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IN A NUTSHELL

Bioinorganic supramolecular coordination complexes and their biomedical applications

Guillermo Moreno-Alcántar and Angela Casini

Department of Chemistry, Technical University of Munich (TUM), Garching bei München, Germany

Correspondence
G. Moreno-Alcántar and A. Casini, Department of Chemistry, Technical University of Munich (TUM), Lichtenbergstr. 4, 85748 Garching bei München, Germany
Tel: +49 89 289 13149 (GM-A and AC)
E-mails: g.moreno-alcantar@tum.de (GM-A); angela.casini@tum.de (AC)

(Received 15 September 2022, revised 21 October 2022, accepted 25 October 2022, available online 17 November 2022)

doi:10.1002/1873-3468.14535

Edited by Martin Högbom

The field of Bioinorganic Supramolecular Chemistry is an emerging research area including metal-based supramolecules resulting from coordination-driven self-assembly (CDSA), whereby metal ions and organic ligands can be easily linked by metal–ligand bonds *via* Lewis' acid/base interactions. The focus of this 'In a Nutshell' review will be on the family of supramolecular coordination complexes, discrete entities formed by CDSA, which have recently captured widespread attention as a new class of versatile multifunctional materials with broad biological applications including molecular recognition, biosensing, therapy, imaging and drug delivery. Herein, we provide a summary of the state-of-the-art use of these systems in biomedicine, with some selected representative examples, as well as our visions of the challenges and possible directions in the field.

Keywords: drug delivery; imaging; metallacages; self-assembly; supramolecular coordination complexes; therapy

Supramolecular chemistry, the chemistry "beyond the molecule" as described by Lehn [1] was cemented on his own, Pedersen's and Cram's works on the construction of molecules capable of recognizing and hosting smaller entities. This concept is reminiscent of the lock-key principle stated early by Emil Fischer [2] to describe the enzyme-substrate selective interaction. These non-covalent host–guest interactions have acquired further significance as synthetic supramolecular chemistry developed in recent decades, reaching high levels of complexity.

The design of supramolecular entities is, in part, driven by the creation of tailored empty spaces capable of hosting guests of interest [3]. Within this area, several supramolecular metal-based structures/molecules were explored. The directionality and dynamic nature of metal coordination and the possibility of designing directional multitopic ligands are the base for the synthesis of Metal–Organic Frameworks (MOFs) and supramolecular coordination complexes (SCCs). The former are highly crystalline porous materials formed by metal centres or clusters linked by bridging ligands forming a 3D network [4,5]. The research on the biomedical applications of MOFs is a rapidly growing field that has been revised thoroughly in recent works [6–9]. On the other hand, SCCs are discrete molecular arrangements [10,11], which can exist and maintain their structure and porosity also in solution and will be the focus of the present manuscript.

Supramolecular coordination complexes can be morphologically classified broadly into three main types: metallacycles, metallacages and helicates [12,13]. The

Abbreviations
BBB, blood–brain barrier; BODIPY, boron dipyrromethene; CDSA, coordination-driven self-assembly; DDS, drug delivery system; DNA, desoxyribonucleic acid; DSPE, 1,2-distearoyl-phosphatidylethanolamine; EPR, enhanced permeability and retention; G4, guanine quadruplex; MOF, metal–organic framework; NIR, near infra-red; PBLG, poly-γ-benzyl-L-glutamate; PDT, photodynamic therapy; PEG, polyethylene glycol; PET, positron emission tomography; PLGA, poly(lactic-co-glycolic acid); PS, photosensitizer; ROS, reactive oxygen species; SCCs, supramolecular coordination complexes; SCXRD, single-crystal X-ray diffraction; SPECT, single-photon emission computed tomography; TPE, tetraphenyl ethylene.

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metallacycles and metallacages are characterized by the existence of a cavity. In metallacycles, the void is delimited only in two dimensions by a ring-shaped coordination compound. In the case of metallacages, the cavity is limited in the three dimensions, with the combination of the ligands and metal centres defining the vertex, faces and edges around it. Instead, helicates are not necessarily porous, but are compact and robust structures with well-defined surfaces that have binding affinities for different target molecules. Perhaps, from this initial description, the reader can already depict the attractive features towards biomedical applications of these families of compounds. For instance, much of the attention given to the metallacages and metallacycles is related to their potential as carriers to host and further deliver cargos of pharmaceutical interest, either for therapy or imaging [11]. On the other hand, helicates have demonstrated the potential to stabilize biological structures, a promising feature for blocking biomolecular processes. Furthermore, the metal-based nature of SCCs provides them with additional valuable characteristics regarding their biomedical applications [10]. Depending on the metal ions and ligands in their structure, SCCs can be intrinsically cytotoxic and act as drugs, be luminescent and act as signalling agents and for molecular recognition, be radioactive for therapy and/or imaging, and can be catalytic to perform bio-orthogonal reactions. Finally, in the pinnacle of SCCs design, more than one type of metal centre and different functional organic moieties can be combined to generate tandem-multifunctional systems. This frontiers review presents, in a nutshell, the basic design principles and some of the most noticeable biomedical applications of SCCs. For deeper insights into structural and synthetic design principles, the reader is referred to extensive review works [14–17].

Supramolecular coordination complexes design

The synthesis of SCCs is based on the concept of coordination-driven self-assembly (CDSA) [18]. This process relies on the rational combination of ligands (Lewis bases) and metal centres (Lewis acids). On one hand, the ligands can be designed to display the donor atoms in certain positions, pre-programming their directionality to bond metal centres. On the other, each transition metal ion is characterized by well-defined preferred coordination numbers and geometries – i.e. the quantity and spatial orientation, respectively, of the coordination bonds it would form – as well as by given affinity for certain ligands. CDSA uses these characteristics to form structures with tailored dimensions, shapes and physicochemical characteristics (Fig. 1A). Two main types of CDSA can be defined, namely, (a) edge-directed self-assembly [17], in which bitopic ligands are used as edges to coordinate to the metal nodes of the self-assembled system – this is the principal strategy for the obtainment of metallacycles and helicates and it is also useful in the assembly of metallacages – and (b) face directed self-assembly combining 2D-multitopic ligands forming the planar faces of polyhedra in which the vertex are typically metal centres, evidently this kind of approach is most valuable in the building of cage-like structures (Fig. 1A) [26]. With these simple approaches, a virtually infinite number of SCCs can be obtained. Conveniently, their size, shape and functionality can be tailored by selecting the combination of ligands and metal centres to form them. However, CDSA is a dynamic process, and other criteria as the moderate stability of metal–ligand bonds, in comparison with typical covalent ones, and other kinetic and thermodynamic effects that can lead to possible competing structures have to be taken into account and frequently need to be sorted to achieve the designed structures [27].

The generation of new SCCs has been a hot topic in the last few decades. From the relatively simple earliest helicates of Lehn [19], and the metallasquares [20,21,28] and metallacages [21] reported in the early '90s (Fig. 1B), the number and variety of these systems have grown incrementally [29]. A plethora of structures with diverse geometries, sizes and shapes have been generated and the current synthetic developments achieve structural complexity that challenges the geometricians (Fig. 1C) [23], but also has granted access to systems including functional features, in particular, component design and functionalization [30]. Both coordination and organometallic metal–ligand bonds have been used to achieve scaffolds with different stability. Thanks to this progress, some applications, particularly in separation [25,31] and catalysis [24,32,33], have proven the huge potential of these types of supramolecular entities (Fig. 1D,E). In the next section, we briefly summarize some selected advances in the application of this type of system in biomedicine. More comprehensive reviews are available [10–12,15,34–38].

Biomedical applications of SCCs

Therapy, imaging and theranostic

Besides surgery, chemotherapy is the most common alternative to treat cancer [39]. The wide use of platinum-based drugs has inspired the investigation of diverse metal complexes as chemotherapeutic agents [40]. The metal-based nature of SCCs renders many of

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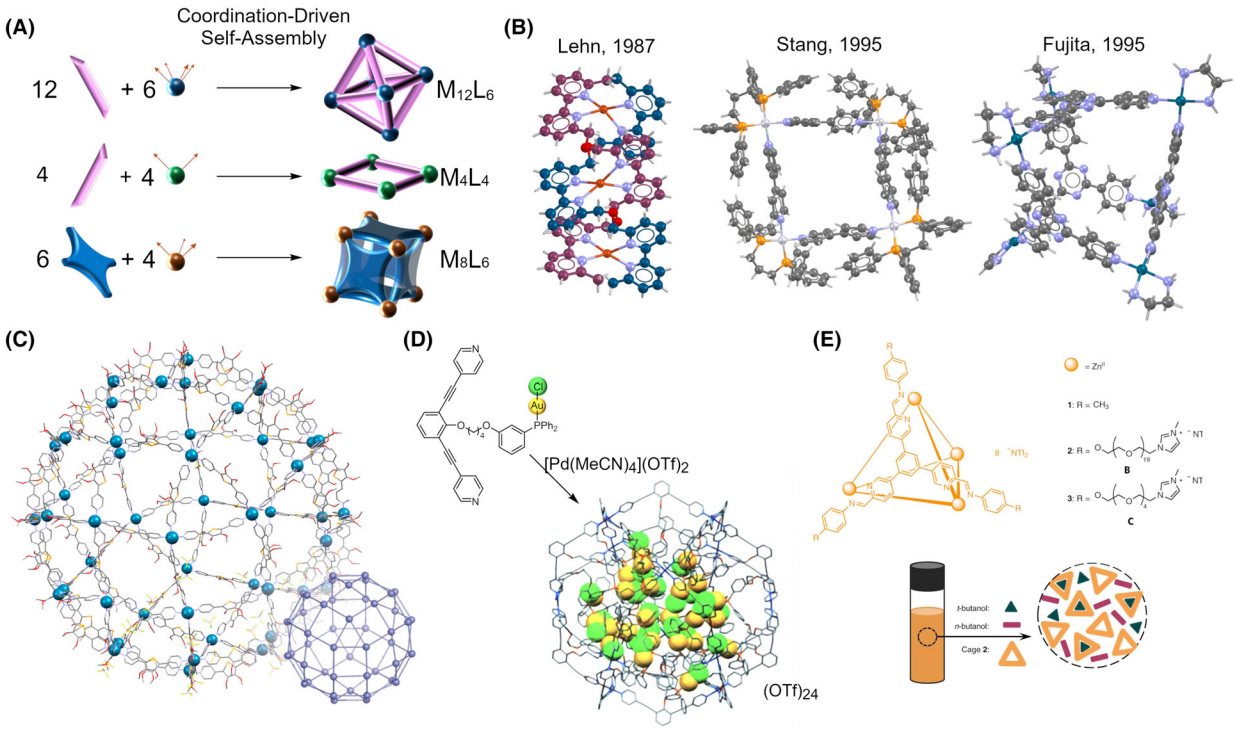

Fig. 1. (A) Coordination-driven self-assembly of: An edge-directed metallacage with linear ligands and metal centres featuring a square pyramidal coordination sphere (top); an edge-directed square metallacycle with the same linear ligand and metal centres with 90° angular coordination (medium); a face-directed metallacage with square ligands and metal centres with trigonal-pyramidal geometry (bottom). (B) Single-crystal X-ray diffraction (SCXRD) structures of pioneer examples of SCCs: A Cu_3L_2 helicate (L = 6,6′-bis(((6′-methyl-[2,2′-bipyridine]-6-yl) methoxy)methyl)-2,2′-bipyridine) [19], a Pt_4L_4 metallasquare (L = 4,4′-bipyridine) [20] and a Pd_6L_4 metallacage (L = 2,4,6-tris(4-pyridyl)-triazine) [21]. Balls and stick representations are generated in mercury [22]. The colour code is as follows: C, grey (burgundy or teal in the left panel); N, blue; O, red; P, orange; Cu, ochre; Pd, cyan; Pt, silver. (C) $Pd_{48}L_{96}$ metallacage (L = 4,4′-(3,4-dimethoxyselenophene-2,5-diyl)dipyridine) [23] the inset shows the unprecedented Goldberg tet-G(2,2) polyhedral structure of the compound. Adapted by permission from reference [23]. (D) $Pd_{12}L_{24}$ metallacage hosting a 1.1 M concentration of catalyst in the inner cavity. Adapted by permission from reference [24]. (E) Tetrahedral metallacages behaving as permanent porous ionic liquid applied in the separation of alcohols and fluorocarbons. Adapted by permission from reference [25].

them attractive as novel inorganic drugs [11,37,41–43]. Moreover, the ability of some SCCs to interact with pharmacologically relevant molecular targets in cancer treatment (e.g. nucleic acid structures) is also attractive and could work synergistically with the metal-related mode of action.

The most intuitive advantage of SCCs in chemotherapeutic applications is their capability to act as a multifunctional platform that contains multiple chemotherapeutic and imaging units within a single molecule. For example, Zhen and collaborators [44] designed a hexagonal metallacycle, composed of three cytotoxic bis-organoplatin linkers which assemble with three bipyridyl ligands (Fig. 2A) [44]. The resulting platform features well-defined size, geometry and Pt drug loading. The sole self-assembled structure showed cytotoxicity comparable to the anticancer drug cisplatin in different cancer cell lines. Furthermore, as the bipyridyl ligands can be functionalized, the metallacycle was used to integrate three Pt(IV) prodrugs into the structure increasing remarkably the cytotoxicity. Importantly, the bioactivity was proven to be due to the self-assembled molecule itself, as the mixture of the non-assembled components did not perform in the same way (Fig. 2A) [44]. Overall, this is a representative example of a supramolecular platform with well-defined size, geometry and Pt drug loading.

In the case of three-dimensional SCCs, these are endowed with the capability to recognize and interact with targets of interest. Remarkably, several SCCs have shown promising behaviours as stabilizers for guanine–quadruplex (G4) structures. These non-canonical secondary DNA structures are present in the promoter and telomer regions of oncogenes and their stabilization has been identified as a strategy to control the transcription and inhibit telomerase activity,

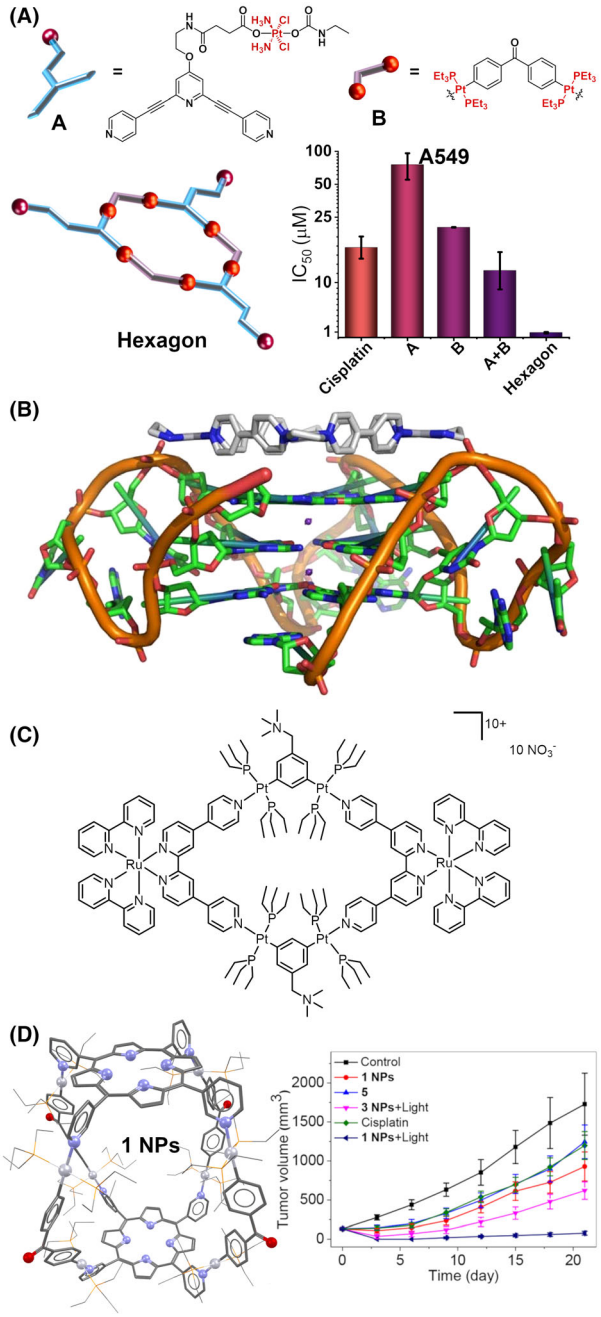

Fig. 2. (A) Self-assembled and cytotoxic hexagonal metallacycle bearing Pt(IV) prodrug units; the inset plot shows the superior cytotoxicity of the assembly in A549 lung cancer compared to that of its components and cisplatin [44]. Adapted by permission from reference [12]. (B) Interaction of Pt(II) metallasquares with telomeric F21T G4. Adapted by permission from reference [45]. (C) Structure of the metallacycle containing $Ru(bipy)_3$-like metalloligands applied in PDT [46]. (D) SCXRD structure of the porphyrin-based cage used as dual cytotoxic/PS agent [47]. The plot shows the efficient tumour-grown suppression obtained by the combination of chemotherapeutic and PDT properties of cage **1**. Adapted by permission from reference [47]. Balls and stick representations are generated in mercury [22]. The colour code is as follows: C, grey; N, blue; O, red; P, orange; Pt, silver. H atoms were omitted for clarity.

processes of great interest in the treatment of cancers [48]. G4s are known to interact preferentially with planar, aromatic and positively charged molecules. Thus, SCCs presenting extended planar ligands have good possibilities of acting as G4 binders. For example, Pt (II) metallasquares assembled with 4,4′-Bipyridine [45] ligands (Fig. 2B) have been shown to stabilize the telomeric F21T G4 structure and inhibit telomerase activity in cancer cells. Other metallacycles [49–52] and some helicates [53] have also been studied as G4 stabilizers. More recently, stabilization of G4s by metallacages has been achieved; in this case, the placement of aromatic-planar domains constituting the faces of the cage can promote interactions with the nucleic acid structures. That is the case of the tetrahedral $[Ni_4L_6]^{8+}$ (L = 4,4′-bis(2-pyridylimine)biphenyl), which was shown to importantly stabilize F22T G4 structures [54].

Besides the cytotoxic potential of SCCs, their design can be directed to endow them with other interesting therapeutic properties, such as achieving photodynamic therapy (PDT). PDT is a non-invasive procedure based on the generation of reactive oxygen species (ROS) at the cancer site by the activity of photosensitizers (PS) that generate ROS as a response to photoexcitation, ideally by red or IR irradiation [55]. The *in situ* generated ROS causes oxidative stress that can lead to apoptosis in cancer cells. As representative examples, $[Ru(bipy)_3]^{2+}$ (bipy = bipyridine) compounds are among the most efficient available photosensitizers. Stang and collaborators [46] studied a Pt(II)-based metallacycle featuring $Ru(bipy)_3$-like metalloligands (Fig. 2C). The assembly efficiently produced singlet oxygen and could undergo two-photon excitation (800 nm), allowing its application in A549 lung cancer-bearing xenograft models *in vivo*. The mice treated with the metallacycle underwent tumour growth suppression only in presence of light irradiation, and the treatment was proven low systematic toxicity. Besides Ru(II) compounds, porphyrins are also benchmarking PSs for PDT and can be designed as panels in SCCs [56]. Noteworthy, porphyrin-containing metallacages are intrinsically cytotoxic [57,58]. Furthermore, their use as PS can lead to remarkable results in terms of cancer treatment. For example, porphyrin metallacage-loaded polymeric nanoparticles can eradicate tumours in 4T1 orthotopic

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breast cancer-bearing mice after a single treatment by a combination of their chemotherapeutic and PDT effects (Fig. 2D) [47]. Besides cancer treatment, the use of SCCs as PS has been recently proposed also in the treatment of rheumatoid arthritis [59], and bacterial infections [60].

Supramolecular coordination complexes can be designed to include in their structure ligands, metal centres or functional groups that provide them with luminescent properties useful to study their cellular accumulation, sub-cellular distribution and overall fate in biological systems by optical imaging methods [61]. Using the intrinsic luminescence of lanthanides [62,63], polyethylene glycol (PEG)-functionalized europium-based helicates proved to stain living cells in a concentration-dependent manner without affecting their viability (Fig. 3A) [64]. In a different approach, the tethering of luminophores in the outer structure of Pd_2L_4 metallacages (L = 3,5-bis(3-ethynylpyridine)phenyl) has been used to unravel their intracellular distribution and uptake mechanisms [68–70]. Organic luminophores can also be modified to generate luminescent ligands capable to assemble into SCCs, as demonstrated by the boron dipyrromethene (BODIPY)-based metallacycles reported by Gupta et al. [71,72].

Benefiting from their host–guest chemistry, metallacages can also be used to encapsulate and transport imaging agents [65]. As an example, fluorescent dyes have been encapsulated in tetrapyridyl-panelled metallacages and subsequently tracked in cancer cells by fluorescence microscopy; furthermore, the functionalization of the cages with morpholine has shown to direct the dye-loaded cages selectively to lysosomes (Fig. 3B) [65]. The possibility to change the encapsulated dye allows a selection of the label wavelength while preserving the targeting unit [65]. Besides fluorescence imaging, metallacages can serve for the encapsulation of radioactive molecules such as pertechnetate $[^{99m}Tc]TcO_4^-$, a γ-emitter used in single-photon emission computed tomography (SPECT) imaging. Hosting the anion in a kinetically robust tetrahedral Co_4L_6 cage (L = 5-(5-bipyridine-2,2′-yl)-2,2′-bipyridine), lead to a radical change in its biodistribution, diminishing thyroid accumulation observed with the free anion (Fig. 3C) [66].

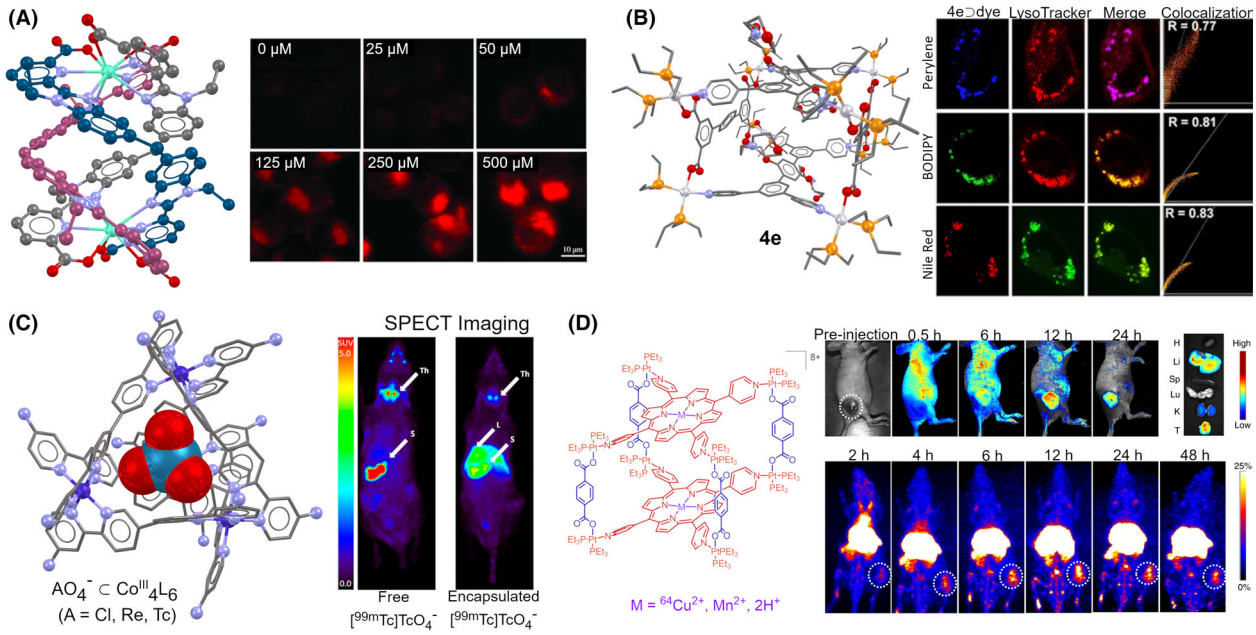

Fig. 3. (A) SCXRD structure of Eu_2L_3 helicate [63] and concentration-dependent emission microscopy in living HeLa cells reached by a PEG-functionalized analogous. Adapted by permission from reference [64]. (B) SCXRD representation of morpholine functionalized metallacage used to transport different dyes for the staining of lysosomes and *in-vitro* fluorescence images of the different transported dyes. Adapted by permission from reference [65]. (C) SCXRD diagram of the Co4L6 metallacage capable of transport $[^{99m}Tc]TcO_4^-$ for SPECT imaging and different distribution profile observed in comparison with the free anion. Adapted by permission from reference [66]. (D) Multimodal theranostic metallacage capable of different imaging techniques together with NIR fluorescence (top) and PET (bottom) imaging of tumour-bearing nude mice following i.v. injection of metallacage-polymer nanoparticles. The white circles denote the tumour site. Adapted by permission from reference [67]. SCXRD balls and stick representations generated in mercury [22]. The colour code is as follows: C, grey (also burgundy and teal in panel a); N, blue; O, red; P, orange; Co, purple; Tc, cyan; La, turquoise; Pt, silver; H atoms were omitted for clarity.

The multifunctional capabilities of self-assembled systems are probably their biggest strength, and it has prompted the next generation of theranostic systems. For example, the group of Zhang reported the synthesis of a platinum-based biotinylated metallacage including tetraphenyl ethylene (TPE) luminophores [73]. Although the system showed moderate cytotoxicity, it was highly selective towards biotin receptors overexpressing cancer cells. The system could also be visualized in cancer cells *in vitro* thanks to TPE's motion-restricted emission [73]. The direct targeting-functionalization of metallacages has both *pros* and *cons*: while the possibility of generating multivalent systems with a high density of targeting units per therapeutic molecule is considered advantageous [74], on the other hand steric and electronic factors may decrease the stability of the resulting SCCs in solution. In order to generate more efficient delivery systems based on SCCs, their integration in nanoparticulated systems, endowed with passive targeting capability *via* the enhanced permeability and retention (EPR) effect, has been explored. The group of Stang designed TPE-bearing metallacages which are highly emissive and possess alkyl chains promoting their self-assembly within the hydrophobic core of PEG/1,2-distearoyl-phosphatidylethanolamine (DSPE) copolymer nanoparticles [75]. Further biotin-functionalized nanoparticles were also generated showing cytotoxicity in biotin receptor-positive cancer cells. The systems showed enhanced antitumor activity and lower toxicity than typical platinum-based drugs in hepatocellular carcinoma (HeLa) xenograft models [75]. A more sophisticated system came using porphyrin-containing metallacages [67]. The porphyrin conferred the metallacages ROS generating capabilities and emission in the near-IR (NIR) region (desirable for imaging in tissues). Furthermore, the chelating structure of the porphyrin ligand was exploited to include metal ions for further imaging application, i.e., ^{64}Cu for positron emission tomography (PET) or Mn(II) for magnetic resonance imaging (Fig. 3D) [67]. While the metallacages showed moderate cytotoxicity *in vitro*, the combination of chemotherapy and PDT displayed synergistic efficacy both *in vitro* and *in vivo*. In particular, the formulation was capable of suppressing orthotopic breast (4T1 and LM3) tumour models [67]. Very recently, a different approach has attained second NIR (1005 nm)-emitting metallacages which were loaded in PEG–PLGA polymeric particles [76]. Second NIR emitters are ideal for fluorescent imaging due to in-depth penetration of the radiation and can be applied also as photothermal sensitizers for anticancer therapy [55,77].

Drug delivery

In 2008, the "complex in a complex" strategy for delivering drugs into cancer cells was first proved by Therrien and coworkers. In their first work, a water-soluble Ru-clipped cage featuring tpt (2,4,6-tri(pyridine-4-yl)-1,3,5-triazine) panels was synthesized and used as a host for square planar metal complexes (Fig. 4A) [78]. In their following works, harvesting from the high affinity of this type of hosts for aromatic pyrene molecules, strong DNA-intercalators, this type of cage was proposed to host and deliver various pyrene-functionalized molecules such as the antimetastatic Floxuridine (Fig. 4A) [79–81]. Similar systems have been used to encapsulate photosensitizers for PDT, e.g., porphin [82].

Another family of prominent SCCs applied as drug delivery systems are those based on the cationic Pd_2L_4 scaffold (L = bitopic monodentate N-donor ligand). These systems attracted attention from the initial observation of Crowley and coworkers regarding the capabilities of cationic Pd_2L_4 cages (L = 2,6-bis(pyridine-3-ylethynyl)pyridine) to encapsulate cisplatin in their cavities (Fig. 4B) [83]. However, the host–guest complex was not preserved in an aqueous environment. Later on, Casini and coworkers reported that the stability of the drug-cage complex can be improved by modifying the ligand structure, replacing the central pyridine ring with phenyl units (L = 3,5-bis(3-ethynylpyridine)phenyl, Fig. 4B), to reduce the hydrophilic character of the internal cavity [84]. Thus, cisplatin encapsulation was favoured over the occupancy of the cavity by water molecules or other polar solvents. Notably, most of the reported metallacages and their precursors were non-toxic in healthy rat liver tissue *ex vivo*, making them suitable for application as drug delivery systems [84]. Based on the latter cage

Fig. 4. (A) "Complex in a complex" tpt-Ru-clipped metallacage (tpt = (2,4,6-tri(pyridine-4-yl)-1,3,5-triazine)) containing oxalate compounds and the same system hosting the pyrene-functionalized floxuridine. (B) Structure of the cationic Pd_2L_4 (X = C or N) used to host and deliver cisplatin, together with the SCXRD structure of the inclusion complex carrying two cisplatin molecules. The cage is represented in balls and sticks and the cargo as a space fill model, the image was generated in mercury [22]. The colour code is as follows: C, grey; N, blue; O, red; Cl, green; Pt, silver. H atoms were omitted for clarity. (C) SEM image of the polymer nanoparticles carrying cytotoxic metallacages (MNPs), together with their application for NIR fluorescence imaging in cells (laser confocal microscopy) and in cancer-bearing mice (time-dependent fluorescence). The plot shows the increased survival when the system was used as PS for PDT in a murine model. Adapted by permission from reference [88].

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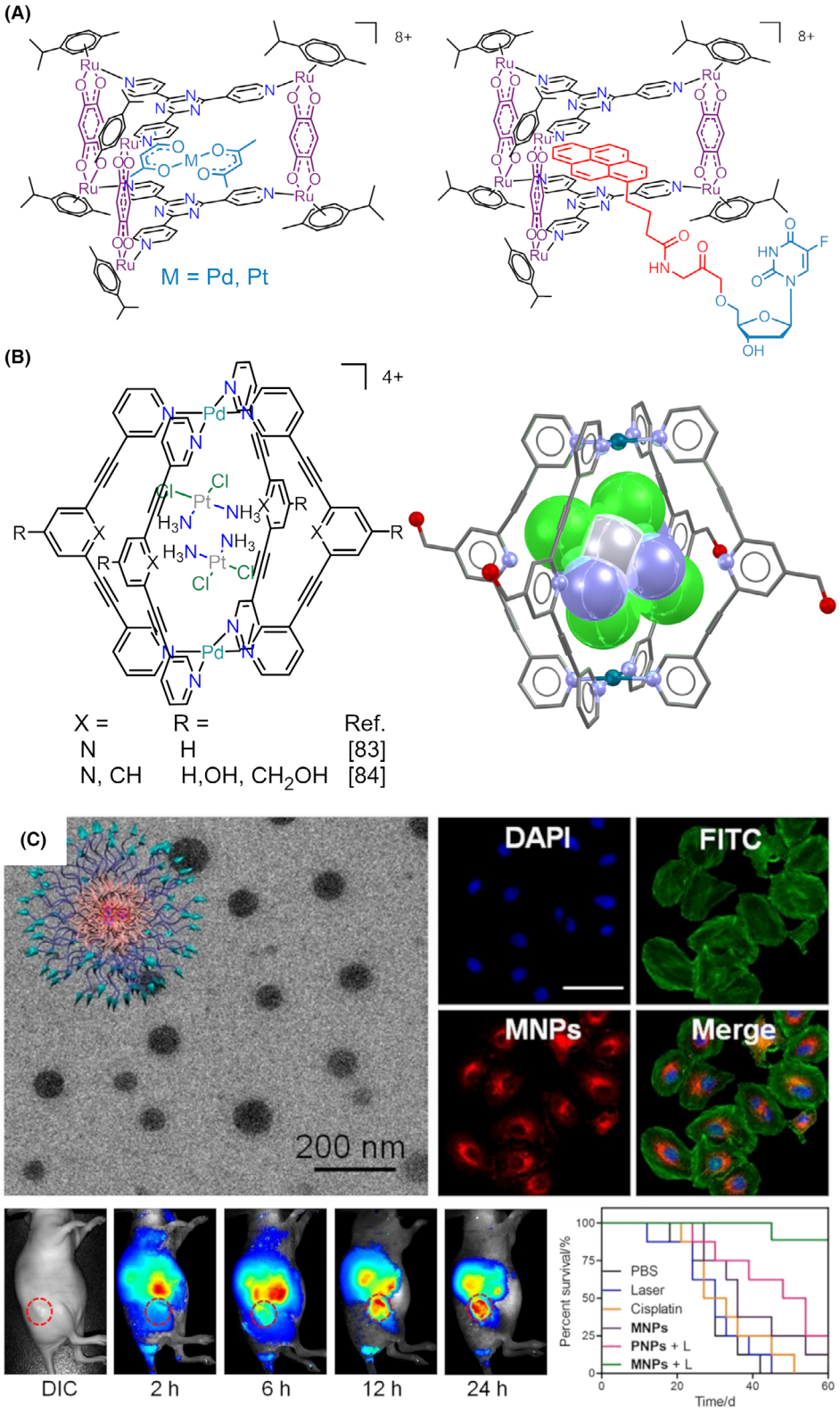
(A)
8+
M = Pd, Pt
8+
(B)
4+
X = R = Ref.
N H [83]
N, CH H,OH, CH2OH [84]
(C)
200 nm
DAPI
FITC
MNPs
Merge
DIC
2 h
6 h
12 h
24 h
Percent survival/%
Time/d
PBS
Laser
Cisplatin
MNPs
PNPs + L
MNPs + L

scaffold, a bioconjugation strategy for the exo-functionalization of these systems with peptide vectors was developed to achieve targeted delivery of cisplatin to cancer cells [69,85]. Different exo-modifications of the L ligands enabled also the introduction of imaging groups as discussed above [68,86]. Furthermore, radioactive pertechnetate was encapsulated in Pd_2L_4 cage exo-functionalized with PepH3 [86], a blood–brain barrier (BBB)-translocating peptide derived from dengue virus capsid protein [87]. The formulation was demonstrated to cross the BBB *in vitro* and *in vivo*. These results highlight the versatility of SCCs to be used as multifunctional platforms and the applicability of their host–guest chemistry to living systems.

Recently, Stang and collaborators used a multicomponent self-assembled cytotoxic cage to encapsulate octaethylporphine as PS for PDT [88]. In order to ensure the stability of the host–guest complex and enhance its solubility in aqueous media, the metallacage was embedded in a polymeric nanoparticle matrix consistent in self-assembled PED-poly-γ-benzyl-L-glutamate (PBLG) micelles, which were also functionalized with RGD peptides as active targeting moieties (Fig. 4C) [88]. The use of the combined cytotoxic cage with PDT in cisplatin-resistant ovarian (A2780cis) tumour-bearing nude mice importantly inhibited tumour growth and increased the survival time with respect to the different control groups used (including cisplatin and non-PDT treated groups). The results showed that the cages benefited from both the EPR effect and active targeting ability, and considerably prolonged the circulation half-life concerning free cisplatin. The systemic toxicity of the nanoformulation was also low vs cisplatin [88].

Perspectives

To date, SCCs have been proven capable of generating supramolecular platforms with singular and multiple functionalities useful for biomedical applications. The formation mechanism of these nanoassemblies relies on the coordination between the functional groups of organic molecules and the metal ions in different conditions. Notably, their multi-constituent nature enables the synthesis of complex assemblies featuring multiple modes of action. From mere cytotoxic supramolecules, SCCs have gotten more and more sophisticated, and can now include phototherapeutic properties, imaging modalities and targeting moieties optimized for drug delivery. Moreover, certain families of SCCs have been shown to bind selectively to undruggable targets, such as RNA domains [89]. Thus, beyond the careful selection of the metal ions and respective ligands, the understanding of the relationships between the resulting SCCs shapes and their interactions is also important.

Overall, the robustness of the synthetic approaches used to generate multifunctional SCCs has been demonstrated–*via* the use of pre- or post-assembly modifications as well as by the design of heteroleptic systems–although the scalability of the synthetic procedures has been in most of the cases set aside. This parameter would be critical for the advance of SCCs-based systems in pre-clinical applications. Another feature that is often overseen in the literature is the stability of the SCCs and their host–guest complexes in biological media. Nevertheless, various strategies could be explored to overcome this challenge, including fine-tuning of both the thermodynamic and kinetic stability of the systems *via* the judicious choice of their building blocks. It is worth mentioning that the introduction of a direct organometallic metal-carbon bond in the SCCs scaffold may also increase the stability of the system, and leads to the formation of different supramolecular organometallic complexes (SOCs) [10].

The efficient loading capacity of metal-coordinated supramolecular nanomedicines can be exploited for delivering all kinds of molecules, including imaging agents, detection probes and therapeutic drugs. Considering radio-pharmacy applications, a critical component of a radiometal-based construct is the chelator, namely, the ligand system that binds the radiometal ion in a tight stable coordination complex, and that can be properly directed to a desirable molecular target *in vivo*. Designing the chelator to perfectly fit the metal ion while guaranteeing its functionalization with different moieties (e.g. for targeting) can be challenging. In this context, it is particularly appealing the possibility to avoid the use of chelators to entrap the radiometals by directly encapsulating them in the cavities of 3D-metallacages, as shown in the case of pertechnetate [66,86].

Although the inclusion of molecular cargos in the cavities of SCCs, particularly in metallacages, is a valid strategy for shielding it from the biological media, the discrete and relatively small nature of the SCCs does not address the problems related to the biodistribution and systemic toxicity that molecular drugs display. This drawback can be mitigated either with active targeting or by the inclusion of metallacages in larger DDS, such as nanoparticles. Recently, the inclusion of SCCs in the scaffold of soft materials, polymers, membranes, etc. has attracted attention [90–92], and we believe that the progress in this area will prompt further application and translation of SCCs-based materials into other bio-related applications.

So far, the design of SCCs has been based mainly on the use of rigid and relatively small ligands that, in some

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cases, feature further functional groups, i.e., luminescent groups, targeting units, solubilizing groups, etc. However, recently, the group of Fujita [93] has reported the first examples of peptide-based metallacages, whereby, upon coordination with metal ions, the flexible peptides adopt a rigid secondary-like structure. While the initial design is based on labile mono-dentate pyridine-Ag(I) coordination, probably not robust enough for biological media, this new strategy can broaden the possibilities in the design of SCCs for biomedical applications considering the therapeutic relevance of peptides [94].

Altogether, SCCs are a diverse and growing family of potential agents with applications in biomedicine. The field is still young, but the proof-of-concept applications pave the way to virtually limitless potential. Noteworthy, the first example of ^{18}F-functionalized Pd_2L_4 cages has been recently reported enabling the study of their biodistribution by PET *in vivo* [95]. The growing complexity of the SCC-based structures stepwise addresses the main challenges of conventional theranostics and drug delivery systems. Therefore, although it is also clear that more research, testing and evaluation and clinical trials need to be done, we may expect in the foreseeable future the first steps of these systems in the clinics.

Acknowledgement

The authors acknowledge support from the TUM Innovation Network "Artificial Intelligence Powered Multifunctional Material Design" (ARTEMIS). G.M.-A. acknowledges the funding by the Carl Friedrich von Siemens Research Fellowship of the Alexander von Humboldt Foundation. Open Access funding enabled and organized by Projekt DEAL.

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