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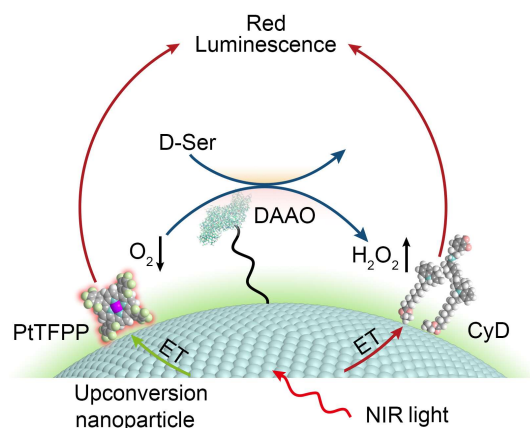
# Enantiospecific Detection of D-Amino Acid through Synergistic Upconversion Energy Transfer

Yongan Tang,<sup>[a][b]</sup> Xiaoyan Zhong,<sup>[c]</sup> Shuangqian Yan,<sup>[a][b]</sup> Xiaowang Liu,<sup>[d]</sup> Liang Cheng,<sup>[c]</sup> Yu Wang,<sup>\*[a]</sup> and Xiaogang Liu<sup>\*[a][b]</sup>

**Abstract:** D-amino acids (DAAs) are indispensable in regulating diverse metabolic pathways. Selective and sensitive detection of DAAs is crucial for understanding the complexity of metabolic processes and managing associated diseases. However, current DAA detection strategies mainly rely on bulky instrumentation or electrochemical probes, limiting their cellular and animal applications. Here we report an enzyme-coupled nanoprobe that can detect enantiospecific DAAs through synergistic energy transfer. This nanoprobe offers near-infrared upconversion capability, a wide dynamic detection range, and a detection limit of 2.2  $\mu\text{M}$ , providing a versatile platform for *in vivo* noninvasive detection of DAAs with high enantioselectivity. These results potentially allow real-time monitoring of biomolecular handedness in living animals, as well as developing antipsychotic treatment strategies.

Although L-amino acids have long been considered to have strict homochirality in mammalian tissues,<sup>[1]</sup> several D-amino acids (DAAs) have recently been found to fulfilled irreplaceable functions in numerous physiological processes of humans.<sup>[2]</sup> For instance, D-serine (Ser) levels are higher in the hippocampus and parietal cortex of patients with Alzheimer's disease and lower in the serum of patients with schizophrenia than in the controls.<sup>[3]-[4]</sup> D-aspartate is essential for synthesizing and secreting several pivotal hormones.<sup>[5]</sup> Additionally, an elevated D-alanine concentration in gastric juice of carcinoma patients can be considered a potential cancer marker.<sup>[6]</sup>

Owing to the medicinal importance of DAAs, innovative strategies have been developed for accurate DAA detection.<sup>[7]</sup> However, most of these strategies rely on complicated instruments. Moreover, they are time- and cost-consuming and infeasible for *in vivo* detection.<sup>[8]</sup> DAA oxidase (DAAO) is a highly enantiospecific enzyme that catalyzes DAA oxidation via  $\text{O}_2$  consumption along with  $\text{H}_2\text{O}_2$  production, while non-reactive



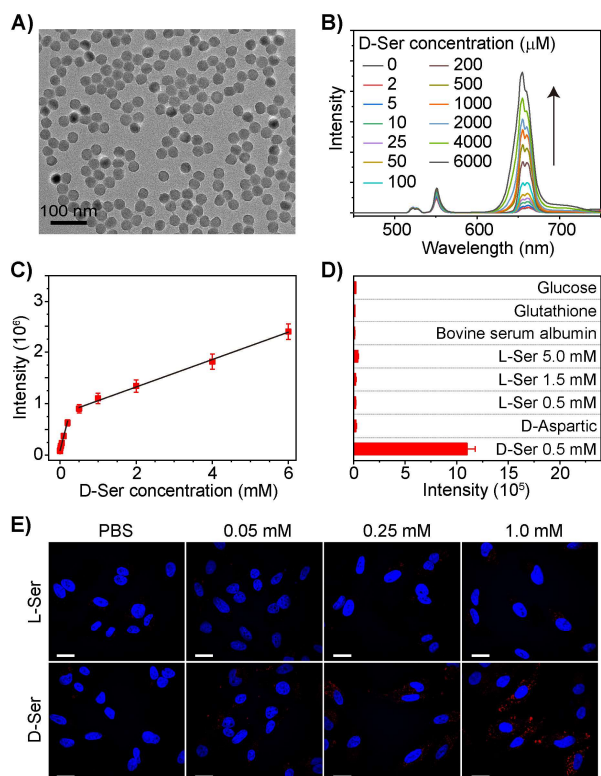
**Figure 1.** Schematic illustration of enantiospecific enzyme-based nanoprobe for D-Ser detection. Enantiospecific oxidation of D-Ser using DAAO results in  $\text{O}_2$  consumption and  $\text{H}_2\text{O}_2$  production, boosting PtTFPP emission and suppressing CyD absorbance. This dual effect leads to synergistic red luminescence enhancement for D-Ser detection through upconversion energy transfer (ET).

to its enantiomeric counterparts, namely, L-amino acids, even at high concentrations.<sup>[9]</sup> Because of the enantiospecific nature of this enzyme, it qualifies for DAA detection, particularly considering the ubiquitous disturbance of chemically similar L-amino acids. DAA detection strategies have been established using DAAO-containing microsensors,<sup>[10]</sup> microelectrode arrays,<sup>[11]</sup> or DNA/silver nanoclusters<sup>[12]</sup> by monitoring the electrochemical or UV-visible spectroscopic signals. However, the limitations of existing probes, such as large physical dimensions, narrow detection range, and limited tissue penetration of UV-visible photons, generally hinder their practical applications (**Table S1**).

To overcome challenges encountered in DAA detection, we fabricated a near-infrared (NIR)-excitable, enzyme-based nanoprobe that could detect DAAs through synergistic upconversion energy transfer (**Figure 1**). This nanoprobe comprises four components: upconversion nanoparticle (UCNP), platinum porphyrin (PtTFPP), cyanine-dopamine conjugate (CyD), and DAAO. The UCNP can convert NIR light into UV/visible photons with minimal background luminescence, offer significant advantages for cellular and animal applications.<sup>[13]</sup> In the absence of DAAs, PtTFPP and UCNP luminescence was quenched by dissolved  $\text{O}_2$  and CyD, respectively. However, in the presence of DAAs, the enantiospecific catalysis by DAAO triggers  $\text{O}_2$  depletion and  $\text{H}_2\text{O}_2$  production, which enhances PtTFPP emission and reduces CyD absorbance, respectively, thereby synergistically boosting red emission intensity. Owing to the large tissue penetration depth of NIR light<sup>[14]</sup> and

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**Figure 2.** DAA detection in solutions and HeLa cells using the proposed nanoprobes. A) Representative transmission electron microscope image of nanoprobes. B) Emission spectra of a mixture of nanoprobes ( $3.0 \text{ mg mL}^{-1}$ ) and D-Ser at various concentrations (Ex., 980 nm). C) Calibration curve for detecting D-Ser. D) Detection selectivity of the nanoprobes. E) Confocal images (Ex., 980 nm,  $0.5 \text{ W cm}^{-2}$ ) of HeLa cells after incubation with nanoprobes ( $0.5 \text{ mg mL}^{-1}$ ) for 4 h. Luminescence is collected at 600–670 nm. Scale bar: 20  $\mu\text{m}$ . Data represent mean  $\pm$  sd.

stereochemical-specific property of DAAO, these nanoprobes enable sensitive *in vivo* DAA detection with noninvasive and strict enantiospecific characteristics.

Yb/Er-codoped UCNP with a well-controlled core-shell-shell structure ( $\text{NaYF}_4\text{:Yb/Er}$  (18/2 mol%)@ $\text{NaYF}_4$ ) emitted intense green ( $\text{Er}^{3+}$ :  $^2\text{H}_{11/2}$ ,  $^4\text{S}_{3/2} \rightarrow ^4\text{I}_{15/2}$ ) and red ( $\text{Er}^{3+}$ :  $^4\text{F}_{9/2} \rightarrow ^4\text{I}_{15/2}$ ) light (Figures S1, S2 and Table S2).<sup>[15]</sup> Amphiphilic polyethylene glycol (PEG) derivatives were used to modify as-synthesized UCNP and assist PtTFPP, CyD, and DAAO loading (Figure S3).<sup>[16]</sup> These nanoprobes exhibited a uniform size with pseudospherical morphology (Figure 2A), as well as clear lattice fringes of (110) planes ( $d = 0.532 \text{ nm}$ ) and a fluffy organic layer with  $\sim 1.61\text{-nm}$  thickness (Figure S4). Moreover, these PEG-modified nanoprobes showed good water dispersibility and a suitable hydrodynamic dimension ( $\sim 123.4 \text{ nm}$ ) for wide detection applications (Figure S4 and Table S3).

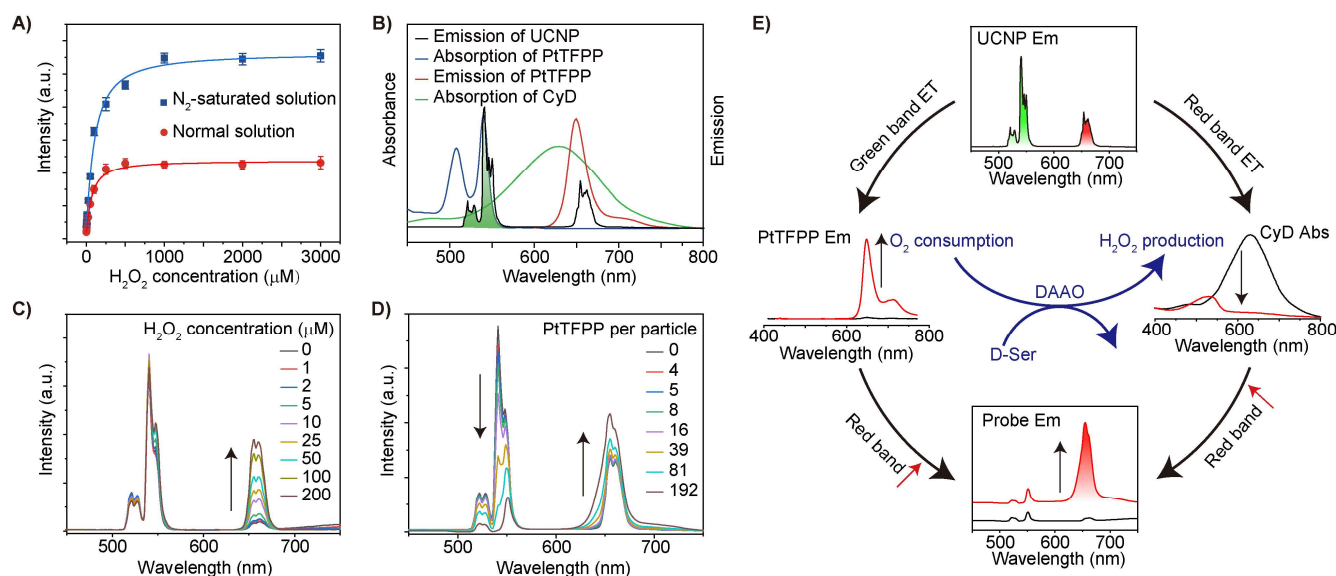
The DAA detection capability of as-prepared probes was verified by upconversion luminescence of a mixture of nanoprobes and D-Ser under 980-nm laser excitation. The red luminescence band significantly increased when the D-Ser concentration was varied from 0 to 6.0 mM (Figure 2B). The evolution profile can be divided into two phases, which may indicate two sensing signs of progress. Red emission band at

600–670 nm was used to quantify D-Ser concentration (Figure 2C). The minimum detection limit is  $\sim 2.2 \mu\text{M}$  with a signal-to-noise ratio of 3, which is encouraging when considering the fact that D-Ser levels in the cerebrospinal fluid of patients with Alzheimer's disease ( $12.32 \mu\text{M}$ ) are significantly elevated than the control ( $2.45 \mu\text{M}$ ).<sup>[3]</sup> We further measured the relative contribution of CyD and PtTFPP to detected signals as well as detection kinetics (Figures S5 and S6). Additionally, our nanoprobes exhibited high enantiospecific selectivity. At considerably high concentrations (3 and 10 times), L-Ser as well as common biological molecules, including bovine serum albumin, glutathione, and glucose, did not produce significant signal (Figure 2D). It is worth noting that our nanoprobes also exhibit high selectivity for D-Ser against other DAAs such as D-aspartate, owing to the intrinsic selectivity of DAAO. Moreover, the acceptable coefficient of variation (5.9–10.5%), analytical recovery (90.5–112.3%), and batch-to-batch reproducibility of our nanoprobes were confirmed (Table S4 and Figure S7).

We next monitored intracellular D-Ser levels on HeLa cells. After 4 h of incubation, red emission remained conspicuous even at a high L-Ser concentration (1.0 mM). Conversely, the red emission brightened at a low D-Ser concentration (0.05 mM, Figure 2E). Further, at D-Ser concentrations of 0.25 and 1.0 mM, luminescence intensity improved by approximately 6- and 12-folds, respectively (Figure S5), strongly indicating the feasibility and specificity of the nanoprobes for monitoring intracellular DAAs.

A comparison of our approach with existing DAA detection strategies shows advantages of our work (Table S1), including both excitation and emission in the NIR window, nanoscale dimension, a wide detection range, and a low detection limit, as well as a cellular detection capability. The outstanding performance of the nanoprobes under investigation was attributed to the on-demand material design and precise engineering control. In nearly all previous DAAO-based detection strategies, DAA was enantiospecifically quantified by solely sensing the  $\text{O}_2$  or  $\text{H}_2\text{O}_2$  level variation triggered by catalytic reactions (Table S1), leading to high noise and limited response range owing to disturbances from  $\text{O}_2$  and  $\text{H}_2\text{O}_2$ . However, our nanoprobes exhibited dual-sensing capabilities for  $\text{H}_2\text{O}_2$  production and  $\text{O}_2$  consumption (Figure 3A), indicating successful integration of these two sensing principles (Figure S8). Additionally, the two sensing principles lead to red-emission amplification, which is favorable due to its convenience and simplicity. This amplification is enabled by manipulating synergistic energy transfer from UCNP to CyD and PtTFPP.

Energy transfer from UCNP to CyD and PtTFPP was investigated using two control probes, CyD-loaded and PtTFPP-loaded UCNP, respectively, to diminish the mutual interference. In CyD-loaded UCNP, CyD was used as the energy acceptor. The absorption spectrum of CyD well matches the red band (640–680 nm,  $\text{Er}^{3+}$ :  $^4\text{F}_{9/2} \rightarrow ^4\text{I}_{15/2}$ ) of UCNP (Figure 3B), indicating potential energy transfer manipulation.<sup>[17]</sup> The efficient energy transfer between them was proved by the results that the UCNP luminescence, particularly the red emission, was significantly quenched through CyD loading (Figure S9). Moreover, CyD exhibited a sharp reduction in red absorption (550–750 nm) in the presence of  $\text{H}_2\text{O}_2$  (Figure S9),<sup>[18]</sup> which could relieve luminescence quenching. Consequently, red



**Figure 3.** Dual sensing of  $O_2$  &  $H_2O_2$  and synergistic upconversion energy transfer. A) Upconversion luminescence intensity of the nanoprobes in a normal or  $N_2$ -saturated solution with varying  $H_2O_2$  concentrations. B) Upconversion emission spectrum of UCNP, absorption and emission spectra of PtTFPP (Ex. = 540 nm), and absorption spectrum of CyD. C) Emission spectra of CyD-loaded UCNPs in normal solutions with varying  $H_2O_2$  concentrations. D) Emission spectra of PtTFPP-loaded UCNPs with varying PtTFPP-loading numbers in  $N_2$ -saturated solutions. E) Dual-sensing of  $O_2$  &  $H_2O_2$  and synergistic upconversion energy transfer. Abbreviation: ET, energy transfer; Em, emission; and Abs, absorption. A 980-nm laser is used as the light source.

luminescence from UCNP recovered with increasing  $H_2O_2$  concentration, suggesting that  $H_2O_2$  can be sensed by 980-nm excited red luminescence through energy transfer (Figure 3C).

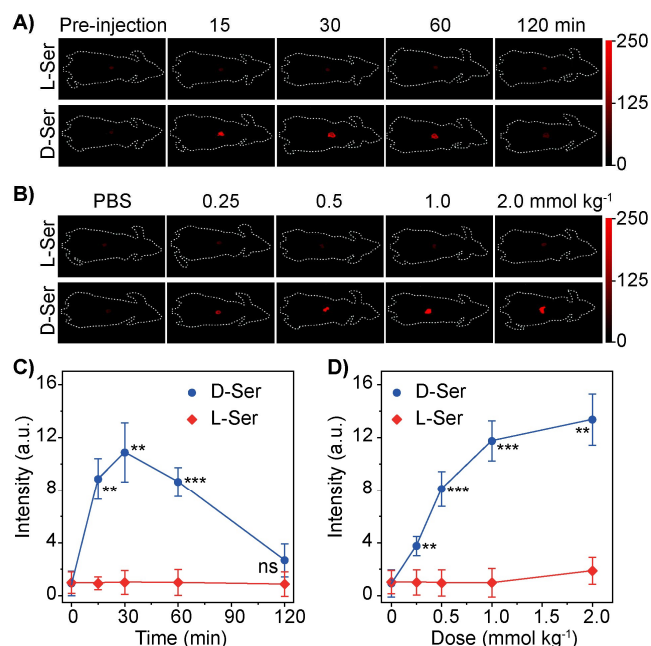
In PtTFPP-loaded UCNP, PtTFPP was used as the energy acceptor for  $O_2$  consumption sensing.<sup>[19]</sup> The emission intensities of free PtTFPP and PtTFPP-loaded UCNP in nitrogen-saturated solutions increased by approximately 2.2- and 6.2-fold, respectively, compared with those in normal solutions (Figure S10), strongly suggesting that the nanoprobes were more sensitive to  $O_2$  consumption than free dyes.<sup>[20]</sup> The luminescence quantum yield of PtTFPP-loaded UCNP was higher than that of free PtTFPP in nitrogen-saturated solutions, further confirming the improved  $O_2$  sensitivity (Figure S10).<sup>[21]</sup> Moreover, the overlap of the PtTFPP absorption and green band (510–560 nm,  $^2H_{11/2}$ ,  $^4S_{3/2} \rightarrow ^4I_{15/2}$ ) of UCNP suggested possible energy transfer (Figure 3B),<sup>[22]</sup> which was investigated by increasing the PtTFPP loading numbers (Figure S10). Under 980-nm excitation, we recorded a strong quenching of the characteristic green emission from UCNP in favor of the red PtTFPP emission at 625–750 nm in nitrogen-saturated solutions (Figure 3D). These findings verified efficient energy transfer between these two primary components, as further confirmed by the decrease in the lifetime (540 nm,  $^4S_{3/2} \rightarrow ^4I_{15/2}$  transition of  $Er^{3+}$ ) from 96.1  $\mu s$  without PtTFPP to 52.9  $\mu s$  with ~192 PtTFPP molecules per particle (Figure S10 and Table S5).<sup>[23]</sup> However, in sharp contrast, the enhanced red PtTFPP emission was barely observed in normal solution (Figure S10), suggesting that  $O_2$  consumption can be sensed using 980-nm excited red luminescence through energy transfer. Core-shell-shell UCNP were designed to maximize energy transfer efficiency (Figures S11 and S12). Particularly, the PtTFPP emission (625–750 nm) well matched the red UCNP band and CyD absorption, which

was purposely used to construct a synergistic energy transfer system.

The  $O_2$  and  $H_2O_2$  dual sensing and synergistic upconversion energy transfer in nanoprobes are illustrated in Figure 3E. The energies of the green and red bands of UCNP were accepted by PtTFPP and CyD, respectively. With D-Ser oxidation,  $O_2$  consumption and  $H_2O_2$  production induced enhanced PtTFPP emission and reduced CyD red absorbance, yielding a synergistic red luminescence (600–750 nm) enhancement for high-sensitive DAA detection with both excitation and emission in the NIR range.

Interestingly, the as-synthesized nanoprobes proved effective for *in vivo* noninvasive DAA detection. These nanoprobes were subcutaneously injected into the back of the mice, followed by intraperitoneal injection of D/L-Ser. The probe injection site rapidly brightened 15 min after the D-Ser injection, and the intensity reached its peak 30 min after the injection (Figure 4A). Compared with that before the D-Ser injection, the maximum luminescence intensity increased about 11 times (Figure 4C), indicating the nanoprobes' sensitive response to D-Ser *in vivo*. In contrast, L-Ser injection induced no marked changes in imaging and emission intensity, further indicating the strict stereoselectivity of the nanoprobes. Finally, the response of nanoprobes to D/L-Ser under various doses was further investigated. Upconversion luminescence signals were positively related to D-Ser doses in both imaging and emission intensity (Figure 4B and 4D). L-Ser did not trigger any significant fluorescence at high doses. In addition, we have preliminarily assessed nanoprobe toxicity using hematoxylin-eosin staining and serum biochemistry assay (Figure S13).

In summary, we have proposed NIR light-excited nanoprobes for DAA detection through synergistic upconversion energy



**Figure 4.** *In vivo* DAA detection (Ex., 980 nm, 0.5 W cm<sup>-2</sup>) by subcutaneously injecting nanoprobe (10.0 mg kg<sup>-1</sup>) into the back of the mice, followed by intraperitoneal injection of 100-μL D/L-Ser. Upconversion luminescence images of the nude mice and corresponding signal intensities acquired 120 min after D/L-Ser injection at a dose of 1.0 mmol kg<sup>-1</sup> (A and C), or acquired 30 min after D/L-Ser injection at varying doses (B and D). n = 3. \*\*p < 0.01, \*\*\*p < 0.001, and ns denotes not significant (p > 0.05), analyzed using Student's t-test. Data represent mean ± sd.

transfer. These nanoprobe exhibit desirable luminescence properties, such as both excitation and emission in the NIR range, small dimension, a wide detection range, a low detection limit, and a dual-sensing capability. By leveraging the deep tissue penetration of NIR light and the high stereochemical specificity of the nanoprobe, D-Ser levels in living cells and mice can be conveniently monitored with high sensitivity and selectivity, enabling noninvasive detection with time- and cost-saving. To the best of our knowledge, this is the first study focusing on UCNP for chiral molecular detection. We envision that these nanoprobe will find critical applications in brain-related biological and medical researches, particularly when considering essential physiological roles of DAAs and other chiral components,<sup>[24]</sup> as well as advantageous optical properties of UCNP.<sup>[25]</sup>

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## Conflict of interest

The authors declare no conflict of interest.

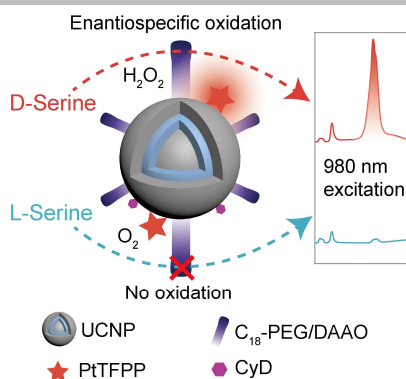
**Keywords:** lanthanide-doped nanoparticles • energy transfer • chiral detection • D-amino acid • near-infrared light

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## Entry for the Table of Contents

A novel nanoprobe for D-amino acid enantiospecific detection was proposed based on synergistic upconversion energy transfer, featuring a wide detection range, low detection limit, and *in vivo* noninvasive detection with high enantioselectivity.



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