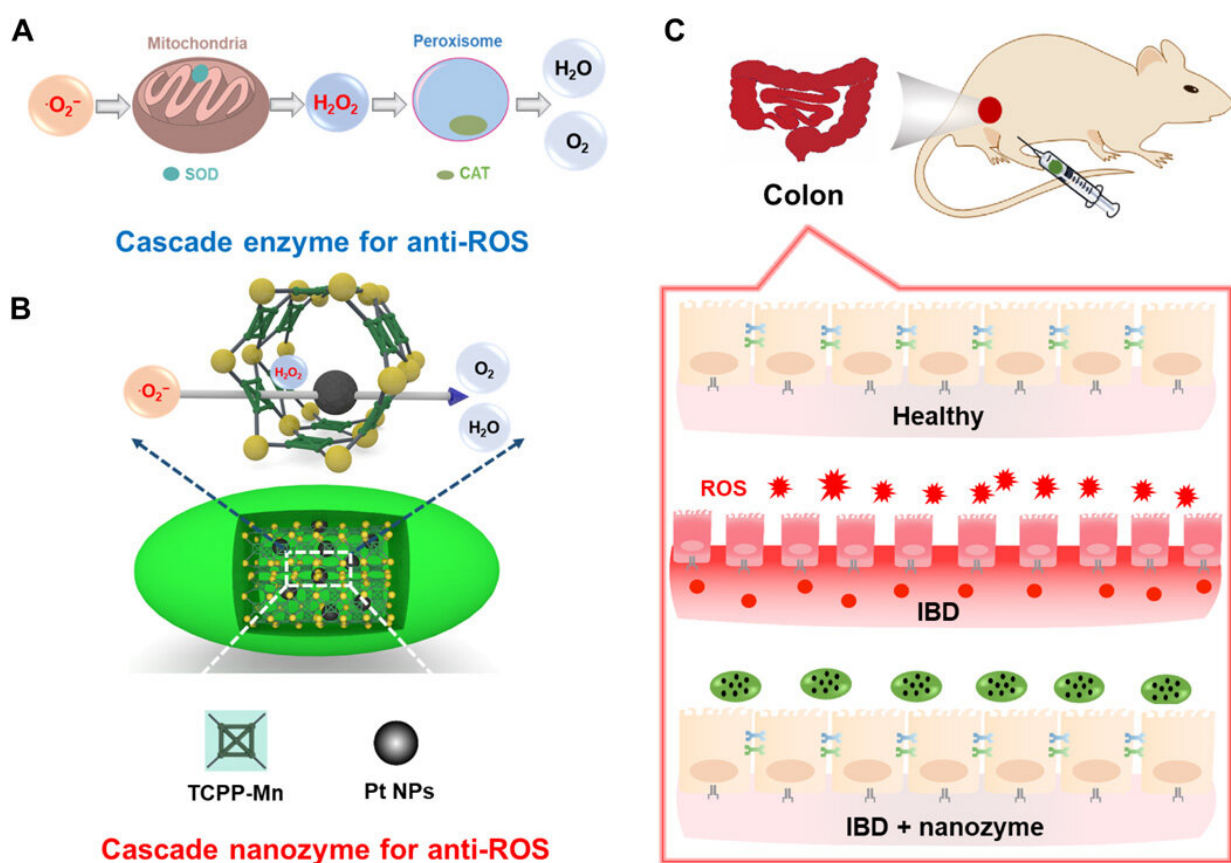


# Designer nanozymes for reactive-oxygen species scavenging anti-inflammatory therapy

July 27 2020, by Thamarasee Jeewandara



Schematic illustration of the design of an integrated nanozyme with cascade anti-ROS activity for IBD therapy. (A) Cellular cascade enzymes for anti-ROS. The therapeutic efficacy of such a system is limited because of the different subcellular locations of SOD and CAT enzymes and limited extracellular stability. (B) Constructing a cascade nanozyme for anti-ROS therapy by embedding Pt NPs inside PCN222-Mn MOF. Nanoscale proximity of catalytic

active sites promotes the cascade reactions. (C) The IBD of mice can be effectively relieved through treatment with the integrated cascade nanozyme. Credit: Science Advances, doi: 10.1126/sciadv.abb2695

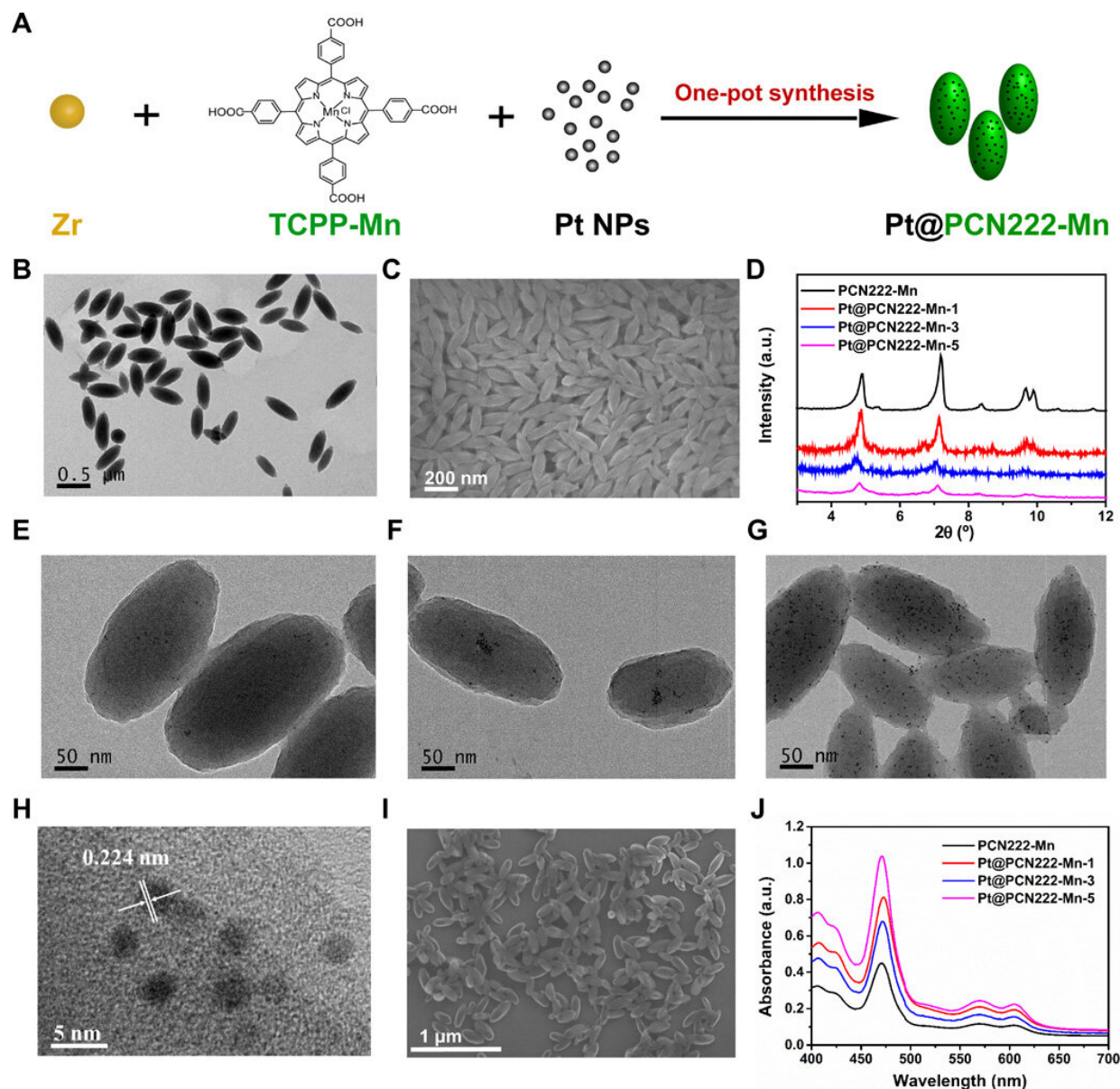
In a recent report, Yufeng Liu and a team of interdisciplinary researchers in China developed an integrated nanozyme cascade to eliminate excessive [reactive oxygen species](#) (ROS; oxygen free radicals). The nanozyme mimicked [superoxide dismutase](#) (a group of enzymes) and incorporated a manganese (Mn)-based [metal-organic framework](#) (MOF) to transform oxygen radicals to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Using in-lab and in vivo experiments, the team showed the ROS-scavenging potential of integrated cascade nanozymes. As proof of concept, they relieved two forms of [inflammatory bowel disorder](#) (IBD)—ulcerative colitis and Crohn's disease using cascade nanozymes as effective treatments. The study provided a new method to construct enzyme-like cascade systems and illustrate the promise of their efficient therapy to treat IBD in vivo. The work is now published on *Science Advances*.

During cascade [catalytic reactions](#) that occur in living organisms, multiple enzymes are combined inside subcellular compartments for accurate signal transduction and [effective metabolism](#). Such confined cascade reactions are advantageous compared to conventional multi-step reactions due to reduced diffusion barriers and enhanced local concentrations of intermediates for improved atom economy and reactions in total. Scientists have made substantial efforts to [mimic such cascade systems](#) on scaffolds, but their high cost and low stability have limited broad practical applications. As a result, researchers have explored enzyme mimics to understand and construct cascade reactions in the lab. In this work, Liu et al. detailed a single-component nanozyme-based cascade reaction system with [high activity](#) and demonstrated their role during the in vivo therapy of reactive oxygen species

(ROS)-associated inflammatory bowel disease (IBD).

## **Design, synthesis and characterization of the enzyme scaffold**

The team designed and synthesized an integrated superoxide dismutase (SOD) and [catalase](#) (CAT) mimetic cascade nanozyme and designated it as Pt@PCN222-Mn. To construct the scaffold, they introduced a SOD-like moiety of [Manganese \(Mn\) \(III\) porphyrin](#) and a CAT-like platinum nanoparticle within a nanoscale Zirconium (Zr)-based [metal organic framework](#) (MOF) named PCN222. The integrated construct (Pt@PCN222-Mn) showed enhanced ROS-scavenging activity to protect mice from ROS-related IBD, an incurable chronic disease as yet, and thereby to broaden the potential of cascade nanozymes for in vivo biomedical applications.



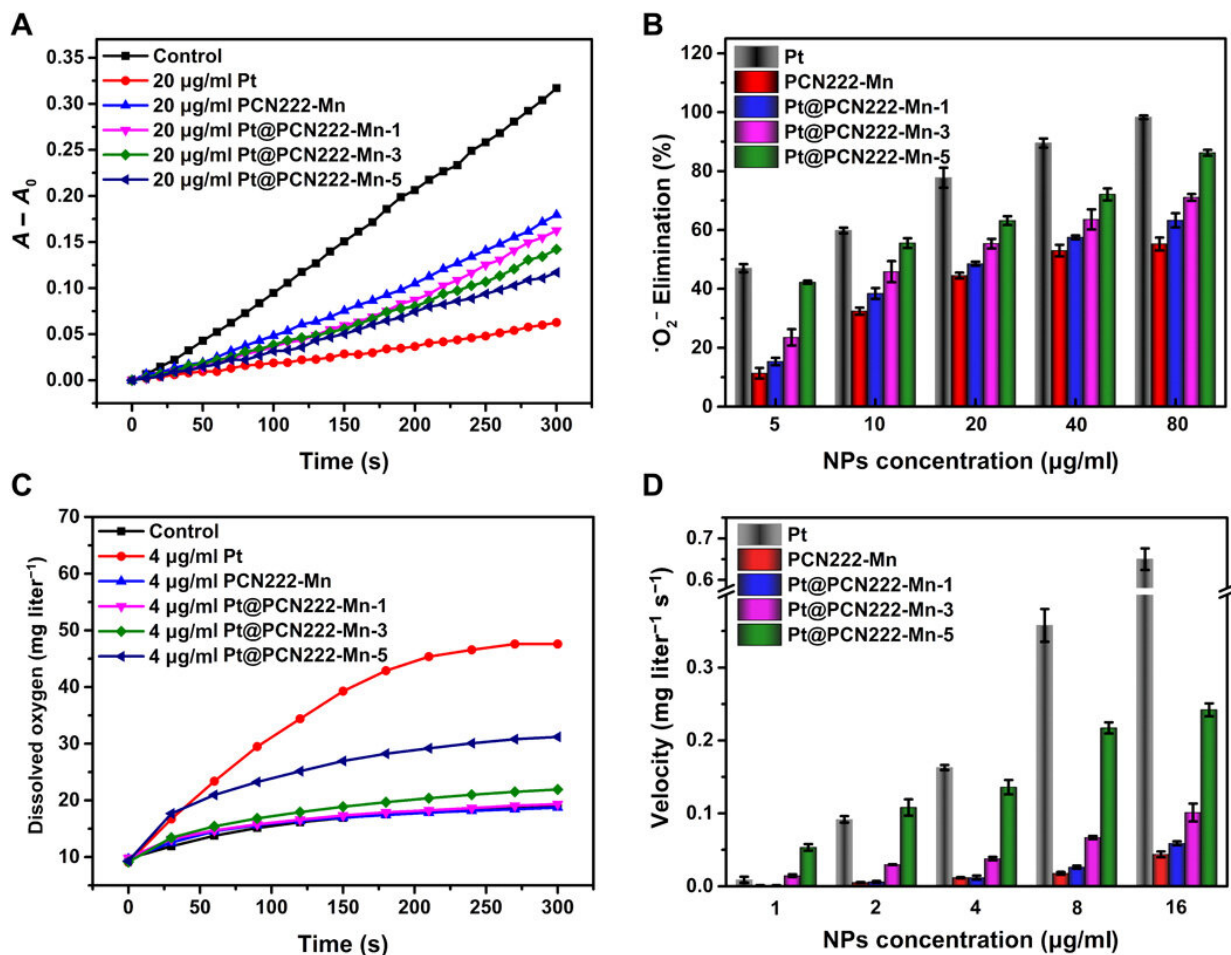
Synthesis and structural characterization of Pt@PCN222-Mn and related materials. (A) Synthesis procedure of Pt@PCN222-Mn. (B) Transmission electron microscopic (TEM) and (C) Scanning electron microscopic (SEM) images of PCN222-Mn. (D) Powder x-ray diffraction (PXRD) patterns of PCN222-Mn, Pt@PCN222-Mn-1, Pt@PCN222-Mn-3, and Pt@PCN222-Mn-5. TEM images of (E) Pt@PCN222-Mn-1, (F) Pt@PCN222-Mn-3, and (G) Pt@PCN222-Mn-5. (H) High-resolution TEM and (I) SEM images of Pt@PCN222-Mn-5. (J) Absorption spectra of PCN222-Mn, Pt@PCN222-Mn-1, Pt@PCN222-Mn-3, and Pt@PCN222-Mn-5. a.u., arbitrary units. Credit: Science

During the experiments, Liu et al. confirmed the successful synthesis of the preliminary manganese based constructs using [nuclear magnetic resonance](#), [Fourier transform infrared spectroscopy](#) and ultraviolet visible spectroscopic measurements. The team synthesized the component containing a nanoscale MOF and confirmed its formation with [transmission electron microscopy](#) (TEM) and [scanning electron microscopy](#) (SEM). The scientists then developed three cascade nanozymes and termed them Pt@PCN222-Mn-1, Pt@PCN222-Mn-3 and Pt@PCN222-Mn-5, respectively. Of these, Pt@PCN222-Mn-5 had a higher surface area compared to other anti-ROS nanozymes investigated thus far.

## **Investigating the catalytic activity of the cascade nanozymes**

Scavenging for oxygen radicals ( $\cdot\text{O}_2^-$ ) is the initial step of the anti-ROS cascade reaction, therefore the team investigated the catalytic activity of the synthetic constructs to monitor their capability to similarly eliminate oxygen radicals. The work highlighted the key role of manganese in [porphyrin](#) to mimic superoxide dismutase (SOD)-like activities of the different enzyme constructs, where Pt@PCN222-Mn-5 constructs showed the highest SOD-like activity among the enzyme mimics. The team confirmed the results using [electron paramagnetic resonance](#) (EPR) spectroscopy.



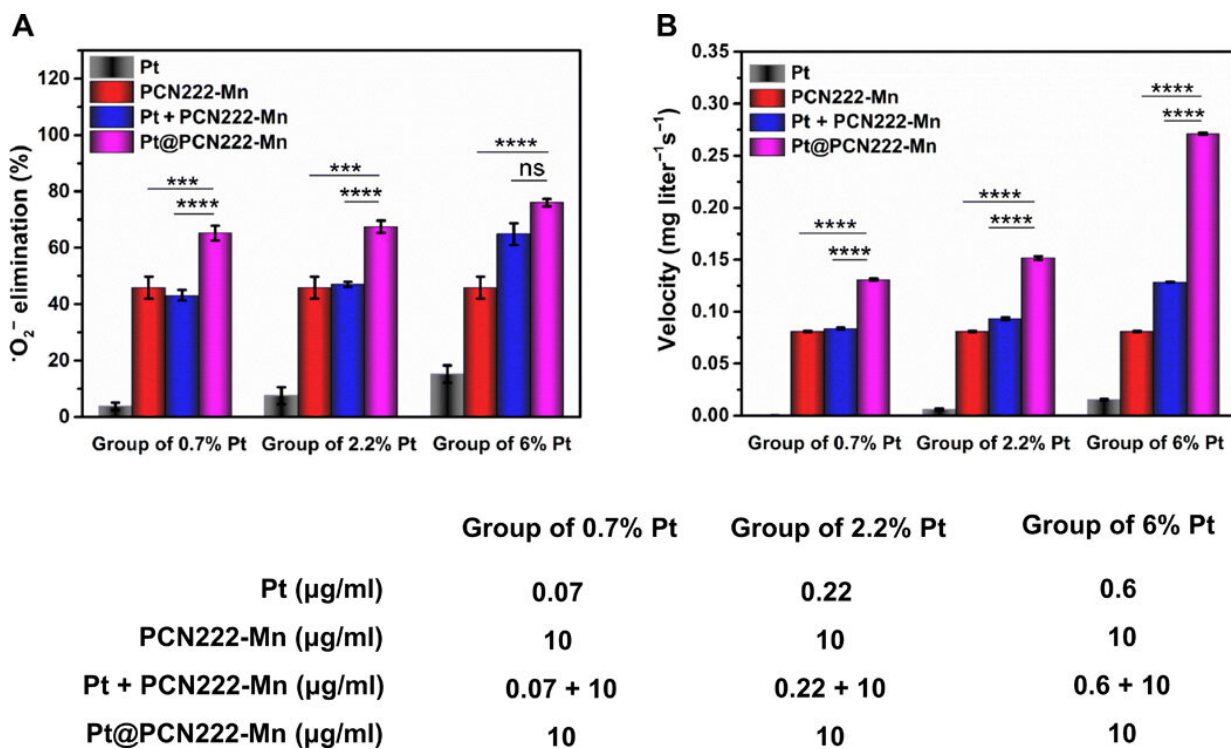


ROS-scavenging activities of Pt@PCN222-Mn and related materials. (A) Typical kinetic curves of  $A - A_0$  (550 nm) for monitoring the reduction of NBT with X and XO in the absence and presence of Pt, PCN222-Mn, Pt@PCN222-Mn-1, Pt@PCN222-Mn-3, and Pt@PCN222-Mn-5. (B) Dependence between the elimination efficiency of  $\bullet\text{O}_2^-$  and concentrations of nanozymes. (C) Typical kinetic curves of oxygen generation from the decomposition of  $\text{H}_2\text{O}_2$  (50 mM) in the presence of Pt, PCN222-Mn, Pt@PCN222-Mn-1, Pt@PCN222-Mn-3, and Pt@PCN222-Mn-5. (D) Dependence between the oxygen-production velocities in the first 60 s and concentrations of nanozymes. The data are shown as means  $\pm$  SD ( $n = 3$ ). Credit: Science Advances, doi: 10.1126/sciadv.abb2695

As a second crucial step in the ROS-scavenging cascade in biological environments, the CAT (catalase) enzyme catalyzed the decomposition of hydrogen peroxide ( $H_2O_2$ ) into water and oxygen. Liu et al. therefore monitored the CAT-like activities of the nanozymes by monitoring oxygen generated from decomposing hydrogen peroxide. As before, Pt@PCN222-Mn-5 showed the highest CAT-like activity among MOF-based enzyme mimics. Based on the results, Liu et al. confirmed the SOD-like activity to result from the manganese-bound moiety of the enzyme construct, while integral platinum nanoparticles were mainly responsible for the CAT-like activity.

### **Focus enzyme [Pt@PCN222-Mn-5](#) and in vivo anti-inflammatory therapy**

To fully comprehend the activity of the cascade nanozyme Pt@PCN222-Mn-5, the team investigated its synergistic SOD-like and CAT-like enzymatic activity and observed pronounced synergistic effects for the latter. The team chose the nanozyme for further investigations and tested its functionality with a cell line during cytotoxicity studies. At a concentration below 80  $\mu\text{g/mL}$ , the nanozyme did not show any cytotoxicity and demonstrated excellent reactive oxygen species scanning potential.

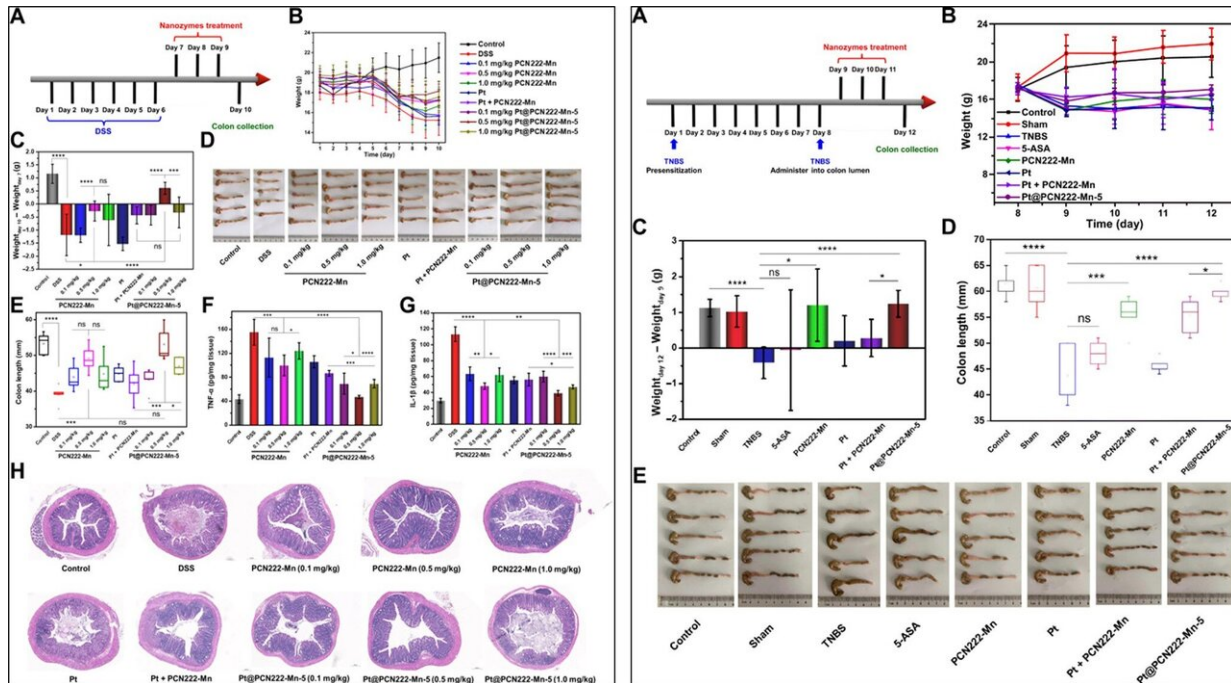


Synergistic ROS-scavenging activity of Pt@PCN222-Mn-5. (A) Elimination efficiency of  $\cdot\text{O}_2^-$  with different concentrations of Pt, PCN222-Mn, Pt + PCN222-Mn, and Pt@PCN222-Mn. (B) Oxygen-production velocities in the first 60 s, with different concentrations of Pt, PCN222-Mn, Pt + PCN222-Mn, and Pt@PCN222-Mn. The data are shown as means  $\pm$  SD ( $n = 3$ ). \*\*\*P

Based on the experimental results, Liu et al. conducted in vivo therapies to treat ulcerative colitis (UC) and Crohn's disease (CD) in mouse models of the disease. Since UC is a form of inflammatory bowel disorder that is [typically accompanied with](#) overproduced reactive oxygen species, the scientists tested the therapeutic effects of Pt@PCN222-Mn-5 together with existing medication for IBD treatment. The team administered the treatment via intraperitoneal injection to each mouse and observed successful therapeutic effects of Pt@PCN222-Mn-5 to relieve the UC disease state in mice. The team optimized the doses of the cascade nanozyme using several treatment groups and found the focus enzyme of interest to be the most favorable. When they similarly explored CD, another type of IBD using a disease-induced mouse model, the treatment strategy indicated greater efficacy for cascade nanozymes compared to traditional small-molecule



medications used in IBD treatment.



LEFT: UC therapy with Pt@PCN222-Mn-5. (A) Overall procedure of the animal experiment (DSS-induced colitis). (B) Daily body-weight development for 10 days. (C) Changes in body weight of mice before (day 7) and after indicated treatments (day 10). (D) Images of the colons and (E) the corresponding colon lengths in indicated groups. (F) IL-1 $\beta$  and (G) TNF- $\alpha$  levels in colon homogenates from indicated groups. (H) H&E-stained colonic sections of mice from indicated groups on day 10. The data are shown as means  $\pm$  SD (n = 5). \*P

In this way, Yufeng Liu and colleagues developed an integrated nanozyme to catalyze cascade reactions and eliminate reactive oxygen species (ROS). The integrated nanozyme had two spatially separated active sites to mimic superoxide dismutase (SOD) and catalase (CAT). Using in-lab experiments they showed the outstanding ROS-scavenging activity of the cascade nanozyme, their excellent biocompatibility and good aqueous dispersibility. The team established an inflammatory animal model to test the anti-ROS capacity of the cascade nanozyme in a biological organism and determined their superior therapeutic potential towards both [ulcerative colitis](#) (UC) and Crohn's disease (CD) models of inflammatory bowel disorder (IBD). The team optimized the concentration of the [nanozyme](#) to achieve effective relief of IBD in animal models. The work showed

excellent ROS-scavenging activities for inflammatory treatment and provides a promising method to construct nanozymes with multiple active sites for further applications in biomedicine.

**More information:** Yufeng Liu et al. Integrated cascade nanozyme catalyzes in vivo ROS scavenging for anti-inflammatory therapy, *Science Advances* (2020). DOI: [10.1126/sciadv.abb2695](https://doi.org/10.1126/sciadv.abb2695)

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