

In vivo Iron-Based Coordination Assembly for Disease Diagnosis and Treatment

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Abstract

Advances in *in vivo* iron-based coordination assembly have enabled the simultaneous detection and treatment of iron-overload disorders. Specific interactions between local Fe^{III} and organic ligands (*e.g.*, indocyanine green and lecithin) facilitate magnetic resonance imaging with enhanced sensitivity and photoacoustic imaging with high contrast, thus overcoming the longstanding limitations of traditional iron quantification approaches. Moreover, enhanced iron depletion can also be achieved in murine genetic models of iron-overload disorders. These advances provide great promise in interdisciplinary leveraging of biology, medicine and materials science to design nanomedicines for addressing unmet clinical needs.

Keywords

In vivo assembly, iron-based coordination assembly, multimodal molecular imaging, theranostics.

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Supramolecular assembly is ubiquitous in living systems, thus enabling construction of a range of fascinating structures with intricate biological functions that meet the essential needs of organisms [1, 2]. A typical example is metal-organic coordination assembly: in the light-harvesting complexes of photosynthetic systems, chromophores with metal-ion centers are assembled *via* coordination with histidineimidazole in proteins, thus forming particular arrangements that absorb light energy [3]. Furthermore, phenolic-iron coordination bonding has been implicated in various properties (*e.g.*, mechanical and adhesive functions) of mussel byssus cuticle [4]. These natural phenomena may provide valuable inspiration for developing metal-organic-assembly materials and strategies for biomedical applications [5–7].

Given the unique chemistry and biological functions of iron, recent research endeavors have paid particular attention to iron-based supramolecular assembly *in vitro* and *in vivo*, aiming at the development of desirable agents and nanomaterials for disease diagnosis and treatment [8, 9]. In biological systems, iron ions are usually bound to molecules with electron-donating atoms (*e.g.*, oxygen and sulfur). This characteristic has inspired pioneering work on *in vitro* nanomaterial assembly using iron-based coordination, wherein interactions between Fe^{III} and various oxygen- and/or sulfur-containing therapeutics lead to the assembly of multifunctional

theranostic nanoparticles. For example, co-assembly of photosensitizers (sinoporphyrin sodium) and chemotherapeutics (doxorubicin) with Fe^{III} has enabled the formulation of metal-organic nanodrugs [10]. The reversible nature of coordination bonding has enabled biological barriers to nanoparticle delivery to be overcome. The metal-organic nanodrugs maintain their structures in the blood circulation under neutral pH (~ 4) but steadily decompose into small drug complexes under the acidic (pH 5.5) tumor microenvironment, thereby enhancing intratumor drug permeability for effective image-guided photodynamic/chemo combinational therapy.

To address the limited tissue penetration of photodynamic therapeutics, researchers have engineered metal-organic nanostructures for cancer sonodynamic therapy using ultrasound, whose deep tissue penetration triggers generation of reactive oxygen species (ROS), which kill cancer cells [11, 12]. Several smart cancer sonotheranostics have been fabricated through co-assembly of Fe^{III} and organic sonosensitizers with a sulfonate group [*e.g.*, meso-tetrakis (4-sulfonatophenyl) porphyrin, indocyanine green (ICG)], and other compounds and therapeutics [13, 14]. In a recent study, Lin *et al.* have reported microbubbles (MBs) loaded with Fe^{III}/ICG coordination complexes for cancer sonotheranostics [14]. Ultrasound not only triggers *in situ* conversion of MBs into small Fe^{III}/ICG nanocomplexes with better tissue penetration but

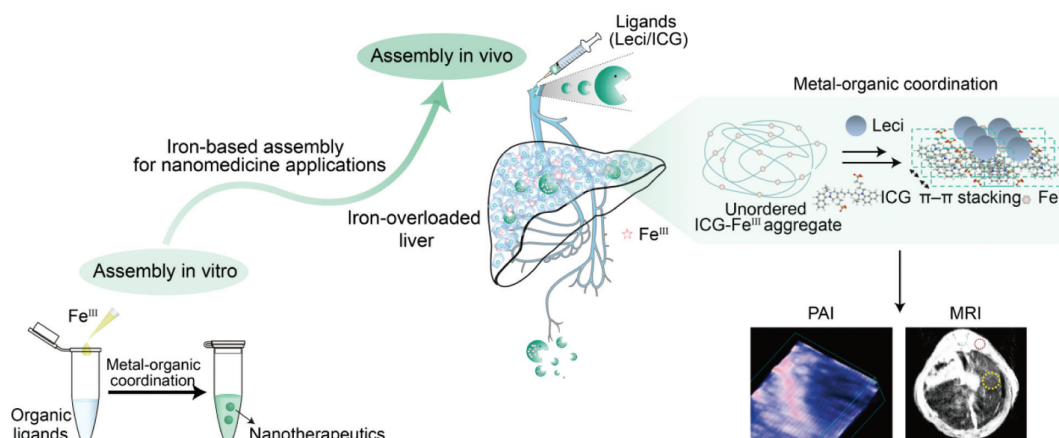


Figure 1 Schematic graph showing recent advances in iron-based coordination assembly, from nanotherapeutic assembly *in vitro* to *in situ* iron-based assembly *in vivo* for iron quantification and depletion [15].

also induces transient opening of leaky tumor vessels. These multiple benefits contribute to a 1.3-fold enhancement in tumoral deposition of Fe^{III}/ICG@MBs, thus increasing ultrasound-mediated ROS generation for tumor ablation.

Encouraged by the positive results regarding *in vitro* material assembly, Lin *et al.* subsequently applied *in vivo* iron-based assembly to noninvasive diagnosis and treatment of iron-overload diseases (Figure 1) [15]. Iron-overloaded organs have abundant Fe^{III} ions available for assembly with administered organic ligands and/or dyes. Such *in situ* assembly can alter iron and ligand forms (*e.g.*, from free to aggregated), thus amplifying alterations in molecular-imaging signals and enabling iron detection. Specifically, the authors have designed an elegant ICG/lecithin (ICG/Leci) system in which the interaction between ICG and local Fe^{III} in the iron-overloaded liver is accelerated by co-administered Leci, thus forming Fe^{III}/ICG/Leci aggregates. The free-to-aggregate conversion by the ICG/Leci system offers several notable advantages as multimodal theranostics: i) the Fe^{III}/ICG/Leci aggregation obstructs the water exchange rate with Fe^{III} and significantly decreases MRI signals in the iron-overloaded liver, thereby enabling the detection of Fe^{III} through MRI; ii) π - π stacking between ICG and Leci results in UV-visible absorption at 890 nm, thus allowing for Fe^{III} quantification through photoacoustic imaging with strong contrast and high sensitivity; iii) the Fe^{III}/ICG/Leci assembly alters the iron excretion pathway and facilitates twice the iron depletion of deferoxamine (a commonly investigated iron chelator), thus achieving better kinetics while avoiding toxicity.

This study provides a promising example of how iron-based coordination assembly can be leveraged to address unmet clinical needs. Liver biopsy, which remains the current gold standard for diagnosis of iron-overload diseases, is limited by sampling errors due to the nonuniform iron

distribution in organs, and the possible risk of hospitalization (1–3%) [16]. Although MRI is becoming a more acceptable approach, its low sensitivity restricts its accuracy in iron quantification. The developed ICG/Leci system, with its enhanced MRI sensitivity and superior photoacoustic-imaging contrast, may aid in addressing the above issues and providing accurate, noninvasive diagnosis of iron-overloaded liver. When coupled with augmented iron depletion, the ICG/Leci system offers a powerful imaging-guided therapeutic platform for iron-overload disorders. Interdisciplinary knowledge is highly desired for nanomedicine design, in which the properties of agents and nanomaterials are tailored according to biological and medical needs. This successful work is expected to inspire the development of more smart probes based on metal-organic assembly for diagnosis and therapeutic purposes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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