Metal-organic framework-capped nanotherapeutics for treatment of ischemic stroke

With the support by the National Natural Science Foundation of China, the research team led by Prof. Chen TianFeng (陈填烽) from Jinan University, recently reported the rational design of zeolitic imidazolate framework-8 capped nanotherapeutics (CeO_2@ZIF-8) for reversal of reperfusion-induced injury in ischemic stroke, which was published in *Science Advances* (2020, 6: eaay975).

Ischemic stroke, accounting for about 85% of strokes and having increasing mortality and long-term disability rates, is one of the most serious public health problems. In recent years, although intravenous thrombolysis and endovascular therapy have been widely used in clinics, however, in the process of reperfusion, blood flow restoration in the ischemic brain not only improves the oxygen supply but also induces the overproduction of reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, and hydroxyl radical, to cause the secondary lesion, called ischemic reperfusion-induced injury. Therefore, the design and development of agents with the potent ROS-scavenging activity and desirable physicochemical property for the treatment of ischemia strokes is urgently needed.

In order to inhibit the oxidative damage caused by reperfusion in ischemic stroke, the researchers explored a new *in situ* synthesis strategy of ZIF-8—capped CeO_2 NPs on the surface of CeO_2 with enhanced catalytic and antioxidative activities. The ZIF-8 encapsulation can control the size and surface charge of CeO_2, and slowly expose the active components of CeO_2 *in vivo*. Most importantly, ZIF-8 encapsulation can also effectively prolong the blood circulation time, reduce the clearance rate, enhance the penetration of BBB and improve the bioavailability. As a result, CeO_2@ZIF-8 NPs exhibit effective ROS-scavenging ability and protect PC12 neuronal cells from free radical—induced apoptosis. Meanwhile, this nanotherapeutics effectively inhibits the lipid peroxidation in brain tissues of middle cerebral artery occlusion (MCAO) model mice, and reduces the oxidative damage and apoptosis of neurons in brain tissue. What's interesting is that CeO_2@ZIF-8 also suppresses the inflammation- and immune response—induced injury by suppressing the activation of astrocytes and secretion of proinflammatory cytokines, thus achieving satisfactory prevention and treatment in neuroprotective therapy during ischemic stroke with high safety.

Taken together, this study not only provides a new *in situ* synthetic approach of synergistic nanotherapeutics by employing ZIF as bioactive surface decoration and CeO_2 NPs as functional core, but also sheds lights on the neuroprotective application mechanisms against reperfusion-induced injury in ischemic stroke.

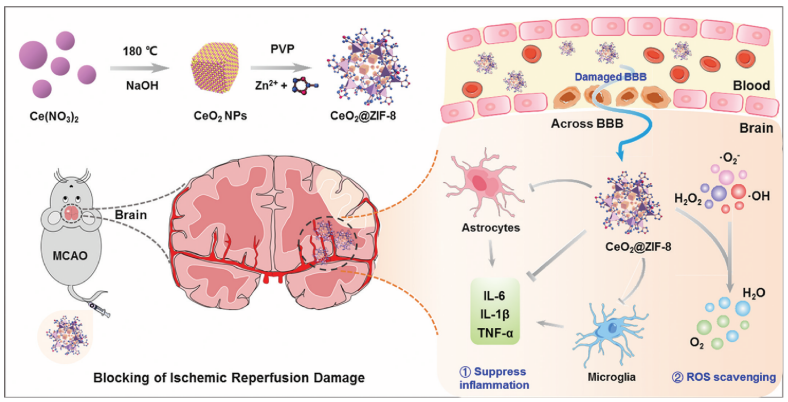

Figure *In situ* synthetic approach of CeO_2@ZIF-8 and its neuroprotective application mechanisms against reperfusion-induced injury in ischemic stroke.