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Self-Assembled Copper Polypyridyl Supramolecular Metallopolymer Achieving Enhanced Anticancer Efficacy

Zushuang Xiong, Lanhai Lai and Tianfeng Chen

Abstract

Metallopolymers, a combination of organic polymers and metal center, contain metal atoms in repeating monomers can change its dynamic and thermodynamic properties through the directionality of coordination bonds and chemical tailoring of ligands. In the past decade, self-assembled functional supramolecular metallopolymers have aroused a surge of research interest, and have demonstrated application potential in cancer therapy. In this chapter, we have summarized the progress in the rational design of biological application of different metallopolymers. Especially, a copper polypyridyl complex was found be able to self-assemble into a supramolecular metallopolymer driven by the intermolecular interactions, which could enhance the uptake in cancer cells through endocytosis, thus effectively inhibit tumor growth in vivo without damage to the major organs. This study may provide a good example to use self-assembled metallopolymer to achieve enhanced anticancer efficacy.

Keywords: progress in self-assemble, metallopolymer, anticancer, copper (II) complex

1. Introduction

Metallopolymers, a combination of organic polymers and metal center, contain metal atoms in repeating monomers can regulate its dynamic stability and thermodynamic properties through the variation of coordination mode of central-metal ions and chemical tailoring of ligands [1]. With purpose to improve material properties, metallopolymers have attracted increasing interest for their potential to supply advanced functional materials for a wide range of applications [2]. Supramolecular polymer, originating from the integration of polymer and supramolecule, is becoming a rapidly developing research area in recent decades [3–7]. Supramolecular metallopolymers received increasing attention, partly motivated by their ready-to-form self-assembly [8–10] and diverse applications in electrochromic materials [11], luminescent [12–14], accelerated guest adsorption [15], interesting magnetic properties [16], and so on [9, 17]. Nitschke et al. synthesized a new type of metallopolymer, by exploring the gel self-assembly process and formation conditions, and explored the electrochemical properties, photoluminescence properties

and thermochromism of the polymer [12]. Che and his co-workers synthesized cyclometalated Au[III] complexes, which can be self-assembled to form supramolecular polymer, through the hydrogen bonding of the guanine-like amino group of the 4-DPT ligand and the π-π stacking interaction of 2,6-diphenylpyridine. The selective growth inhibition of supramolecular polymers on tumor cells and its possible mechanism were also investigated (**Figure 1**) [17].

Weak noncovalent interactions, such as hydrogen bonding, hydrophobic-hydrophobic, metal-metal and π-π interactions [18–24], have been identified as driving forces to stabilize the self-assembled structures of metallopolymers [8, 25, 26]. Studies also showed that most metallopolymers were under thermodynamically changing processes with change of temperature [8, 12, 25]. Ian Manners group synthesized various self-assembled metallopolymers, and studied its formation mechanism and its applications in nanolithography, biomedicine, magnetic or responsive materials (**Figure 2**) [24]. Till now, many supramolecular metallopolymers of gold, copper and platinum complexes, have been well documented [2, 10, 17, 24, 26–30], and the search for application potential has become new research focus.

While most of supramolecular metallopolymers are "high-molecular-weight" with relatively large ligands [31], the discovery of low molecular-weight metallopolymers with tunable structures have fostered a new growth in recent years [3, 4, 32–35]. Rissanen et al. reported a terpyridine-Zn (II) compound that can self-assemble into metallopolymers with fibrous structured microscopic morphology. Their studies show that this compound can realize the detection of nanomole pyrophosphate in aqueous solution and the detection of pyrophosphate in the competitive environment of cytoplasmic ions [33]. Study has showed a low-molecular-weight metallopolymer in nanofiber form demonstrating potent anticancer properties. [17, 36] Nano-formulation has been showed to be able to improve the stability and selectivity of metal complexes, and hence emerges as an appealing strategy to increase anticancer activity and reduce their toxic side effects [37–39]. For example, Wu et al. have synthesized photosensitive triblock copolymers, which can be self-assembled to form polymer nanosystems to improve their biocompatibility and prolong their blood circulation time to achieve the purpose of regional enrichment of tumor tissue. Under the excitation of red light, the nanosystem dissociates spontaneously, releases anticancer Ru complexes and triggers the generation of a large amount of singlet oxygen to inhibit tumor growth [37]. Therefore, the formation of nanostructures of metallopolymer could have a
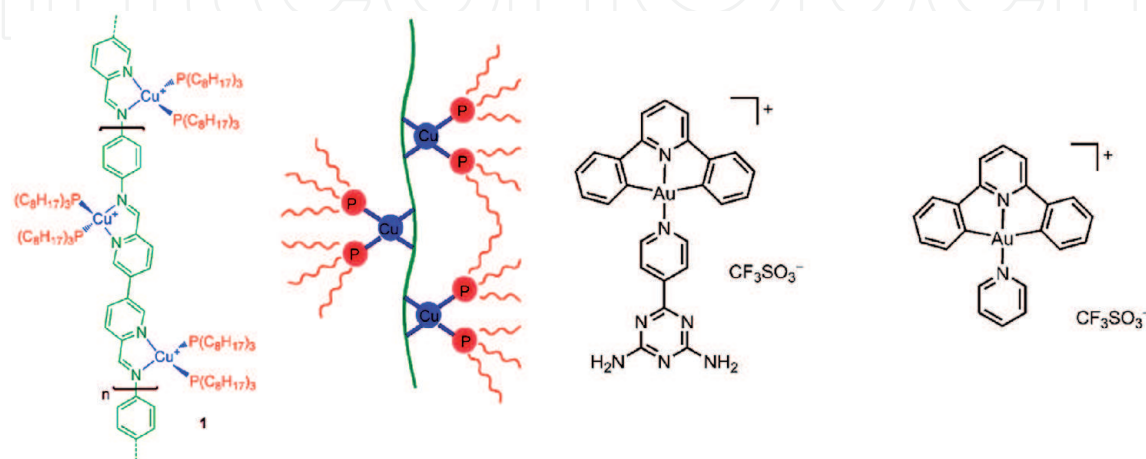

Figure 1.
Schematic representation of polymer and chemical structure of [Au^III(C^N^C)(4-dpt)]-(CF₃SO₃) from Ref. [12, 17].
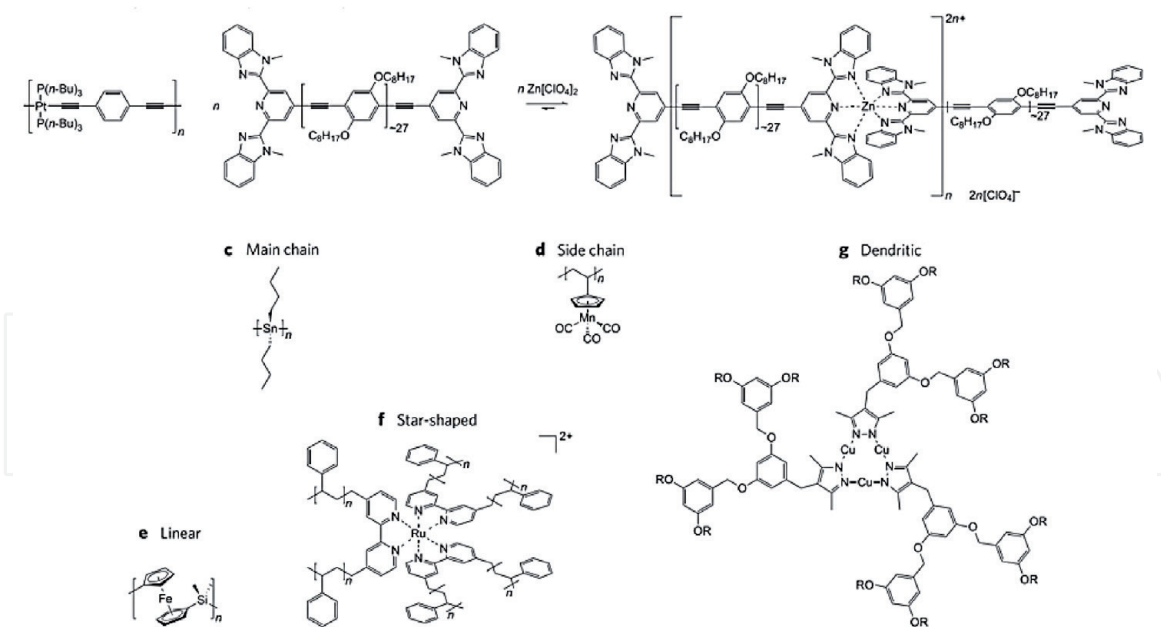
Figure 2.
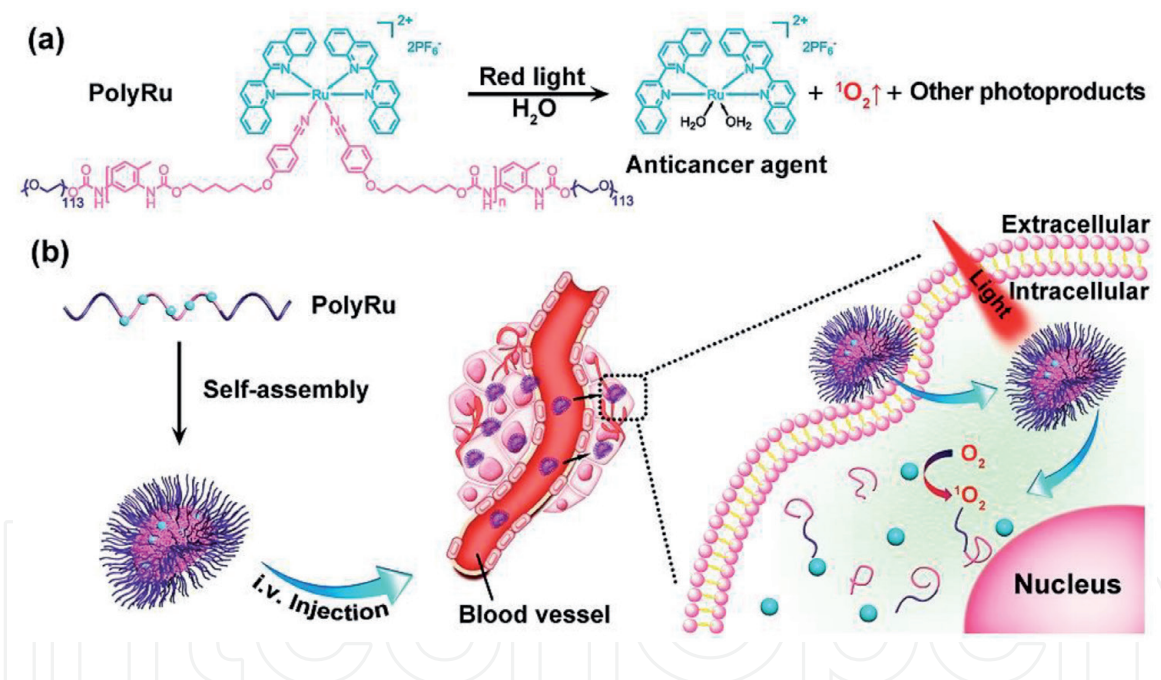*Metallopolymers of different metal centers [24].*

Figure 3.
(a) Structure and photo-induced dissociation of Ru complexes, (b) synthesis of nano-system and its inhibitory effect on tumor growth [37].

promising improvement on the biological activities. Recently, studies have found that, metal complexes with 2-phenylimidazo [4,5-f]-[1,10]phenanthroline (pip) as ligand displayed potent anticancer activities (**Figure 3**) [17, 34, 40–43].

2. Synthesis and characterization

Possibly, the plane structure and NH group of the ligand could form π-π interactions and hydrogen bonds between adjacent molecules. Interestingly, in this study, we synthesized a simple Cu(II) complex, [CuCl(pip)$_2$]Cl, capable of self-assembling into a metallopolymer driven by diverse intermolecular interaction,
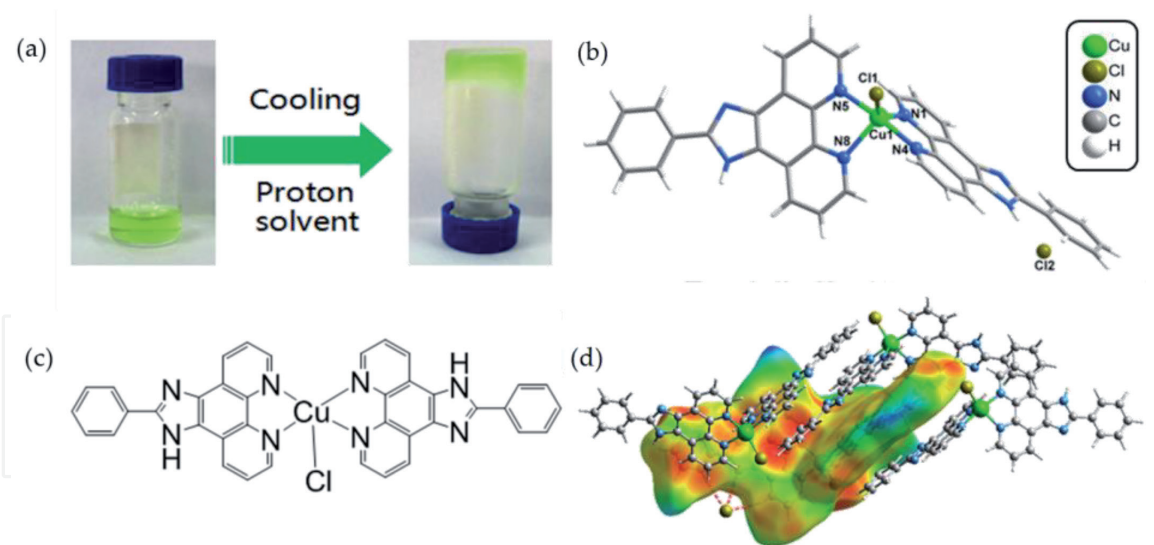
Figure 4.
[CuCl(pip)₂]Cl: (a) formation of the viscous fluid upon cooling in ethanol/water (v/v = 5:1). (b) Crystal structure, (c) chemical structure, (d) illustration of Hirshfeld surface in the crystal packing: the mapping range is shown from red (short distance) through green to blue (long distance) [44].

which demonstrated potent in vivo anticancer efficacy. Addition of pip in ethanol to $CuCl_2$ in water resulted in a clear green solution. The solution turned to be viscous after 2 h at room temperature. Upon cooling in a refrigerator, stable green viscous solution was formed (**Figure 4a**). When the viscous solution stood at room temperature for 25 days, green single crystals suitable for X-ray diffraction could be obtained in a capped vial. The crystal unit of $[CuCl(pip)_2]Cl$ is in a trigonal pyramidal coordination geometry (**Figure 4b**). Hirshfeld surface [45] clearly illustrates that rich supramolecular interactions of conjugated π-π interactions, C(N)—H × × × Cl hydrogen bonds, and edge-to-face C—H × × × π interactions are involved (**Figure 4c** and **d**) in the crystal packing. These results indicate that weak interactions including cooperative π-π and multiple unconventional C—H···X hydrogen bonding interactions are strong enough to from the metallopolymer.

UV/Vis and FT-IR spectroscopy was employed to examine the intermolecular aggregation of $[CuCl(pip)_2]Cl$ during the assembly process. As shown in **Figure 5a**, UV/Vis spectra of the complex in CH_3CH_2OH/H_2O (5:1) exhibits a red shift with peaks from 409 to 423 nm when the concentration increased. This is ascribed to the enhancement of molecular interactions due to the increase of the concentration. The FT-IR spectra of $[CuCl(pip)_2]Cl$ displayed significant difference in different solvents (**Figure 5b**). The red shifts in proton solvent could be attributed to the enhancement of C—H × × × X hydrogen bond and π-π interaction.

Tyndall effect was observed in the solution of $[CuCl(pip)_2]Cl$ in proton solvent CH_3CH_2OH/H_2O (**Figure 6**), indicating the formation of self-assembled species [46], while no Tyndall phenomenon observed in aprotic solvent DMF. Therefore, the presence of proton solvent could be a determining factor for the self-assembly, as proton solvent could provide H atom feasible for the aggregation driven by hydrogen bond. In contrast, Tyndall phenomenon could not be observed in the solution of 0.8 mM (**Figure 6a**), possibly due to the unfavorable intermolecular distances in a dilute solution. Moreover, the mean size of the metallopolymer was found at about 95 nm (**Figure 6b**), indicating the presence of nanoscale aggregates in this solution.

From the TEM images, we found that metallopolymer were highly monodisperse with the size of 83 nm in diameter. And AFM measurement confirmed the spherical nanoparticle morphology of the supramolecular metallopolymer in the
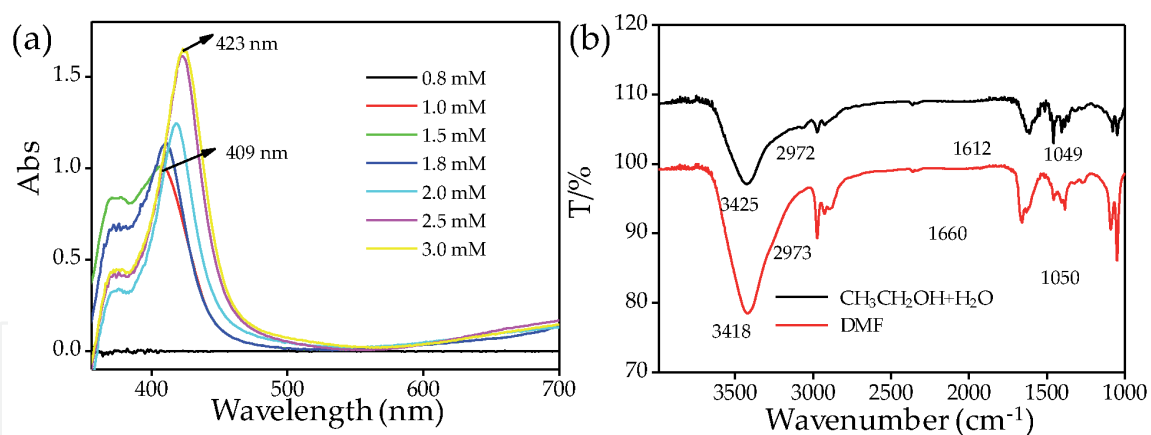
Figure 5.
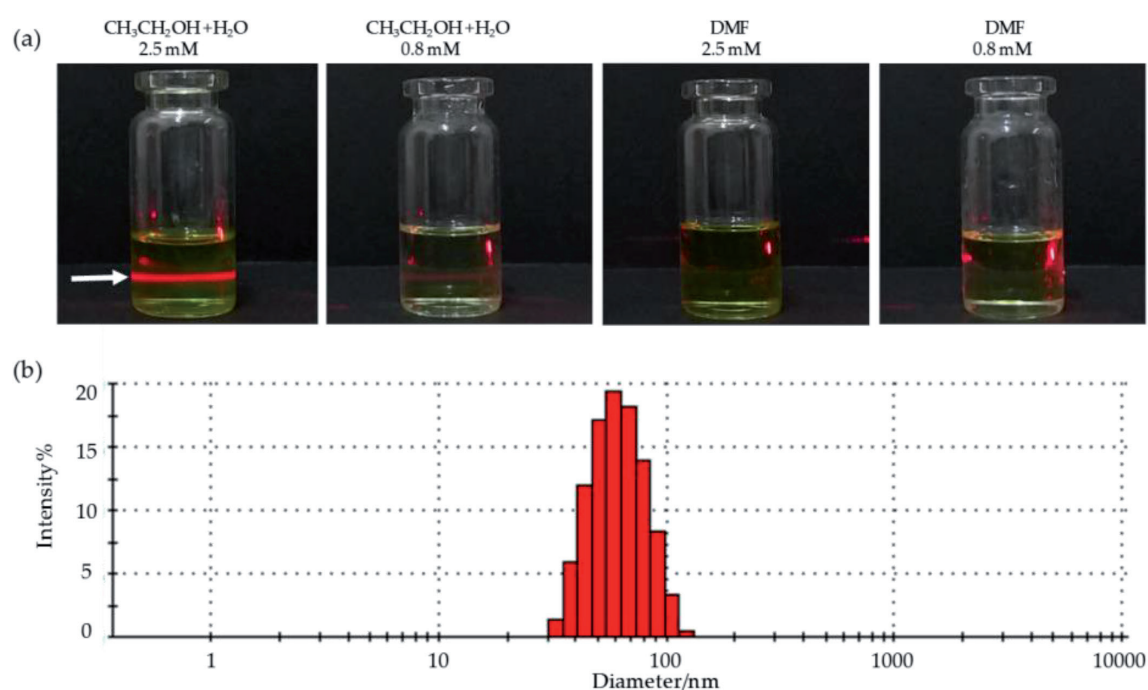*UV/Vis (a) and FT-IR (b) spectroscopy changes in the self-assembly process [44].*

Figure 6.
Nanostructure of metallopolymer. (a) Tyndall effect of [CuCl(pip)$_2$]Cl under different solvent and concentration conditions. (b) Size distribution of [CuCl(pip)$_2$]Cl (2.5 mM) in ethanol/water (5:1) [44].

proton solvent (**Figure 7a** and **b**). The metallopolymer was further confirmed by XRD (**Figure 7c**). The results of MALDI-TOF-MS analysis also demonstrated the presence of monomeric species, and dimer and trimer aggregation peaks of [CuCl(pip)$_2$]Cl (**Figure 7d**).

To further understand the phase transition, the effects of temperature, concentration and solvent on the viscosity of [CuCl(pip)$_2$]Cl were examined by Ubbelohde viscometer. Significant temperature-, solvent- and concentration-dependent changes in the viscosity were recorded (**Figure 8b** and **c**). The stacking mode of [CuCl(pip)$_2$]Cl showing hydrogen bonds (C—H...Cl = 3.681 Å; N—H⋯Cl = 3.279 Å) and π-π interactions (3.524–3.777 Å) (**Figure 8a**). High viscosity was detected when incubating in CH$_3$CH$_2$OH/H$_2$O (5:1), which decreased obviously when the temperature increased from 5 to 75°C. However, the viscosity showed no significant increase in aprotic solvent DMF (**Figure 8d**). Additionally, the decreased viscosity induced by rising temperature when the temperature decreased from 75 to 5°C (**Figure 8e**), which demonstrated the recovering ability of the metallopolymer. The viscosity of
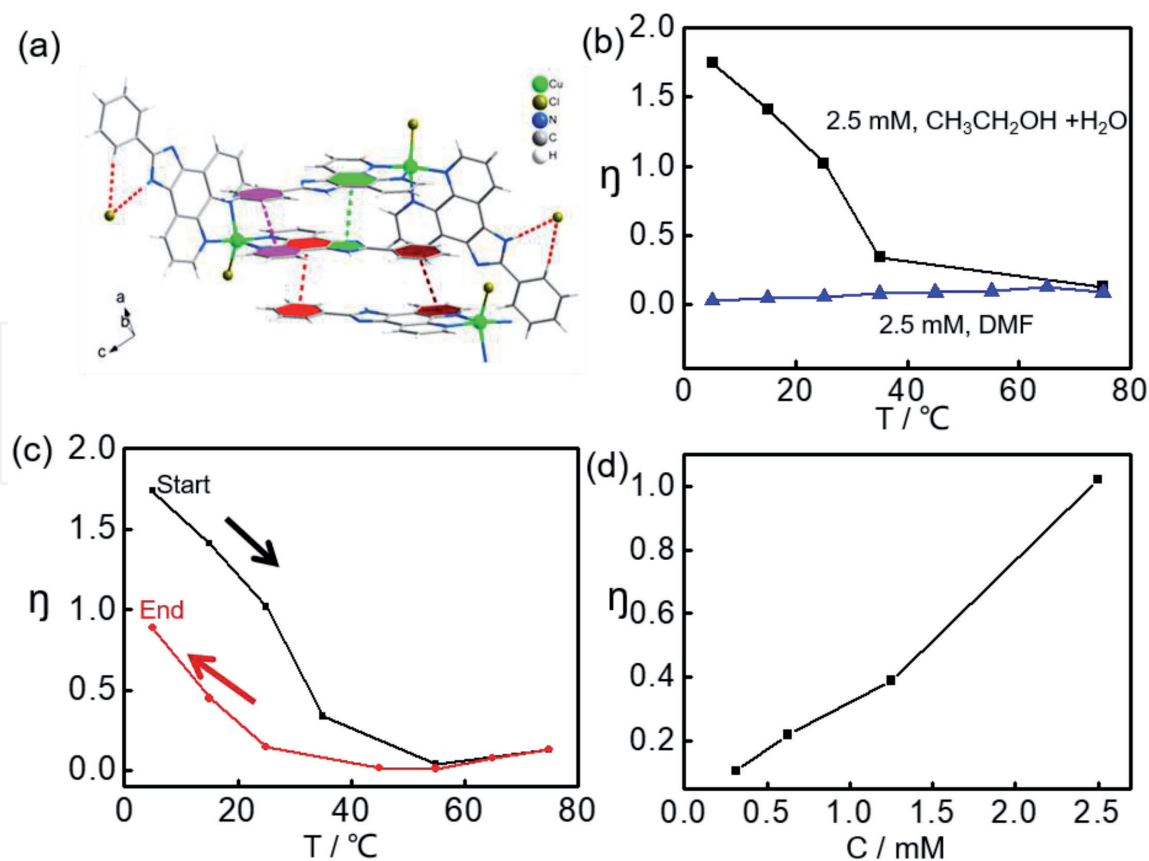
Figure 7.
Characterization of metallopolymer. TEM (a) and AFM (b) images of metallopolymer. (c) Powder XRD pattern of [CuCl(pip)$_2$]Cl (2.5 mM) in ethanol/water (5:1). (d) MALDI-TOF-MS analysis of the [CuCl(pip)$_2$]Cl in ethanol/water (5:1). Insets specific peaks representing different aggregation patterns [44].
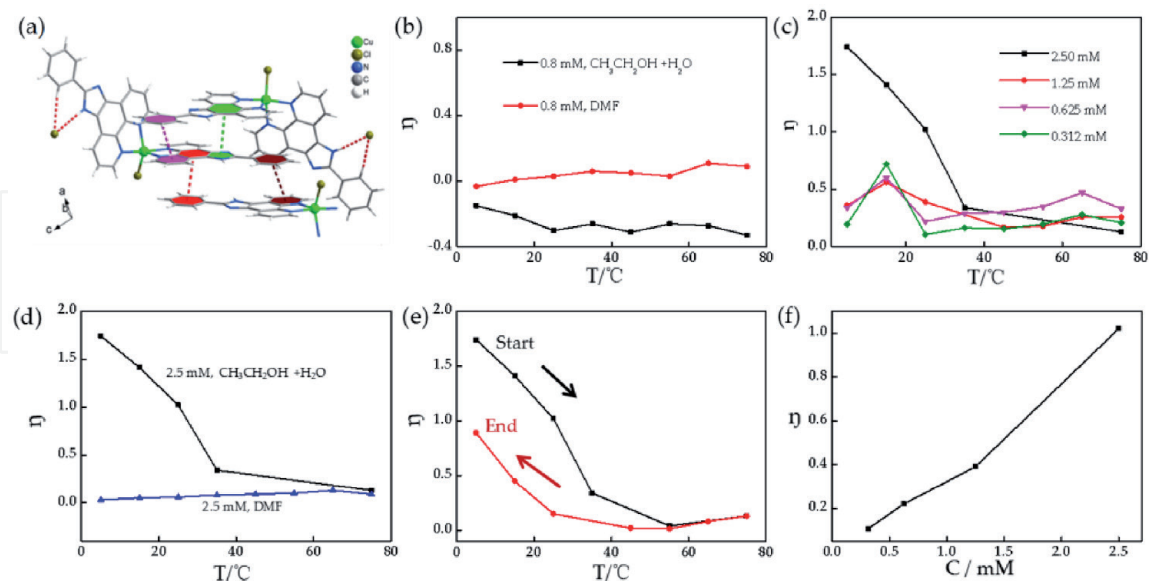

Figure 8.
Dynamic change of metallopolymer with different treatment. (a) The stacking mode of [CuCl(pip)$_2$]Cl showing hydrogen bonds (C–H...Cl = 3.681 Å; N–H···Cl = 3.279 Å) and π-π interactions (3.524–3.777 Å), and viscosity change of [CuCl(pip)$_2$]Cl in different solvents and temperatures, (b) viscosity of [CuCl(pip)$_2$] Cl (0.8 mM) dissolved in different solvents with temperature range from 5 to 75°C, (c) the viscosity of [CuCl(pip)$_2$]Cl was recorded on temperature variation with the concentration raised, (d) dynamic change with temperature varying in the cycle 5–75–5°C in ethanol/water (5:1), (e) concentration dependent at 25°C, and (f) dynamic change of metallopolymer with different concentration [44].

[CuCl(pip)$_2$]Cl increased dramatically upon increasing the concentration, which confirms the contribution of enhanced intermolecular interactions during the self-assembly of the metallopolymer (**Figure 8f**).

3. Cell proliferation inhibition of metallopolymer

Further studies were also carried out to examine the effects of the matter forms (metallopolymer and monomeric complex) on the anticancer activity of [CuCl(pip)$_2$]Cl, by in vitro and in vivo models as previously described [39, 47]. As shown in **Figure 9a**, the metallopolymer demonstrated much higher anticancer activities against the tested cancer cells than the monomeric complex. In order to understand the reasons accounting for the different activities induced by the matter forms, we compared their cellular uptake in HepG2 hepatocellular carcinoma cells. Consistently, the metallopolymer exhibited much higher cellular uptake than monomeric complex in different time points (**Figure 9b**). From **Figure 9c**, we found that significant concentration-dependent changes in the cellular uptake were
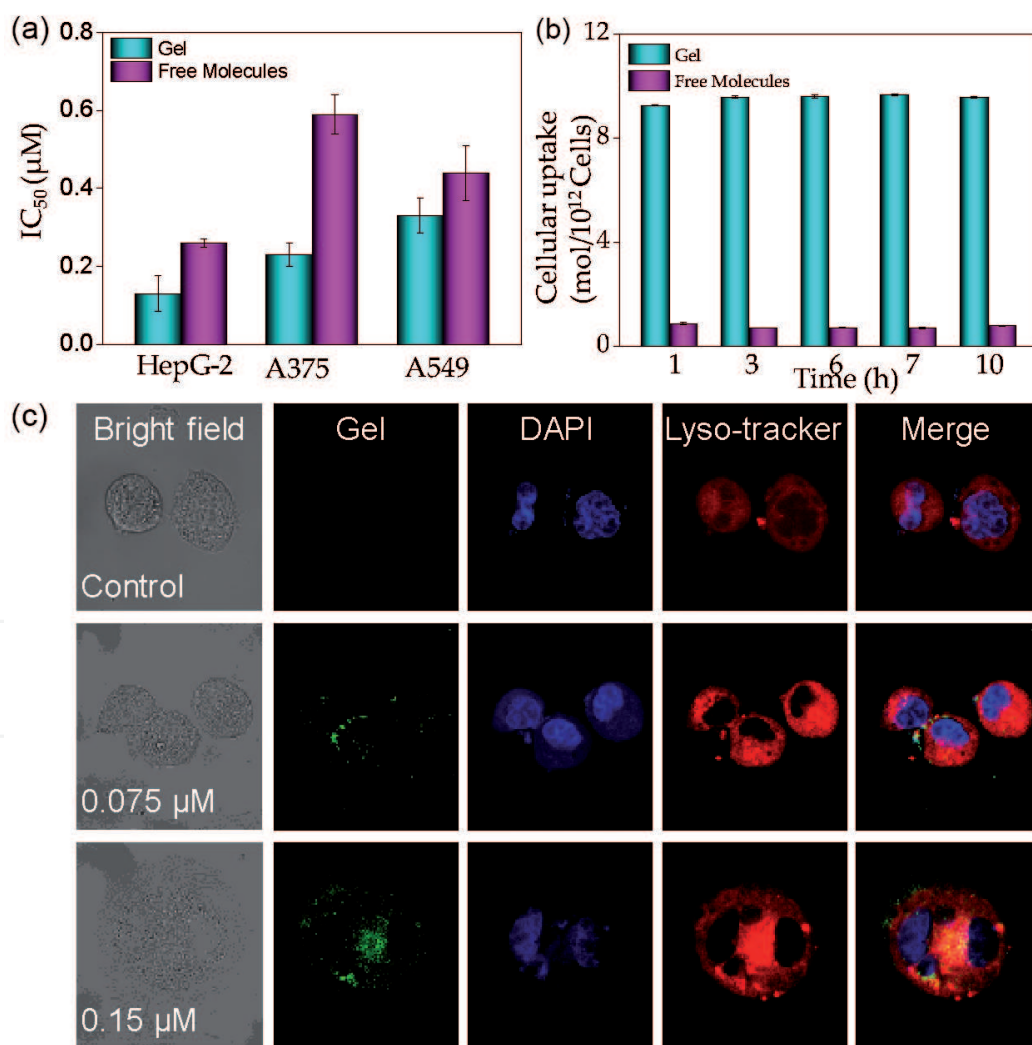

Figure 9.
Cancer cell growth inhibition of metallopolymer and monomeric [CuCl(pip)$_2$]Cl. (a) The cytotoxic effects of monomeric [CuCl(pip)$_2$]Cl, metallopolymer, (b) time-course cellular uptake of monomeric [CuCl(pip)$_2$]Cl, metallopolymer in HepG2 cells (10 μM), and (c) cellular uptake of metallopolymer by confocal fluorescence images [44].
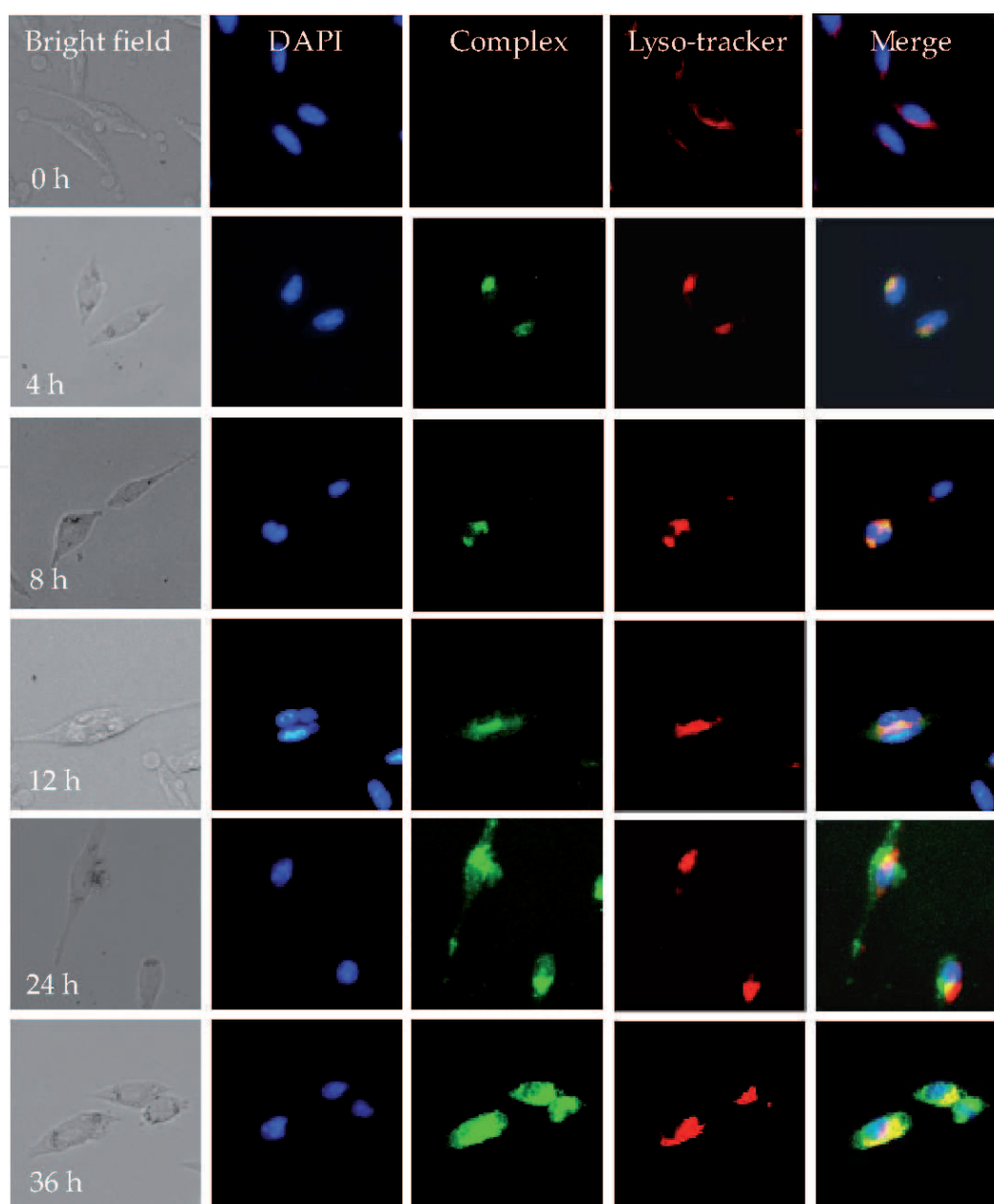
Figure 10.
Cellular localization of metallopolymer after incubation with HepG2 cells for different periods of time [44].

recorded. It is likely that metallopolymer could assembly into nanoparticles, which enter cancer cells through endocytosis in a high efficiency, thus increasing the cellular uptake and anticancer efficacy. Moreover, the results of confocal fluorescence images revealed that, the metallopolymer were internalized by cancer cells through endocytosis, and could be released into cytoplasm after 12–24 h (**Figure 10**).

4. In vivo tumor growth inhibition of metallopolymer

Furthermore, we assessed the in vivo therapeutic efficacy of the metallopolymer in HepG2 xenografts nude mice. In this study, metallopolymer was dispersed in PBS and injected into the tumor-bearing nude mice intravenously. As shown in **Figure 11**, the metallopolymer significantly inhibited the tumor growth, as evidenced by the decrease in tumor volume and tumor weight in a time-dependent manner. Moreover, under the effective dose, the metallopolymer showed no damage to these major organs, including heart, liver, spleen, lung and kidney (**Figure 12**),
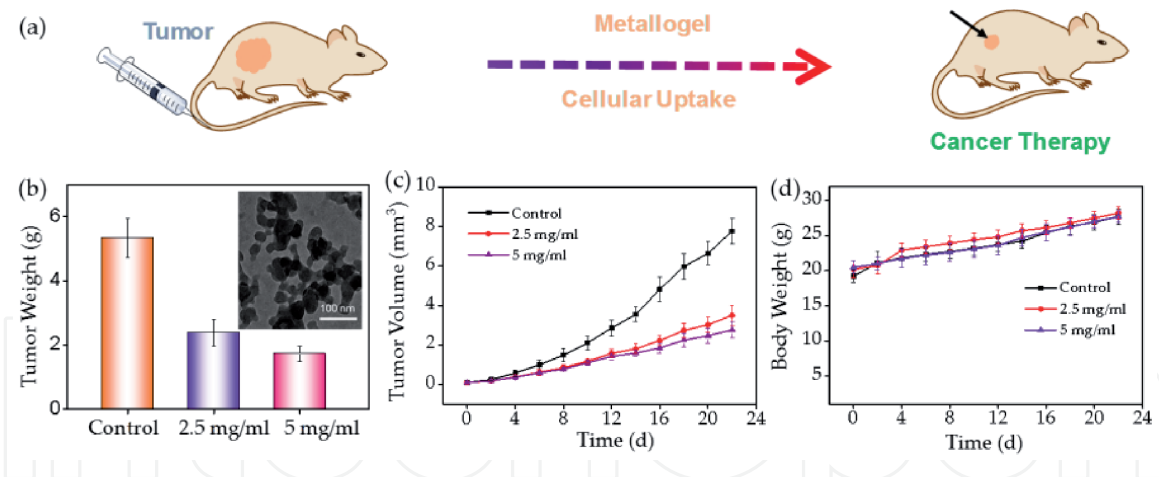
Figure 11.
(a) Schematic demonstration for tumor growth inhibition by metallopolymer. (b and c) In vivo anticancer activity of the metallopolymer against HepG2 cells xenografts. Inset is TEM images of the metallopolymer in DMEM medium (24 h), and (d) body weight of HepG2 cells xenografts in nude mice (n = 5) [44].
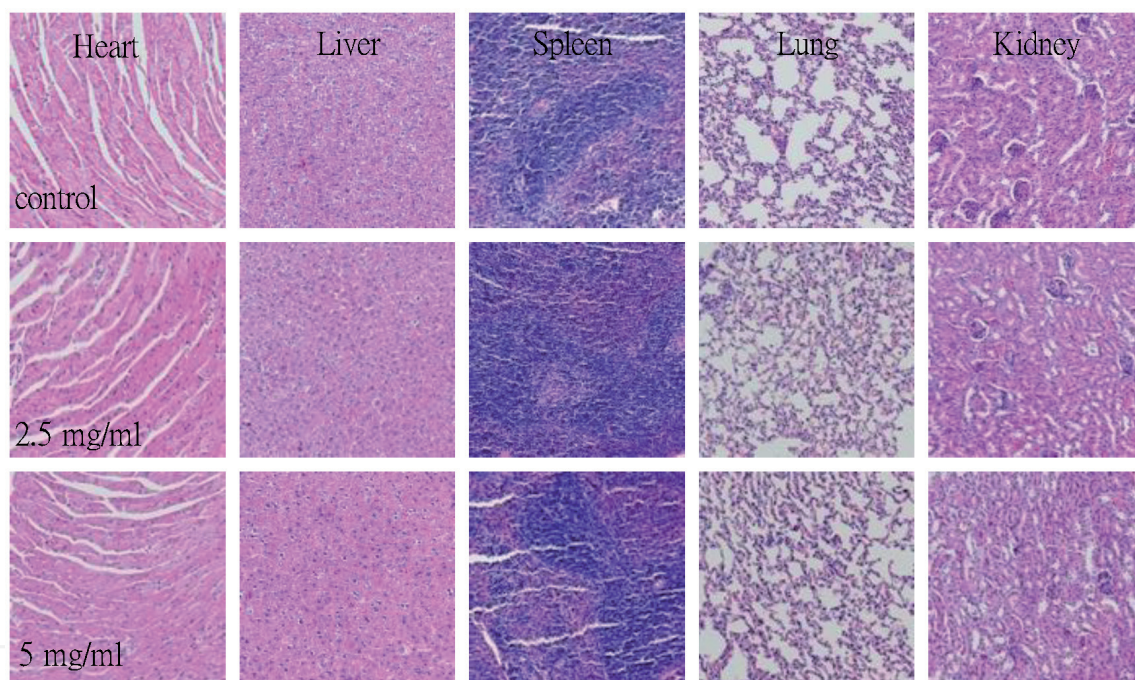

Figure 12.
H&E staining of major organs after treatments [44].

demonstrating the cancer therapeutic potential and safety of this kind of self-assembled functional metallopolymer.

5. Conclusions and prospects

In the past decade, self-assembled functional supramolecular metallopolymers have aroused a surge of research interest, and have demonstrated application potential in cancer therapy. In this chapter, we have summarized the progress in the rational design of biological application of different metallopolymers. Especially, a simple Cu(II) complex, $[CuCl(pip)_2]Cl$, was found be able to self-assemble into surpramolecular metallopolymer driven by diverse intermolecular interactions, including π-π interactions and hydrogen bonds under a proton solvent condition. The functional metallopolymer could enter cancer cells through endocytosis, thus

effectively inhibit tumor growth in vivo without damage to the major organs. This study provides a simple strategy for rational design of Cu-based metallopolymer with novel anticancer potency. For further development of self-assembled nano-structures with clinical application prospect and value in tumor diagnosis and treatment, here are some issues that should be considered. (1) Firstly, how to make the self-assembly of compounds more efficient? This may require structural opti-mization of ligands, metal centers, bonding methods, or modification of polymers or biological macromolecules to adjust the overall hydrophilicity and lipophilicity of complex molecules. (2) Secondly, how to make the assembly more selective and targeted to the tumor? It is necessary to transform the structure or add targeted groups to make the assembly more specific to tumor tissue, cells and intracellular molecules, so as to distinguish normal cells. (3) In order to use as clinic treatment, more research is needed in the aspect of medicinal properties, such as toxicology, pharmacokinetic analysis, etc., so that researchers can have a better understanding of the medicinal properties of different types of assembled structures.

Acknowledgements

Conflict of interest

There are no conflicts to declare.

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References

[1] Winter A, Schubert US. Synthesis and characterization of metallo-supramolecular polymers. Chemical Society Reviews. 2016;**45**(19):5311-5357. DOI: 10.1039/C6CS00182C

[2] Theis S, Iturmendi A, Gorsche C, et al. Metallo-supramolecular gels that are photocleavable with visible and near-infrared irradiation. Angewandte Chemie International Edition. 2017;**56**(50):15857-15860. DOI: 10.1002/anie.201707321

[3] Yang L, Tan X, Wang Z, et al. Supramolecular polymers: Historical development, preparation, characterization, and functions. Chemical Reviews. 2015;**115**(15):7196-7239. DOI: 10.1021/cr500633b

[4] Wu H, Zheng J, Kjøniksen AL, et al. Metallogels: Availability, applicability, and advanceability. Advanced Materials. 2019;**31**(12):1806204. DOI: 10.1002/adma.201806204

[5] Wei P, Yan X, Huang F. Supramolecular polymers constructed by orthogonal self-assembly based on host-guest and metal-ligand interactions. Chemical Society Reviews. 2015;**44**(3):815-832. DOI: 10.1039/C4CS00327F

[6] Lin Q, Lu TT, Zhu X, et al. A novel supramolecular metallogel-based high-resolution anion sensor array. Chemical Communications. 2015;**51**(9):1635-1638. DOI: 10.1039/C4CC07814D

[7] Dong R, Zhou Y, Huang X, et al. Functional supramolecular polymers for biomedical applications. Advanced Materials. 2015;**27**(3):498-526. DOI: 10.1002/adma.201402975

[8] Janeček ER, McKee JR, Tan CSY, et al. Hybrid supramolecular and colloidal hydrogels that bridge multiple length scales. Angewandte Chemie International Edition. 2015;**54**(18):5383-5388. DOI: 10.1002/anie.201410570

[9] Goor OJGM, Hendrikse SIS, Dankers PYW, et al. From supramolecular polymers to multi-component biomaterials. Chemical Society Reviews. 2017;**46**(21):6621-6637. DOI: 10.1039/C7CS00564D

[10] Pal A, Malakoutikhah M, Leonetti G, et al. Controlling the structure and length of self-synthesizing supramolecular polymers through nucleated growth and disassembly. Angewandte Chemie International Edition. 2015;**54**(27):7852-7856. DOI: 10.1002/anie.201501965

[11] Lahav M, van der Boom ME. Polypyridyl metallo-organic assemblies for electrochromic applications. Advanced Materials. 2018;**30**(41):1706641. DOI: 10.1002/adma.201706641

[12] de Hatten X, Bell N, Yufa N, et al. A dynamic covalent, luminescent metallopolymer that undergoes sol-to-gel transition on temperature rise. Journal of the American Chemical Society. 2011;**133**(9):3158-3164. DOI: 10.1021/ja110575s

[13] Zhou Y, Zhang HY, Zhang ZY, et al. Tunable luminescent lanthanide supramolecular assembly based on photoreaction of anthracene. Journal of the American Chemical Society. 2017;**139**(21):7168-7171. DOI: 10.1021/jacs.7b03153

[14] Gao Z, Han Y, Wang F. Cooperative supramolecular polymers with anthracene-endoperoxide photo-switching for fluorescent anti-counterfeiting. Nature Communications. 2018;**9**(1):1-9. DOI: 10.1038/s41467-018-06392-x

[15] Li J, Su Z, Xu H, et al. Supramolecular networks of hyperbranched poly (ether amine) (hPEA) nanogel/chitosan (CS) for the selective adsorption and separation of guest molecules. Macromolecules. 2015;**48**(7):2022-2029. DOI: 10.1021/ma502607p

[16] Li H, Sadiq MM, Suzuki K, et al. Magnetic metal-organic frameworks for efficient carbon dioxide capture and remote trigger release. Advanced Materials. 2016;**28**(9):1839-1844. DOI: 10.1002/adma.201505320

[17] Zhang JJ, Lu W, Sun RWY, et al. Organogold (III) supramolecular polymers for anticancer treatment. Angewandte Chemie International Edition. 2012;**51**(20):4882-4886. DOI: 10.1002/anie.201108466

[18] Mahadevi AS, Sastry GN. Cooperativity in noncovalent interactions. Chemical Reviews. 2016;**116**(5):2775-2825. DOI: 10.1021/cr500344e

[19] Kuosmanen R, Rissanen K, Sievänen E. Steroidal supramolecular metallogels. Chemical Society Reviews. 2020. DOI: 10.1039/C9CS00686A

[20] Kurbah SD, Lal RA. Vanadium (V) complex based supramolecular metallogel: Self-assembly and (metallo) gelation triggered by non-covalent and $N^+ H...O$ hydrogen bonding interactions. Inorganic Chemistry Communications. 2020;**111**:107642. DOI: 10.1016/j.inoche.2019.107642

[21] Fu HLK, Leung SYL, Yam VWW. A rational molecular design of triazine-containing alkynylplatinum (ii) terpyridine complexes and the formation of helical ribbons via Pt···Pt, π-π stacking and hydrophobic-hydrophobic interactions. Chemical Communications. 2017;**53**(82):11349-11352. DOI: 10.1039/C7CC06293A

[22] Zhou Z, Yan X, Cook TR, et al. Engineering functionalization in a supramolecular polymer: Hierarchical self-organization of triply orthogonal non-covalent interactions on a supramolecular coordination complex platform. Journal of the American Chemical Society. 2016;**138**(3):806-809. DOI: 10.1021/jacs.5b12986

[23] Okesola BO, Smith DK. Applying low-molecular weight supramolecular gelators in an environmental setting—Self-assembled gels as smart materials for pollutant removal. Chemical Society Reviews. 2016;**45**(15):4226-4251. DOI: 10.1039/C6CS00124F

[24] Whittell GR, Hager MD, Schubert US, et al. Functional soft materials from metallopolymers and metallosupramolecular polymers. Nature Materials. 2011;**10**(3):176-188. DOI: 10.1038/nmat2966

[25] Chan MHY, Ng M, Leung SYL, et al. Synthesis of luminescent platinum (II) 2, 6-bis (N-dodecylbenzimidazol-2′-yl) pyridine foldamers and their supramolecular assembly and metallogel formation. Journal of the American Chemical Society. 2017;**139**(25):8639-8645. DOI: 10.1021/jacs.7b03635

[26] Fu HLK, Po C, He H, et al. Tuning of supramolecular architectures of l-valine-containing dicyanoplatinum (II) 2, 2′-bipyridine complexes by metal-metal, π-π stacking, and hydrogen-bonding interactions. Chemistry - A European Journal. 2016;**22**(33):11826-11836. DOI: 10.1002/chem.201601983

[27] Wang Y, Astruc D, Abd-El-Aziz AS. Metallopolymers for advanced sustainable applications. Chemical Society Reviews. 2019;**48**(2):558-636. DOI: 10.1039/C7CS00656J

[28] Shi B, Zhou Z, Vanderlinden RT, et al. Spontaneous supramolecular

polymerization driven by discrete platinum metallacycle-based host-guest complexation. Journal of the American Chemical Society. 2019;**141**(30): 11837-11841. DOI: 10.1021/jacs.9b06181

[29] Kumar A, Bawa S, Ganorkar K, et al. Synthesis and characterization of acid-responsive luminescent Fe (II) metallopolymers of rigid and flexible backbone N-donor multidentate conjugated ligands. Inorganic Chemistry. 2020. DOI: 10.1021/acs. inorgchem.9b02985

[30] Gee WJ, Batten SR. Instantaneous gelation of a new copper (II) metallogel amenable to encapsulation of a luminescent lanthanide cluster. Chemical Communications. 2012;**48**(40):4830-4832. DOI: 10.1039/ C2CC30170A

[31] Zhang KY, Liu S, Zhao Q, et al. Stimuli-responsive metallopolymers. Coordination Chemistry Reviews. 2016;**319**:180-195. DOI: 10.1016/j. ccr.2016.03.016

[32] Kuwahara RY, Yamagishi H, Hashimoto K, et al. Easy preparation and characterization of conducting polymer-low molecular weight organogel system. Polymer. 2015;**61**:99-107. DOI: 10.1016/j. polymer.2014.12.059

[33] Bhowmik S, Ghosh BN, Marjomäki V, et al. Nanomolar pyrophosphate detection in water and in a self-assembled hydrogel of a simple terpyridine-Zn^{2+} complex. Journal of the American Chemical Society. 2014;**136**(15):5543-5546. DOI: 10.1021/ ja4128949

[34] Bentz KC, Cohen SM. Supramolecular metallopolymers: From linear materials to infinite networks. Angewandte Chemie International Edition. 2018;**57**(46):14992-15001. DOI: 10.1002/anie.201806912

[35] Yan D, Evans DG. Molecular crystalline materials with tunable luminescent properties: From polymorphs to multi-component solids. Materials Horizons. 2014;**1**(1):46-57. DOI: 10.1039/C3MH00023K

[36] Tsai JLL, Zou T, Liu J, et al. Luminescent platinum (II) complexes with self-assembly and anti-cancer properties: Hydrogel, pH dependent emission color and sustained-release properties under physiological conditions. Chemical Science. 2015;**6**(7):3823-3830. DOI: 10.1039/ C4SC03635B

[37] Sun W, Li S, Häupler B, et al. An amphiphilic ruthenium polymetallodrug for combined photodynamic therapy and photochemotherapy in vivo. Advanced Materials. 2017;**29**(6):1603702. DOI: 10.1002/ adma.201603702

[38] Lai H, Zhang X, Feng P, et al. Enhancement of antiangiogenic efficacy of iron (II) complex by selenium substitution. Chemistry, an Asian Journal. 2017;**12**(9):982-987. DOI: 10.1002/asia.201700272

[39] Zhao Z, Zhang X, Li C, et al. Designing luminescent ruthenium prodrug for precise cancer therapy and rapid clinical diagnosis. Biomaterials. 2019;**192**:579-589. DOI: 10.1016/j. biomaterials.2018.12.002

[40] Lai H, Zeng D, Liu C, et al. Selenium-containing ruthenium complex synergizes with natural killer cells to enhance immunotherapy against prostate cancer via activating TRAIL/FasL signaling. Biomaterials. 2019;**219**:119377. DOI: 10.1016/j. biomaterials.2019.119377

[41] Zhao J, Zhang X, Liu H, et al. Ruthenium arene complex induces cell cycle arrest and apoptosis through activation of P53-mediated signaling pathways. Journal of Organometallic

Chemistry. 2019;**898**:120869. DOI: 10.1016/j.jorganchem.2019.07.020

[42] Xie L, Luo Z, Zhao Z, et al. Anticancer and antiangiogenic iron (II) complexes that target thioredoxin reductase to trigger cancer cell apoptosis. Journal of Medicinal Chemistry. 2017;**60**(1):202-214. DOI: 10.1021/acs.jmedchem.6b00917

[43] Zhao Z, Gao P, You Y, et al. Cancer-targeting functionalization of selenium-containing ruthenium conjugate with tumor microenvironment-responsive property to enhance theranostic effects. Chemistry - A European Journal. 2018;**24**(13):3289-3298. DOI: 10.1002/chem.201705561

[44] Lai L, Luo D, Liu T, et al. Self-assembly of copper polypyridyl supramolecular metallopolymers to achieve enhanced anticancer efficacy. ChemistryOpen. 2019;**8**:434-443. DOI: 10.1002/open.201900036

[45] Seth SK, Bauzá A, Frontera A. Screening polymorphism in a Ni (II) metal-organic framework: Experimental observations, Hirshfeld surface analyses and DFT studies. CrystEngComm. 2018;**20**(6):746-754. DOI: 10.1039/C7CE01991B

[46] Xiao W, Deng Z, Huang J, et al. Highly sensitive colorimetric detection of a variety of analytes via the Tyndall effect. Analytical Chemistry. 2019;**91**(23):15114-15122. DOI: 10.1021/acs.analchem.9b03824

[47] Deng Z, Gao P, Yu L, et al. Ruthenium complexes with phenylterpyridine derivatives target cell membrane and trigger death receptors-mediated apoptosis in cancer cells. Biomaterials. 2017;**129**:111-126. DOI: 10.1016/j.biomaterials.2017.03.017