A]. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images indicate an amorphous MAF-1 without using regulators (Fig. 2B). Acetic acid (HAc), the regulator to cause a slow deprotonation effect, strongly affects the nucleation process and the kinetic growth of MOFs to facilitate the oriented crystal (44, 45). Here, HAc-caused slow deprotonation effect generates a highly structured hexagonal starfish-like MAF-2 (Fig. 2C). Water as a coregulator normally changes the polarity of the surface of MOFs to alter their morphology (46). Using HAc and water as regulators, we obtained a monodisperse olive-like MAF-3 (Fig. 2D). Water plays an essential role in the unique morphology. Either less or excess water produces nonuniform MAFs (fig. S1). Simply adding water without HAc results in amorphous products (fig. S2). Adjusting the mass ratio of TCPE:ZrCl₄ strongly regulates MAFs. A preferable ratio of 1:1 produces monodisperse MAF-3 with uniform size and mesoporous morphology. Other ratios yield MAFs with bad control of size and shape (fig. S3).

Surfactants regulate the kinetic growth of nanomaterials with preferential crystal orientation and morphology (47, 48). We further introduced PVP, polyethylene glycol (PEG), or cetyltrimethylammonium bromide (CTAB). CTAB and PEG regulate MAFs into a mixture of spherical and spiky particles (fig. S4). PVP undergoes dynamic adsorption and desorption on surfaces of MAFs through the interactions between Zr⁴⁺ and pyrrolidinone group. The dynamic process affects the kinetic growth of MAFs to generate the mesoporous shuttle-like MAF-4 with smaller size than MAF-3 (Fig. 2E). This inhibition effect of PVP is concentration dependent. A low concentration of PVP does not affect their morphology (fig. S5). MAFs show bright sky-blue fluorescence under ultraviolet (UV) light (e.g., MAF-4; Fig. 2A). High-resolution TEM images of MAF-4 reveal a layer-by-layer stacking structure (fig. S6). High-angle annular dark-field scanning TEM (HAADF-STEM) images of MAF-4 depict the refined crystalline texture with a lattice spacing of 1.52 nm (Fig. 2, F and G, and fig. S7). Powder x-ray diffraction (PXRD) tests further prove the amorphous MAF-1 (no distinct 2θ peaks) and crystalline MAF-2/MAF-3/MAF-4 (Fig. 2H). The 2θ peak at 5.8° is consistent with TEM-measured lattice spacing.

MAFs have three absorption bands at 250 to 350 nm, except for MAF-2, which displays a broad extinction band at 505 nm (Fig. 3A). From MAF-1 to MAF-4, the excitation/emission peaks shift to a shorter wavelength (MAF-4, 310/465 nm; Fig. 3B and table S1). QY of MAF-4 in solution is above 78%. Fluorescent lifetime (τ) tests indicate the longest value of 3.5 ns for MAF-4 (Fig. 3C). The monodisperse MAF-4 has a diameter of 500 ± 100 nm (Fig. 3D). The surface of MAF particles consists of TCPE ligands and Zr⁴⁺ ions. Their surface zeta-potential values are determined by the relative amount of TCPE/Zr⁴⁺ exposed to the solution. MAF-1 and MAF-2 are negatively charged owing to more TCPE ligands exposed on the surface of particles. In comparison, introducing water during the synthesis altered the distribution to expose more Zr⁴⁺ on

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**Fig. 1. Schematic illustrations.** (A) The synthesis of different MAFs. (B) The fabrication of MAFs@QDs-PVP hydrogel complex for HDS and the digital sensing strategy.
the surface of particles. Thus, MAF-3 and MAF-4 are positively charged (Fig. 3E). Fourier transform infrared (FTIR) spectra reveal that the stretching vibration $\nu_{\text{C}=\text{O}}$ (1690 cm$^{-1}$) of TCPE nearly disappears in MAF-4, indicating the strong coordination of metal ions and TCPE (fig. S8) (49, 50). X-ray photoelectron spectroscopy (XPS) analysis of MAF-4 proves the surface coating of PVP (the C-N band matched to alkylpyrrole groups; Fig. 3, F to I).

We chose different MAFs according to their properties. MAF-1/MAF-2 with micrometer size are not stable regarding dispersity. They precipitate from the solution within an hour (Fig. 4A). Their negative surface charges may cause nonspecific aggregation through electrostatic binding with metal ions. Positively charged MAF-3/MAF-4 are stable because of their small size and monodisperse distribution. The positive surface charge helps avoid nonspecific electrostatic binding when incubated with metal ions. The hydrophilic PVP can disperse MAF-4 in aqueous solutions compared to MAF-3.

At low concentrations of Cr$^{3+}$, MAF-4 is more sensitive than MAF-3, showing a bigger fluorescence change (Fig. 4B). We tested their responses to metal ions. MAFs (0.5 µg/ml) fit the best performance of the spectrophotometer. We tested the stability by suffering hypersaline, organic, and highly acidic conditions. MAF-4 has excellent tolerance to salinity (against saturated NaCl solution; fig. S9), most organic solvents (fig. S10), and acid (against 1 M HCl solution; fig. S11).

Cr$^{3+}$-induced quenching of MAFs is a fast reaction. Within 2 min, the fluorescence change reaches a maximum level (fig. S12). Figure 4C and fig. S13 show the concentration-dependent fluorescence spectra and the intensity change ratio curve. A good linear detection range is 2.5 to 500 nM [adjusted coefficient of determination (Adj. $R^2$) > 0.97]. A calculated limit of detection (LOD) value is about 0.1 nM (3σ per slope), which is more sensitive than current MOF sensors and other sensors (Fig. 4D and table S2) (51–63). Cr$^{3+}$-incubated MAF-4 has a slight increase of hydrodynamic diameter (Fig. 4E), which indicates Cr$^{3+}$ attaching on surfaces of MAF-4. The massive Cr$^{3+}$ ions change the surface charge of MAF-4 (~21 to ~36 mV; Fig. 4F). After incubation, MAF-4 maintains its intact morphology and size (Fig. 4G). The XRD tests do not reveal any distinct 2θ shift (fig. S14A). No evident structural ion exchange of Zr$^{4+}$/Cr$^{3+}$ and structural damage were observed. A uniform distribution of chromium in elemental mapping reveals the homogeneous interaction between mesoporous MAF-4 and Cr$^{3+}$. XPS analysis further proves that the chromium is Cr$^{3+}$ (2p$_{3/2}$/2p$_{1/2}$, 586.9 eV/577.3 eV; Fig. 4, H and I). Comparing 19 kinds of metal ions, the Cr$^{3+}$ ion–induced quenching has good selectivity (fig. S15). The optical spectra reveal the notable overlap between the absorption spectrum of Cr$^{3+}$ and the fluorescence emission spectrum of MAF-4 (fig. S14B). However, other weakly interfering ions, such as Fe$^{2+}$/Cu$^{2+}$/Ag$^{+}$, do not show significant
spectral overlap. It may suggest that the energy transfer between MAF-4 and the absorbed Cr\textsuperscript{3+} causes selective fluorescence quenching. We tested the potential application in biological fluids, such as saliva, urine, and serum. A slight fluorescence increase of these biological samples is probably due to biological fluorescence (fig. S16). For the spiked tests, Cr\textsuperscript{3+}-induced quenching is robust with a recovery range of 103 to 110%.

To achieve the proposed HDS, we designed a smart hydrogel to load MAFs. The hydrogel-based detection is highly stable for the operation to avoid interferences and storage problems. The optical sensing requires hydrogel substrate to be nonemissive, colorless, and transparent to visible light. PVP hydrogel meets these criteria (64–66). We synthesized the cross-linked PVP hydrogel using K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} as the promoter and glycerin as a dopant (Fig. 5A). After being freeze-dried, the hydrogel becomes a white spongy-like solid. Once immersed into water, the spongy-like solid rapidly swells upon water absorption to become a colorless and transparent hydrogel. This solid is ultrastable and storable for at least 1 year (fig. S17).

PVP solution (5%) has high transmittance at the range of 400 to 700 nm (>97%). After cross-linking, the PVP hydrogel is colorless and transparent without transmission loss (<1%; Fig. 5B). The high-transmittance area covers the emission of MAFs, which is advanced for fluorometric detection. The optimized cross-linking conditions are time (1 hour), temperature (80°C), and K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (40 mg/ml) (Fig. 5C). Low temperature and short reaction time do not cause gelation. The higher temperature and concentration of K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} generate bubbles. Overreaction will produce a yellow gel (fig. S18). Immersing the freeze-dried hydrogel in water, the white solid slowly absorbs water for a few hours. Many air bubbles fill the pores, and the hydrogel turns back to being colorless and transparent. Increasing the hydroexpansivity helps to eliminate the bubbles. A fast water absorption and swelling will squeeze out the bubbles to accelerate the conversion into a colorless and transparent hydrogel. We tested different dopants, including glycerin, Tween 80, Triton X-100, PEG, polyvinyl alcohol (PVA), and soluble starch (Fig. 5D and fig. S19). Except for PVA, other dopants promote the water absorption. PEG and soluble starch enhance the swelling. Glycerin show strongly enhanced water absorption and swelling to achieve the desired conversion. The freeze-dried PVP hydrogel with glycerin dopant rapidly absorbs water and swells to squeeze out air bubbles. This promotion is concentration dependent. The more glycerin dopant, the faster the conversion is. However, at high concentrations, glycerin breaks the gelation (fig. S20).

Aiming to POC detection with an easy readout signal, we modulated the fluorescence quenching signal into a fluorescence color transition signal by cooperating with R-QDs because red is the most
recognizable color for naked eyes. By in situ embedding the B-MAFs and R-QDs into the designed PVP hydrogel, we obtained the white-emissive MAF-4@QDs-PVP hydrogel complex (Fig. 5E). In this complex, the analyte-induced quenching of blue fluorescence turns into the fluorescence color transition from white to red. The fluorescence intensity change signal is not easy to discriminate when the analyte is at low concentrations. The white-to-red fluorescence color change is easy to be read by naked eyes and digital analysis. To fit the excitation at 310 nm, we modulated MAF-4 [emission, 465 nm; Commission Internationale de L’Eclairage (CIE) color coordinates, 0.16 and 0.18] and QD (emission, 604 nm; CIE, 0.62 and 0.37; fig. S21) components with optimized fluorescence intensity (i.e., concentration) in hydrogel to formulate the composite white fluorescence (CIE, 0.29 and 0.23; Fig. 5F). The equal fluorescence intensity of MAF-4 and QDs in HDS enables that, once the blue fluorescence of MAF-4 decreases, the white-emissive HDS changes to display the red fluorescence of QDs. Immersing the MAF-4@QDs-PVP hydrogel complex in Cr³⁺ solution, we can easily observe the fluorescence color change with naked eyes (Fig. 5G). In contrast, the fluorescence intensity change of the MAF-4-PVP hydrogel complex is hardly readable.

For the scale-up fabrication, we used a commercial 96-well plate to manufacture the HDS arrays (Fig. 6A). Each well is filled with 100 μl of 5% PVP solution containing MAF-4, QDs, 2% glycerin, and 4% K₂S₂O₈. The plate is coated with a food wrapper and placed at 80°C for 1 hour to gelate. After freeze-drying, we obtained the white HDS arrays. SEM images reveal a cellular structure of the hydrogel complex (Fig. 6B and fig. S22). The overlap of N and Zr in elemental mapping images indicates that MAF-4 is attached to or embedded in the hydrogel frameworks. The HDS arrays can be stored after being vacuum-sealed (Fig. 6C). We took videos to monitor the fast water-absorbing and swelling behavior of the HDS (Fig. 6D and movies S1 and S2). Once exposed to water, the HDS immediately absorbs water and swells to squeeze out air bubbles. Within 1 min, the HDS becomes a colorless and transparent hydrogel with consistent white fluorescence.

We tested the HDS on responding to aqueous Cr³⁺ ions. Chromium is a trace element necessary for life. Cr³⁺ disorder (either deficiency or excess) is correlated to diabetes, cardiovascular diseases, and kidney toxicity (67–69). The gold standard of chromium (Cr³+/⁶⁺) in drinking water set by the U.S. Environmental Protection
Agency is less than 100 μg/liter (or 1.92 μM). The World Health Organization/European Community/Chinese national standard is less than 50 μg/liter (or 0.96 μM). As the concentration of Cr^{3+} increases, the blue fluorescence of MAF-4 decreases. The red fluorescence of QDs does not change (Fig. 6E). The corresponding CIE chromaticity coordinates shift from the white area to the red area. This change is recognizable at 10 nM Cr^{3+} by naked eyes (Fig. 6F). Cr^{6+} can be easily reduced to Cr^{3+} by ascorbic acid. The HDS fully satisfies the water quality standards and has big potential for water/food safety applications. For the POC digital detection, we captured...
the RGB values from the photographs using the smartphone and used the B value as a readout signal. The color images are extracted from the central area of photographs. The captured B value reduces as the concentration of Cr$^{3+}$ increases (Fig. 6F). The full dynamic response range covers five orders of magnitude. A good linear quantitative digital detection range is 10 to 10,000 nM with Adj.$R^2$ of 0.99 (fig. S23).

We demonstrated that MAFs-based HDS has advantages in fluorescent POC detection. Besides the potential application in water/food safety, the sensitive protein labeling and immunodetection for clinical macromolecular diagnosis is another powerful application of strongly fluorescent MAFs. We used MAFs to label Abs for ultrasensitive fluorescent LFIA. To fit the immunochromatography in the nitrocellulose membrane, we further synthesized negatively charged MAF-5 particles with a size of ~100 nm and spiky morphology (Fig. 7A). The negatively charged, relatively small particles help avoid the nonspecific binding (false signal) and reduce the flow time. The multivalent Zr$^{4+}$ ions on the surface of particles are favored to bind proteins through electrostatic interactions and coordinations (70–72).

MAF-5 can directly label Abs without using polymer coating or covalent linking agents (Fig. 7B). Compared to conventional QDs-based LFIA (fig. S24), it greatly simplifies the fabrication and reduces the cost but retains the required sensitivity.
We selected alpha-fetoprotein (AFP), a serum marker for clinical diagnosis of hepatocellular carcinoma (HCC) and the therapeutic monitoring, as a target to establish MAFs-based LFIA. During incubation with excess Abs, the zeta-potential change indicates strong binding between $MAF-5$ and primary Abs (AFP-Ab1; fig. S25). The absorption spectra have a slight red shift (Fig. 7C), while the fluorescence intensity of $MAF-5@AFP-Ab1$ has no significant decrease (Fig. 7D). $MAF-5$ is stable to label proteins for LFIA or other applications. XPS profiles reveal the appearance of N element, which confirms the attached proteins (Fig. 7E and fig. S26). To confirm the correlation studies of the MAFs-based LFIA and the clinically used CLIA.
AFP-Ab on surfaces of MAF-5, we carried out SDS–polyacrylamide gel electrophoresis tests. The mixture was centrifuged to gather the MAF-5@AFP-Ab1 complex. The complex was suspended in loading buffer and boiled to denature proteins. After electrophoresis and staining with Coomassie brilliant blue, we observed two protein fragments near 25 and 55 kDa (Fig. 7F). They are exactly the same as the control (pure Abs) where the light chain and heavy chain of the Abs appear as separate blots on the gel.

We fabricated the LFIA strips following the optimized conditions of AFP-Ab1 (8 µg/ml), secondary Ab (2 mg/ml, AFP-Ab2), and anti-Ab (2 ng/ml) (Fig. S27). A balanced running buffer [phosphate-buffered saline (PBS) with 1% Triton X-100 (pH 7.4)] ensured the fast immunochromatography within 15 min and minimized the nonspecific signal (Fig. S28). For the standard curve tests, we prepared a gradient dilution in PBS. As the AFP amount increases, the test line becomes bright with blue fluorescence under UV light (Fig. 7G). The linear detection range is 1 pg/ml to 20 ng/ml (Adj. R² > 0.99). A calculated LOD value is about 0.6 pg/ml (3σ per slope). MAFs-based LFIA has excellent sensitivity (10²- to 10³-fold enhancement) compared to the traditional QDs-based LFIA (Fig. 7H and table S3) (12, 73). MAFs-based LFIA is even more sensitive than some surface-enhanced Raman spectroscopy–based LFIA. The good selectivity is shown against other proteins (fig. S29). A highly sensitive and selective detection method is important and practical. It makes sense of a lower serum volume for testing and is thus friendly to reducing sample volume requirement for the sick by using only fingertip blood tests (instead of venous blood sampling). We tested the standard curve in spiked serum (fig. S30). A clinical cutoff line makes sense of a lower serum volume for testing and is thus friendly and avoids sacrificing the required convenience and cost-efficiency.

DISCUSSION
In conclusion, we demonstrated the rational design and utilization of MAFs for ultrasensitive and convenient POC detections based on HDS and LFIA. Combining the high QY and synthetic modulation, the sensitivity of POC sensors increases a hundredfold to a thousandfold and avoids sacrificing the required convenience and cost-efficiency. It has the potential to develop smart sensors for small molecules and macromolecules by designing specific responsive MAFs with molecular engineering. Combining with metal nanoparticles/clusters, microfabrication, and barcode technologies, MAFs may greatly facilitate POC sensors.

MATERIALS AND METHODS

Instruments and characterizations
Scanning electron microscope characterizations are performed using a Regulus8200 cold-field emission scanning electron microscope (Hitachi, Japan). Samples are prepared by drop-casting on the conductive tape, dried, and then plasma sputtering–coated with gold. Transmission electron microscope, HAADF-STEM, and elemental mapping characterizations are performed using a Tecnai G2 F20 U-TWIN field-emission transmission electron microscope (FEI, USA) equipped with EDAX Genesis 2000 XMS accessory. Samples are prepared by drop-casting on the carbon-coated copper grid. UV-visible optical spectra are recorded using a UV-2450 spectrophotometer (Shimadzu, Japan). Excitation and emission spectra are recorded using an RF-5301PC fluorescence spectrophotometer (Shimadzu, Japan). Hydrodynamic diameter and zeta-potential distribution profiles are measured by a Zetasizer Nano ZS instrument (Malvern, UK). Fluorescent lifetime profiles and absolute QY of different MAFs are measured by an FLS980 transient steady-state fluorescence spectrometer (Edinburgh Instruments, UK). PXRD characterizations are performed using a D/MAX-TTRIII (CBO) instrument (Rigaku, Japan). XPS characterizations are performed using an ESCALAB 250Xi instrument (Thermo Fisher Scientific, USA). FTIR spectra are measured by a Spectrum One instrument (PerkinElmer, USA).

Synthesis of Zr@TCPE MAFs without regulators (MAF-1)
Typically, 23 mg of ligand TCPE and 23 mg of anhydrous ZrCl₄ are dissolved in 6 ml of DMF solvent. After sonication for 5 min, the mixture is transferred into a glass bottle (Φ 3.25 cm by 15 cm) and sealed and then immersed into the oil bath at 90°C. The mixture solution is clear liquor until it is fully heated. During the reaction, white precipitates reveal the formation of MAFs. The reaction without regulators takes much more time to form Zr@TCPE MAFs. Over 24 hours, there is no apparent increase of precipitates. The precipitates are centrifuged (5000 rpm, 5 min) and washed twice with DMF and ethanol. The final product is suspended in ethanol and placed in the refrigerator (4°C) or at room temperature.

Synthesis of Zr@TCPE MAFs with regulators (MAF-2, MAF-3, and MAF-4)
All procedures and operations are the same as described above, except for the addition of different regulators of HAc, H₂O, and PVP. For the synthesis of MAF-2, 2 ml of HAc is added before undergoing the oil bath. For the synthesis of MAF-3, 2 ml of HAc is added before undergoing the oil bath. Then, 0.1 ml of H₂O is added when the mixture turns to clear liquor under heating. For the synthesis of MAF-4, 230 mg of PVP is dissolved in the DMF mixture, which contains 23 mg of ligand TCPE and 23 mg of anhydrous ZrCl₄. HAc (2 ml) is added before undergoing the oil bath. Then, 0.1 ml of H₂O is added when the mixture turns to clear liquor under heating. For the synthesis of MAF-4, 230 mg of PVP is dissolved in the DMF mixture, which contains 23 mg of ligand TCPE and 23 mg of anhydrous ZrCl₄. HAc (2 ml) is added before undergoing the oil bath. Then, 0.1 ml of H₂O is added when the mixture turns to clear liquor under heating. For the synthesis of MAF-4, a necessary synthetic time is greatly reduced from over 24 hours to 5 hours.

Synthesis of cross-linked PVP hydrogel
Typically, 5% PVP solution containing K₂S₂O₈ (40 mg/ml) is gelated at 80°C for 1 hour. For the glycerin–dopped PVP hydrogel, 5% PVP solution containing K₂S₂O₈ (40 mg/ml) and 2% glycerin is gelated at 80°C for 1 hour.
Fabrication of freeze-dried hydrogel solid
Typically, the above PVP hydrogel is frozen at −80°C and then freeze-dried overnight to obtain the white, sponge-like solid.

Synthesis of MAF-4@QDs@PVP hydrogel complex
Typically, the appropriate amounts of MAF-4 and QDs are added into the 5% PVP solution, which contains K₂S₂O₈ (40 mg/ml) and 2% glycerin, and mixed. Then, the mixture is gelated at 80°C for 1 hour.

Fabrication of MAF-4@QDs@PVP hydrogel complex sensor array
For the freeze-dried hydrogel solid sensor array, the mixture solution of MAF-4, QDs, 5% PVP, K₂S₂O₈ (40 mg/ml), and 2% glycerin is piped into the commercial 96-well plate for 100 μl per well. The plate is covered with the food wrapper and placed at 80°C for 1 hour. The hydrogel complex is frozen at −80°C and then freeze-dried overnight to obtain the white, sponge-like solid sensor array.

Synthesis of Zr@TCPE MAFs for LFIA (MAF-5)
For the synthesis of small-sized MAF-5, we increased the mass ratio of TCPE:ZrCl₄ with HAc as regulators. TCPE (96 mg), 23 mg of ZrCl₄, and 2 ml of HAc were added into 6 ml of DMF and heated under vigorous stirring. Other procedures and operations are the same as MAF-1, except for the centrifuge condition of 8000 rpm for 15 min.

Synthesis of Ab@MAF-5 complex for LFIA
Typically, MAF-5 with appropriate dilution was incubated with Ab (10 μg/ml). The mixture was placed on the shaker for 3 hours. Then, a blocking solution of bovine serum albumin (BSA) was added into the mixture with a concentration of 10 mg/ml. The mixture was further incubated for 1 hour on the shaker. At last, the mixture was centrifuged (8000 rpm, 15 min) to obtain the precipitates of the Ab@MAF-5 complex. The precipitates were resuspended using a PBS buffer containing 1% BSA and placed in the refrigerator (4°C) for usage.

Clinical samples
The used clinical serum and urine samples were collected from the Department of Hepatobiliary and Pancreas Surgery, Shenzhen People’s Hospital (The First Affiliated Hospital of Southern University of Science and Technology), and approved by the institutional ethics committee (LL-KT-2018207).

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at https://science.org/doi/10.1126/sciadv.abo1874

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Acknowledgments: We thank SUSTech Core Research Facilities for the material characterizations. We thank Wuhan Jiayuan Quantumdots Co. LTD (Wuhan, China) for providing the QDs. Funding: This work was supported by the National Key R&D Program of China (2018YFA0902600), the National Natural Science Foundation of China (22104049, 22005195, and 81730051), Shenzhen Science and Technology Program (KQTD20190929172743294, JCYJ20200109110608167, and JCYJ20210324105006017), the Chinese Academy of Sciences (QYZDJ-SSW-SLH039), Guangdong Innovative and Entrepreneurial Research Team Program (2019ZT08Y191), Shenzhen Key Laboratory of Smart Healthcare Engineering (ZDSYS20200811144003009), Guangdong Provincial Key Laboratory of Advanced Biomaterials (2022B1212010003), and Tencent Foundation through the XPLORER PRIZE. Author contributions: J.Z., Y.L., B.Z.T., and X.J. designed the research. J.Z. and F.C. performed the research. Q.L. helped with the TEM studies. D.W. helped with the fluorescence studies. L.L. collected the clinical samples. J.Z., Y.L., F.C., L.L., and X.J. analyzed the data. J.Z., B.Z.T., and X.J. wrote the paper. Competing interests: The authors declare that they have no competing interests. Data and materials availability: All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials.

Submitted 19 January 2022
Accepted 13 June 2022
Published 27 July 2022
10.1126/sciadv.abo1874