The ferritin nanocage is an endogenous protein that exists in almost all mammals. Its hollow spherical structure that naturally stores iron ions has been diversely exploited by researchers in biotherapeutics. Ferritin has excellent biosafety profiles, and the nanosized particles exhibit rapid dispersion and controlled/sustained release pharmacokinetics. Moreover, the large surface-to-volume ratio and the disassembly/reassembly behavior of the 24 monomer subunits into a sphere allow diverse modifications by chemical and genetic methods on the surface and inner cage of ferritin. Here, we critically review ferritin and its applications. We (i) introduce the application of ferritin in drug delivery; (ii) present an overview of the use of ferritin in imaging and diagnosis for biomedical purposes; (iii) discuss ferritin-based vaccines; and (iv) review ferritin-based agents currently in clinical trials. Although there are no currently approved drugs based on ferritin, this multifunctional protein scaffold shows immense potential in drug development in diverse categories, and ferritin-based drugs have recently entered phase I clinical trials. This golden shortlist of recent developments will be of immediate benefit and interest to researchers studying ferritin and other protein-based biotherapeutics.

**FERRITINS IN BIOThERAPEUTICS**

The hollow spherical core of ferritin allows the loading of various cargo. This is generally achieved via the mineral pores on the surface or pH-mediated disassembly/reassembly of the nanocage. There have been many investigations, mainly in anticancer therapy that attempted the targeted delivery of chemotherapeutic agents to tumors using ferritin as a delivery vehicle. Most of these studies resulted in successful tumor growth inhibition, superior efficacies, and diminished adverse effects compared to the free drug in both in vitro and in vivo models. Substantial progress has been made in the development of ferritin nanocages for use in drug delivery for cancer therapy. Doxorubicin-loaded ferritins have shown successful tumor growth inhibition in numerous mouse cancer models by many groups. In one example, Dox-loaded ferritin targeted and was internalized by transferrin receptor 1 (TfR1)-overexpressing tumor...
cells to mediate 10-fold higher intracellular levels compared to free doxorubicin. Moreover, the encapsulation of paclitaxel in ferritin showed potent apoptosis of MDA-MB-231 breast cancer cells in vivo models. This is an example of insoluble drug delivery via ferritin, with specific targeting to tumor cells alleviating the adverse effects of this chemotherapeutic agent. Similarly, gemcitabine was loaded onto ferritin and coadministered for photothermal therapy, showing effective adjunctive therapy against breast cancer models. Effective delivery of cisplatin was also achieved by ferritin, resulting in an improved therapeutic index of antiblastic therapy in an advanced, refractory gastric cancer model. Doxorubicin was also achieved by ferritin, resulting in an improved therapeutic index on the surface of ferritin nanocages. A successful attempt has been made to deliver this apoptosis-inducing ligand, IC\textsubscript{3} tumour growth inhibition, TR\textsubscript{1} transferrin receptor-1, PTT photothermal therapy, CD\textsubscript{3} carbon dot, ADNIR ADS-780 near-infrared (NIR) fluorescent dye, \textit{RB} rose bengal, \textit{DBN} 1,1-dioctadecyl-3,3,3-tetramethylindocarbocyanine iodide, CSCs cancer stem cells, PDT photodynamic therapy, \textit{PB} Prussian blue.

Table 1. Use of ferritin for chemotherapy.

| Encapsulated drug | Target disease      | Therapeutic effect                     | Ferritin | References |
|-------------------|---------------------|----------------------------------------|----------|------------|
| Cisplatin         | Melanoma            | Improved therapeutic index             | Human HFn| 8          |
| Co(II)            | Melanoma            | Tumor cell apoptosis                   | Human HFn| 34         |
| Doxorubicin       | Gastric cancer      | Tumor growth inhibition (91.1%) (TR\textsubscript{1} \textsuperscript{+} cells) | Human HFn| 35         |
| Doxorubicin       | Liver cancer        | Reduced cell viability in Hepa1-6 cells after PTT | Apoferritin (Au nanoshell) | 36         |
| Doxorubicin       | Breast cancer       | Tumor growth inhibition                | Human HFn (CD-modified) | 37         |
| Doxorubicin and ADNIR | Colon cancer    | Tumor growth inhibition (80.8%)        | Apoferritin | 38         |
| Doxorubicin (Cu(II complex) | Glioblastoma | Tumor growth inhibition (89.6%)        | Human HFn | 6          |
| Doxorubicin, \textit{RB} | Breast cancer      | Cell inhibition rate 83%               | Apoferritin | 39         |
| Epirubicin, \textit{DBN} | Breast cancer      | Killed 80% of cancer stem cells (PDT) | Apoferritin | 40         |
| Gefitinib         | Breast cancer       | In vitro tumor inhibition              | Human HFn | 41         |
| Gemcitabine (\textit{GEM}) | Breast cancer      | PB-Ft NPs damaged 4T1 cells            | Human HFn (PB-modified) | 7          |
| Paclitaxel        | Breast cancer       | Tumor growth inhibition (64.6%)        | Human HFn | 7          |

\textit{TGI} tumor growth inhibition, \textit{TR\textsubscript{1}} transferrin receptor-1, \textit{PTT} photothermal therapy, \textit{CD} carbon dot, \textit{ADNIR} ADS-780 near-infrared (NIR) fluorescent dye, \textit{RB} rose bengal, \textit{DBN} 1,1-dioctadecyl-3,3,3-tetramethylindocarbocyanine iodide, CSCs cancer stem cells, PDT photodynamic therapy, \textit{PB} Prussian blue.

In another interesting work, the phagocytosis-inducing peptide \textit{SIRPa} was displayed by doxorubicin-loaded ferritin to achieve an intrinsic vaccination effect. By the cross priming of effector CD\textsubscript{8} \textsuperscript{+} T cells, the simultaneous delivery of SIRP\textalpha{\textit{a}}s and doxorubicin, an immunogenic cell death (ICD)-inducer, achieved potent tumor growth inhibition in a melanoma model and even against tumor rechallenge in a colon cancer model. This study attempted to trigger the presentation of cancer cell neoantigens to the host immune system, facilitating the persistent amplification of antitumour T cells, which resulted in an especially interesting and effective therapeutic approach. There are also other interesting approaches using ferritin in addition to the abovementioned studies, such as a study by Seo et al. that proposed a thrombolytic ferritin expressing multivalent clot-targeting peptides and fibrin degradation enzymes for coadministration with chemotherapy. Similarly, a study by Lee et al. used \textit{y}-carboxyglutamic acid of protein C (PC-Gla) and thrombin receptor agonist peptide (TRAP) to treat acute inflammatory sepsis in vivo mouse models.

Table 2. Use of ferritin for immunotherapy.

| Immunotherapy agent | Target disease | Therapeutic effect | Ferritin  | References |
|---------------------|----------------|--------------------|-----------|------------|
| PD-L1\textsubscript{pep1} | All types | Promotion of PD-1 immune checkpoint | Human HFn | 42         |
| PD-1                | All types    | Promotion of T-cell activation in the lymph node | Human HFn | 43         |
| \textit{SIRP\alpha} | Colon cancer | Effective tumor growth inhibition, tumor-specific CD\textsubscript{8} \textsuperscript{+} T-cell activation | Human HFn | 13         |
| \textit{Trimer-mimetic TNF} | Colon cancer | Effective induction of apoptosis of tumor cells in vivo model | Human HFn | 10         |
| \textit{Superfamily ligand} | All types  | Effective induction of apoptosis of tumor cells in in vivo model | Human HFn | 10         |
| \textit{Trimeric TRAIL} | All types   | Tumor growth inhibition in breast and pancreatic cancer model | Human HFn | 11         |
| \textit{Tumor-specific antigens or IC} | All types | TSA-specific CD\textsubscript{8} \textsuperscript{+} T-cell activation | Human HFn | 11         |

\textit{PD-L1}\textsubscript{pep1} PD-L1 binding peptide, \textit{PD-1} programmed-cell death receptor 1, \textit{SIRP\alpha} signal-regulatory protein alpha, \textit{TNF} tumor necrosis factor, \textit{TRAIL} TNF-related apoptosis-inducing ligand, \textit{IC} immune checkpoint molecule, \textit{TSA} tumor-specific antigens.

**FERRITINS IN IMAGING AND DIAGNOSIS**

Ferritin nanocages have been readily modified to develop diagnostic agents for various imaging methods (computer tomography, CT/magnetic resonance imaging MRI). Fluorescent molecules can be incorporated or loaded as cargo at the same time as targeting peptides on the ferritin surface for targeting...
disease biomarkers. This would allow multimodal imaging techniques for ferritin-based agents with enhanced diagnostic accuracy, and the ferritin-based agents developed are listed below (Table 3).

Table 3. Use of ferritins in imaging and diagnosis.

| Application                      | Ferritin Cargo | Modification                                                                 | References |
|----------------------------------|----------------|-------------------------------------------------------------------------------|------------|
| Fluorescence imaging             | Short ferritin | Tumor-targeting proapoptotic peptide, GFP                                    | Genetic modification | 44 |
| CT imaging,                      | Horse spleen ferritin | Bi2S3                          | Incubation (Inlaying) | 7 |
| Peroxidase nanoenzyme            | Pyrococcus furiosus ferritin | Co2O4                          | Mineralization | 46 |
| Fluorescence imaging, MRI        | Human HFn      | Cy5.5, Fe3O4                    | Chemical conjugation, mineralization | 24 |
| SPECT, MRI                       | Human HFn      | Fe3O4, 125I                     | Mineralization, chemical conjugation (Iodogen method) | 18 |
| Peroxidase nanoenzyme            | Horse spleen ferritin | Prussian blue                   | Mineralization | 46 |
| MRI                              | Horse spleen ferritin | Mn(III)OOH                      | Mineralization | 47 |
| Fluorescence imaging, MRI        | Archeoglobus fulgidus ferritin | GQDs, Fe                         | Disassembly/reassembly | 48 |
| Fluorescence imaging, MRI        | Human HFn      | GFP, Fe3O4                      | Genetic modification, mineralization | 49 |
| Fluorescence imaging             | Human HFn      | RFP                             | Genetic modification | 21 |
| Fluorescence imaging             | Human HFn      | Indocyanine Green               | Disassembly/reassembly | 23 |
| Fluorescence imaging, PAI        | Human HFn      | Tricarbocyanine                 | Disassembly/reassembly | 19 |
| Fluorescence imaging             | Human HFn      | ZnF16PC, ZW800                  | Disassembly/reassembly, chemical conjugation | 6 |
| PET imaging, fluorescence imaging | Human HFn      | Cy5.5, 64Cu                     | Chemical conjugation, genetic modification, disassembly/reassembly | 50 |
| PET imaging, MRI, PAI            | Horse spleen ferritin | Melanin, 64Cu                   | Disassembly/reassembly, incubation | 51 |
| Fluorescence imaging             | Human HFn      | Cy5.5, BHQ-3                    | Bioconjugation, chemical conjugation, disassembly/reassembly | 50 |

CT computed tomography, MRI magnetic resonance imaging, SPECT single-photon emission computed tomography, GQD graphene quantum dot, GFP green fluorescent protein, RFP red fluorescent protein, PAI photoacoustic imaging, ZW800 zwitterionic near-infrared fluorophore, PET positron emission tomography, BHQ black hole quencher.

FERRITIN-BASED VACCINES IN IMMUNOTHERAPY

Ferritin-based vaccines have attracted considerable interest due to their potency and safety. Conventional vaccines composed of inactivated viruses or organisms carry the potential risk of triggering reversion, and thus, attempts to develop more immunogenic yet safe vaccines continue. Antigen display on the ferritin surface has many desirable features, such as the uniform presentation of 24 epitopes, as well as monodispersity and thermal and pH stability of the ferritin nanocage. Furthermore, the particle-mediated delivery of peptides has been shown to trigger more potent stimulation than soluble peptides.

Ferritin nanocages, due to their size (10–12 nm), can be readily taken up by dendritic cells (DCs) for migration to the lymph node to augment cellular and humoral immune responses. Due to these numerous advantages, ferritin-based vaccines have proven especially potent and can be applied not only to infectious diseases but also to cancer vaccines and vaccines for autoimmune diseases.

Representative ferritin-based vaccines target influenza, SARS-CoV-2 and Epstein–Barr viruses, and some have entered phase I clinical trials. Ferritin-based vaccines have proven biocompatible yet immunogenic with no significant adverse effects. However, the challenging features of ferritin-based vaccine development are nanoparticle heterogeneity, inadequate folding of antigens and intersubunit interactions resulting in antigen interference. Since antigens are encoded onto the ferritin protein...
scaffold, the self-assembled expression and purification of ferritin-based vaccines still require careful optimization. The selected clinical trials of ferritin nanocages currently in vaccine development are listed below (Table 4).

### FERRITINS IN CLINICAL TRIALS

Clinical trials with ferritin-based vaccines are in the early stages (Table 5). One example is the work of Kanekiyo et al.\(^{29}\), in which trimeric hemagglutinin (HA) was fused to the 3-fold axis of ferritin, giving the display of eight trimeric viral spikes. The ferritin-HA trimeric hemagglutinin (HA) was fused to the 3-fold axis of ferritin, providing many possibilities for modification. Ferritin has excellent biocompatibility and biodegradability and the hollow cage structure allows the delivery of various poorly soluble proteins, which can be achieved by one-step genetic modification or direct conjugation via chemical methods. Furthermore, the triggering of immunomodulatory responses. Additionally, the hollow cage structure allows the delivery of various poorly soluble or cytotoxic drugs by disassembly/reassembly or mineralization.

### Table 4. Ferritin-based vaccines.

| Application       | Ferritin                           | Antigen                  | Target                                | References |
|-------------------|------------------------------------|--------------------------|---------------------------------------|------------|
| DC-targeting      | P. furiosus                        | OT-1, OT-2               | T-cell receptors OT-1, OT-2           | 19         |
| Tumor targeting   | Human HFn                          | RGD4C peptide            | Tumor vasculature (αvβ3 integrin)     | 52         |
| Tumor targeting   | Human HFn                          | RFP                      | RFP-expressing melanoma               | 21         |
| Tumor targeting   | Human Fn                           | HPV16 E7 peptide         | MC38 colon cancer                     | 7          |
| Viral vaccination | H. pylori                          | S protein                | SARS-CoV-2                            | 28         |
| Viral vaccination | H. pylori                          | S protein                | SARS-CoV-2                            | 32, 53     |
| Viral vaccination | H. pylori-bullfrog hybrid          | RBD of S protein         | SARS-CoV-2                            | 15         |
| Viral vaccination | –                                  | S protein                | SARS-CoV-2                            | 23         |
| Viral vaccination | E. coli K12                        | hRID-RBD of S protein    | MERS-CoV                              | 54         |
| Viral vaccination | H. pylori-bullfrog hybrid          | RBD of HA                | Influenza virus                       | 55         |
| Viral vaccination | H. pylori-bullfrog hybrid          | gp350(D123)              | EBV                                   | 33         |
| Viral infection   | H. pylori                          | VP6                      | Rotavirus A                           | 7          |
| Bacterial infection | H. pylori-bullfrog hybrid        | OspA                     | B. burgdorferi outer membrane surface | 56         |

| Agent          | Disease     | Results                                           | Phase/Status | Trial number       | References |
|----------------|-------------|---------------------------------------------------|--------------|--------------------|------------|
| Ferritin-HA    | Influenza   | Seroconversion rates of 40% or 90% and ICON50 titers of 1×10³ or 3×10³ | I/Completed  | NCT03186781        | 31         |
| Ferritin-HA    | Influenza   | –                                                 | I/Completed  | NCT03814720        | 29, 30     |
| Ferritin-HA    | Influenza   | –                                                 | I/Ongoing    | NCT04579250        | 29, 30     |
| Ferritin-gp140 | SARS-CoV-2  | –                                                 | I/Ongoing    | NCT04784767        | 32         |
| Ferritin-gp350 | EBV         | –                                                 | I/Recruiting | NCT04645147        | 33         |

OT-1/2 CD8\(^+\) and CD4\(^+\) T-cell epitopes corresponding to res 257-264 and 323-339 of ovalbumin, respectively, RGD4C active peptide targeting the αvβ3 integrins, RFP red fluorescent protein, HPV16 human papillomavirus type 16, MC38 murine colon adenocarcinoma, S protein spike protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), MERS-CoV Middle East respiratory syndrome coronavirus, RBD receptor binding domain, HA hemagglutinin from influenza virus, gp350(D123) res 2-415 of the ectodomain of glycoprotein 350/220 from Epstein–Barr virus (EBV), VP6 intermediate capsid protein of human rotavirus A, OspA lipoprotein on Borrelia burgdorferi outer membrane surface when the bacteria reside in the tick gut.

### Table 5. Ferritin in clinical trials.

| Agent          | Disease     | Results                                           | Phase/Status | Trial number       | References |
|----------------|-------------|---------------------------------------------------|--------------|--------------------|------------|
| Ferritin-HA    | Influenza   | Seroconversion rates of 40% or 90% and ICON50 titers of 1×10³ or 3×10³ | I/Completed  | NCT03186781        | 31         |
| Ferritin-HA    | Influenza   | –                                                 | I/Completed  | NCT03814720        | 29, 30     |
| Ferritin-HA    | Influenza   | –                                                 | I/Ongoing    | NCT04579250        | 29, 30     |
| Ferritin-gp140 | SARS-CoV-2  | –                                                 | I/Ongoing    | NCT04784767        | 32         |
| Ferritin-gp350 | EBV         | –                                                 | I/Recruiting | NCT04645147        | 33         |

OT-1/2 CD8\(^+\) and CD4\(^+\) T-cell epitopes corresponding to res 257-264 and 323-339 of ovalbumin, respectively, RGD4C active peptide targeting the αvβ3 integrins, RFP red fluorescent protein, HPV16 human papillomavirus type 16, MC38 murine colon adenocarcinoma, S protein spike protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), MERS-CoV Middle East respiratory syndrome coronavirus, RBD receptor binding domain, HA hemagglutinin from influenza virus, gp350(D123) res 2-415 of the ectodomain of glycoprotein 350/220 from Epstein–Barr virus (EBV), VP6 intermediate capsid protein of human rotavirus A, OspA lipoprotein on Borrelia burgdorferi outer membrane surface when the bacteria reside in the tick gut.

**CONCLUSION**

Protein nanocarriers contribute numerous advantages to the field of disease diagnosis and drug development, and current approaches in diverse categories of biotherapeutics, immunotherapy, and vaccines will in no doubt provide therapeutic benefit. Ferritin has excellent biocompatibility and biodegradability and provides many possibilities for modification. The subunit structure of ferritin allows the uniform display of 24 peptides on its surface, which can be achieved by one-step genetic modification or direct conjugation via chemical methods. Furthermore, the triggering of a more potent response by the particle-mediated delivery of peptides is a well-known phenomenon in peptide delivery, as is the triggering of immunomodulatory responses. Additionally, the hollow cage structure allows the delivery of various poorly soluble or cytotoxic drugs by disassembly/reassembly or mineralization.

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through surface pores. Ferritin is an all-in-one multifunctional protein scaffold.

The major strength of ferritin nanocages in nanomedicine is in vaccine development. Three vaccines against influenza have entered phase I clinical trials, and one has provided positive results. The efficacy of ferritin-based vaccines has triggered investigations into optimizations for developing other ferritin-based vaccines in clinical trials. Ferritin holds great potential in disease diagnosis, prevention and therapy.

DATA AVAILABILITY
All data are included in this published article.

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