

Abstract

# Protein Nanocages for Anticancer Metal-Based Drug Delivery <sup>†</sup>

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<sup>†</sup> Presented at the 1st International Electronic Conference on Biomedicine, 1–26 June 2021; Available online: <https://ecb2021.sciforum.net/>.

Published: 31 May 2021

Supramolecular protein assembly, such as cages, rings, and tubes can be used as reaction vessels and molecular templates for applications in catalysis, imaging and drug delivery. Ferritin (Ft) is a member of ferroxidase family of enzymes that forms a spherical nanocage [1]. It sequesters iron by concentrating it in its internal cavity for storage and detoxification. Ft is very promising as a drug loading and releasing system since it is non-immunogenic, bio-compatible, highly stable, soluble in the bloodstream [2]. It can be internalized via Ft-binding receptors (like transferrin receptor 1 [3] or Scara5 [4]) that are over-expressed in a variety of malignant cells. Well established metallodrugs like cisplatin, carboplatin [5], a Pt-terpyridine compound [6], three different gold-based anticancer compounds (Auoxo3, Au2phen, Auoxo4) [7], [8–9] a bimetallic Pt-Au compound [10], a bimetallic Pt-As compound and a di-ruthenium complex [11] have been trapped within the Ft nanocages, taking advantage of the alkaline pH disassembly/reassembly protocol. The drug-loaded nanocomposites have been characterized by circular dichroism, to evaluate the protein secondary structure content upon drug encapsulation, and by UV-vis absorption spectroscopy, to assess the drug loading within the protein cage. ICP-MS allowed to quantify the amount of drug trapped inside the nanocage and to define metal/Ft stoichiometry, while X-ray crystallography unveiled the metallodrugs binding sites on the proteins structure and the nature of the interaction of the different compounds with Ft. The compounds often degrade upon encapsulation within the protein cage; metal-containing fragments coordinate Cys or His side chains. However, the coordination does not affect the overall cytotoxicity of the encapsulated anticancer agents, since many molecules of the metallodrugs remain trapped in the bulk within the inner core of the cage. Biological activity studies show that, even though the presence of the cage reduces the overall toxicity of the metallodrugs, the adducts of the selected compounds with Ft are generally more selective towards cancer cells than to non-malignant cells. Altogether these data indicate that encapsulation of metal-based drugs within Ft nanocages is a promising strategy to deliver these molecules to their final targets [12].

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