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Applications of Endohedral Fullerenes in Medical Diagnosis & Therapy

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Abstract: *The endohedral fullerenes are a well established class of carbon nanostructures. The interplay of carbon cages and encaged species results in new nanomaterials with exciting electronic states and properties. This review deals with the prospective applications of endohedral fullerenes in biomedicine including MRI contrasting agents, X-ray contrasting agents, radiotracers and radiopharmaceuticals, antitumour agents and antimicrobial agents*

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I. Introduction

Spherical fullerenes were discovered by British scientist Harry Kroto in 1985 and are commonly referred to as bucky balls. American architect Richard Buckminster Fuller designed a geodesic dome in 1960s which resembled the shape of newly discovered C_{60} fullerene which led to its name Buckminster Fullerene. Along with American researchers Richard Smalley and Robert Curl, Kroto synthesized bucky balls in the laboratory and were awarded a Nobel Prize in Chemistry in 1996. Fullerenes also referred to as Buckminster fullerenes or Bucky balls have sp^2 carbons that showed unique chemical and physical properties and a highly symmetrical cage with different sizes (C_{60}, C_{76}, etc.). The most abundant fullerene in the synthesized composition is C_{60} . C_{60} consists of 60 carbon atoms with C5–C5 single bonds (12 pentagons), and C5 = C6 double bonds (20 hexagons). Indeed, each fullerene with 2n + 20 carbon atoms contains 'n' hexagons. C_{60} and C_{70} are produced at 1000^{o}C and the concentration increases as pulse duration increases. The IUPAC recommendation proposed the term "incar fullerene" for fullerene encapsulating atoms, ions or molecules, the specification endohederal is now a days used throughout for fullerenes. This term originates from a combination of Greek words ("endon"- within), ("hedra"- face of a geometrical figure).

When some other atoms can be enclosed inside the hollow shell of fullerenes, it results in the formation of inclusion compounds known as endohedral fullerenes. When the atom trapped inside is a metal, they are called metallofullerenes. Most of the endohedral materials are made out of C_{82}, C_{84} or even higher fullerenes. As it is extremely difficult to open up carbon cage molecules to surround a far off atom inside endohedral material must be synthesized while formation of cage itself.

Endohederalmetallofullerene (EMFs) attracted a booming increase of attention in the first decade after the discovery of macroscopic fullerene production in 1990.The yield of EMFs in the 1990s were still rather low and there was virtually no control over the molecular composition of the products. In 1999 it was found that the presence of small amount of nitrogen gas in the arc burning reactor resulted in metal nitride cluster fullerenes (NCFs). The yield of NCFs were much higher than those of conventional EMFs and they exhibited improved kinetic stability due to larger HOMO-LUMO gaps.

The discovery of NCFs was soon followed by the elucidation of the molecular structure of the first carbide cluster fullerene. This finding emphasized an ambiguity of the structural assignments of polymetallo fullerenes and the high abundance of carbide cluster fullerenes was then established after extended structural studies of a series of EMFs, many of which were initially thought to be dimetallo fullerenes. Enormous progress was achieved in the structure studies of EMFs. It was earlier precluded the use of single crystal X-ray diffraction for the structure elucidation. Conventional and paramagnetic NMR also delivered invaluable information about the structure and dynamics of many EMF molecules.

Extended knowledge on the molecular structures of EMFs served as a basis for advanced computational studies, which allowed the formulation of the general principles governing the stability of EMFs and carbon cage isomerism. Nowadays, the structures of new EMFs can be routinely predicted from the first principles with the high reliability rivaling that of single crystal X-ray diffraction studies. Many cyclo as well as radical addition reactions of EMFs are described forming a basis for the targeted synthesis of EMF based functional materials. The application for EMFs as MRI contrasting agent and electron accepting block in photovoltaic devices are now considered as the most promising. The reactivity and additional patterns of EMFs are significantly different from those of empty fullerenes.

Biomedical applications are a developing field that holds special promise for fullerene-based products, since relatively small amounts of the material are required for effective dosing. The non-toxicity of the carbon cage makes endohedral fullerene-based drugs potentially feasible for medical applications. The internal metal of an endohedral fullerene is effectively isolated from its surrounding environment, giving the endohedral fullerene a distinct advantage of high stability and low toxicity over the metal chelate complexes commonly used in radio-medicine and diagnostic radiology.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is one of the most common techniques for the diagnostic examination of human patients, using a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body.The visibility of the internal body structures in MRI can be drastically improved by the use of MRI contrast agents, which act by the change of the proton relaxation times in tissues and body cavities. Nowadays the most commonly used commercially available MRI contrast agents are gadolinium (Gd) chelate complexes such as GdDTPA (DTPA: diethylene triamino-penta acetic acid) which uses the Gd^{3+} (S = 7/2) ion to enhance the relaxation rate of water protons.

The remarkably inert interiors of fullerenes are suitable for the isolation of atomic and small molecular species. One species of particular use for biomedical applications is the paramagnetic gadolinium(III) ion (Gd^{3+}). Its large magnetic moment and seven unpaired, isotropically distributed 4f electrons mean it has found use in clinically deployed MRI CAs because it can dramatically reduce T^1 relaxation time of surrounding water protons, thus improving the contrast of T^1-weighted images. However, there is a growing body of evidence that the chelates currently used as CAs do not bind the gadolinium as strongly as thought in physiological conditions: repeated administration leads to gadolinium deposition in the brain, and environmental gadolinium concentrations have increased with increasing use of MRI CAs. Most concerning is the link between use of gadoliniumcontaining CAs and the onset of nephrogenic systemic fibrosis (NSF) in patients with renal failure. Given these concerns, the European Medicines Agency (EMA) has recently suspended and restricted the clinical use of certain gadolinium-chelating MRI CAs. The stage is seemingly set for fullerenes to be exploited as MRI CAs as the endohedral gadolinium species cannot escape the cage and, as will be shown, many of the Gd-EMFs outperform currently used agents, giving the same T^1-weighted contrast at lower concentrations. One of the earliest examples of a Gd-EMF CA was polyhydroxylated$Gd@C_{82}(OH)_{20}$. The observed T^1 relaxivity (r1) of 47 mM1 s^1(at 9.4 T magnetic field) is an order of magnitude greater than clinically used CAs. These chelating agents typically allow one water molecule to interact directly (inner-sphere mechanism) with Gd^{3+} at a time, whereas water protons can exchange with the twenty hydroxyl groups on the fullerene – this was posited to be the reason for the higher r1 value, even though there is no direct interaction between Gd^{3+} and the water protons (second-sphere mechanism). This effect is likely enhanced by the transfer of gadolinium's three electrons to the fullerene cage. A more highly functionalised cage, $Gd@C_{82}(OH)_{40}$ gave a higher r1 value of 81 mM1 s 1 at the clinically used 1.0 T field. Given, however, that highly hydroxylated cages have been shown to lead to open structures which may let the endohedral species escape, a less hydroxylated derivative, $Gd@C_{82}(OH)_{16}$ has also been synthesised. Even this species, with r1 of 19.3 mM1 s 1 (4.7 T field), outperformed a clinically used chelate. Other examples of synthetic routes to $Gd@C_{82}$ derivatives with better r1 values cf. clinical agents include a one-pot reaction with b-alanine (r1¼9.1 mM1 s 1 at 1.5 T) and functionalisation with bone-targeting organophosphates (r1¼37 mM1 s 1 at 0.35 T). Another Gd-EMF which has been extensively studied as an MRI CA is the trimetallic nitride template (TNT) EMF, $Gd3N@C_{80}$. It would be expected that this fullerene, with three gadoliniums per cage, would outperform $Gd@C_{82}$ with one per cage, and indeed this was shown to be the case. This derivative was functionalised with a PEG-functionalised malonate (PEG average Mw¼5000) via the Bingel reaction, before the introduction of multiple hydroxyl groups. At 2.4 T, r1 was measured to be 143 mM1 s 1. The replacement of the "stealth" PEGylated addend with a carboxylic acid-functionalised moiety increases the r1 value to 207 mM1 s 1 (2.4 T) . This was ascribed to a unimodal distribution of larger aggregates of 78 nm in pure water (cf. PEG-$Gd3N@C_{80}$), as measured by DLS. In phosphate buffer solution (PBS), this aggregate size decreased to 44 nm, accompanied by a decrease in r1 to 35 mM1 s 1. This dependence of r1 on aggregate size has been further confirmed by the conjugation of lower molecular weight PEG chains (average Mw¼350), which gave 95 nm aggregates (cf. 37 nm for PEG5000) and r1 of 237 mM1 s 1.Other examples of Gd-EMF MRI CAs include the mixed-metal EMFs, Sc_xGd_3-$xN@C_{80}Om(OH)_n$ and the exotic, egg-shaped $Gd_3N@C_{84}(OH)_x$. The mixed-metal EMFs were produced in higher yield than solely $Gd_3N@C_{80}$ during arc discharge, and gave r1 values (14.1 T) of 20.7 (x¼1) and 17.6 mM1 S 1 (x¼2), still better than clinically used agents. The unusual egg-shaped Gd-EMF outperformed its more highly symmetric C_{80} analogue at all measured field strengths (e.g., 173 vs. 140 mM1 s1 at 1.4 T). This is likely due to, as observed, larger aggregate size and a larger number of hydroxyl groups on the surface of the cage available for exchange with surrounding water protons. Application-wise, the carboxylated $Gd_3N@C_{80}$ derivative has proved a useful scaffold for the conjugation of IL-13 peptides, known for their ability to target glial tumours due to over expression of the IL-13 receptor . The resultant structure is thus an efficient imaging tool for brain tumour cells. This Gd-EMF has also been used as a scaffold for the grafting of radioactive label species in order to produce unique theranostic and dual-modal imaging systems. Functionalisation of the cage with chelate, tetra azacyclododecane tetraacetic acid (DOTA) labelled with β-emitter, 177Lu, allows for both MR imaging and delivery of brachytherapy for the treatment of brain tumours. Hydroxylating the cage instead, followed by iodination with 124I, gives a dual-modal PET and MR imaging agent. Hydroxylated $Gd_3N@C_{80}$ has been used to track stem cells in the lung and has been incorporated into targeted liposomes for the detection of atherosclerotic plaque lesions

Radio tracers and radio pharmaceuticals

Another practical application for endohedral fullerenes in biomedicine is in the field of nuclear medicine with radiotracers and radiopharmaceuticals. At present radiopharmaceuticals generally use small quantities of drugs containing specially chelated radioisotopes of metals for imaging or therapeutic applications. But these drugs have the problem of *in vivo* kinetic instability, which can result in the release of small amounts of toxic radioactive metal ions.

Radiopharmaceuticals used for cancer therapy is highly selective, designed to kill malignant cells and spare healthy tissues. Side effects rates are generally less than other treatments. But it is still the utmost concern to minimize normal organ toxicity and maximize radiation dose to the target lesions in applying radiopharmaceuticals[RPTs]. Most commonly affected normal organs include bone marrow, kidneys and liver. The impact of RPTs to renal function is generally considered low.Radiotracer techniques are extensively used for troubleshooting, measuring hydrodynamics parameters, and the process visualization in industrial systems

Antitumor and Anticancer Activity

Antitumor Activity & anticancer activity of $[Gd@C_{82}(OH)_{22}]_n$ nanoparticles has been extensively studied since 2005. In 2005 Zhao *et al*. reported that $Gd@C_{82}(OH)_{22}$ nanoparticles with the average size of *ca.* 22 nm exhibited a high antineoplastic activity in mice against H_{22} hepatoma. At the same time, this study proved the low toxicity of nanoparticles *in vivo* and *in vitro*, showing that the antitumor activity is not due to toxic effects to cells. Subsequent studies showed that $Gd@C_{82}(OH)_{22}$ nanoparticles can regulate the oxidative stress in tumor cells *in vivo* and act as scavengers of reactive oxygen species, which can be a reason of their antitumor activity. In 2009 Zhao, Chen et al. found that at high concentrations $Gd@C_{82}(OH)_{22}$ nanoparticles enhanced the immune responses and stimulated immune cells to release more Th1 cytokines, thus helping the immune system to eliminate tumor cells. It was also shown that $Gd@ C_{82}(OH)_{22}$ can protect cells against oxidative damage by scavenging the reactive oxygen species; the work included both *in vitro* studies of H_2O_2-induced cytotoxicity as well as ESR spin trap technique of the free radical scavenging. In 2010 Liang and Zhao showed that $Gd@C_{82}(OH)_{22}$ nanoparticles help to solve the problem of acquired tumor resistance to chemotherapeutic cisplatin.In the same year these authors reported that $Gd@C_{82}(OH)_{22}$ nanoparticles act as efficient angiogenesis inhibitors by simultaneously down-regulating multiple angiogenic factors. The anticancer efficiency of nanoparticles *in vivo* was comparable to that of the clinic anticancer drug Paclitaxel, but without pronounced side effects. In 2012 these authors showed that $Gd@C_{82}$-fullerenol nanoparticles significantly inhibit cancer metastasis.

The mechanism of the anti metastasis activity was shown to be not in the cytotoxicity but in the inhibition of the matrix metalloproteinase production. The formation of a thick fibrous cage served as a physical barrier cutting the communication between cancer and tumor-associated macrophages. In 2012 it was shown that $Gd@C_{82}(OH)_{22}$ can effectively block tumor grow thin human pancreatic cancer xenografts as was shown by experiments at animal, tissue, and cellular levels. In the same work, molecular dynamics (MD) simulations were applied to explain the action of $Gd@C_{82}(OH)_{22}$ at the molecular level. MD simulations were also used to model the interaction between $Gd@C_{82}(OH)_{22}$ and a small protein domain. Several reviews on the properties and biological effects of $Gd@C_{82}(OH)_{22}$ and other functionalized fullerenes, in particular their use for cancer therapy, were recently published.

X-ray contrast agents

Because of the large cross section of the lutetium (Lu) atoms, $Lu_3N@C_{80}$ was reported by Dorn et al. in 2002 to provide a good X-ray contrast. Such a contrast effect was not found for C_{60}, providing evidence that the contrast cannot be attributed to the carbon cage. Accordingly, the authors proposed that mixed-metal species (e.g., Lu_3−xAxN$@C_{80}$, where A is Gd or Ho, and x = 0−2) may prove useful as a multimodality contrast agent (e.g., X-ray and MRI). Using a contrast agent that provides enhancements for a variety of spectroscopic methods would simultaneously provide directly comparable images with minimum exposure to the patient.

Antimicrobial activity

In 2009 Stevenson, Phillips et al. discovered the singlet oxygen sensitization by $Sc_3N@C_{80}$. The NCF was then embedded into polystyrene-block- polyisoprene-block-polystyrene copolymer pressure sensitive adhesive films. Stemming from in situ generation of $^1 O_2$, such films exhibited animicrobial activity evaluated in a number of assays.

Research on fullerenes occupies a unique position in the scientific arena. Synthesis and characterisation of this nano material blur the line between materials science and chemistry. Careful tuning of the processing methods give birth to a whole family of molecules and their functionalised derivatives. Some of their major biomedical applications of fullerenes are listed.

Fullerenes as carrier of drug.

The fullerene cage is structurally stable, but readily functionalized, thus serving as versatile three-dimensional scaffolds for carrying various drugs. Many drug molecules are often attached to a fullerene. The medicine loaded fullerene can then be attached to an antibody which is Y-shaped proteins that can recognize and attach to antigens. Viruses, bacteria and diseases within the body have unique antigens. The antibody finds the disease in the body, and then the attached fullerene delivers the appropriate medicine.

Antioxidant and Radical Scavenging

The presence of free radical species in human body is natural, but their overproduction may be harmful and cause serious diseases. Fullerenes possess great deal of conjugated double bonds and low lying lowest unoccupied molecular orbital (LUMO). This property helps in taking up an electron, making an attack of radical species highly possible. All these make fullerene capable for antioxidant property.

In Photodynamic therapy and cancer treatment.

In some sorts of cancer and premalignant conditions, photodynamic therapy represents an alternate treatment with great potential. Singlet oxygen ($^1O_2$) is toxic for cells. Using this principle, photodynamic therapy combines a nontoxic photosensitizer (PS) that upon visible light activation generates singlet oxygen ($^1O_2$) which is reactive oxygen species (ROS). The PS causes localized oxidative damage after accumulation in tumor cells.

Photodynamic therapy (PDT) is lauded as an attractive cancer therapy for localised smaller lesions and carcinomas, as well as an aid during surgery of larger masses. It is non-invasive, precise targeting and devoid of long-term side effects. It works by irradiating an intravenously administered photo sensitising molecule at a particular wavelength, which excites it into its very short-lived (nanosecond scale) first excited singlet state, S^1. Non-radiative decay of this S^1 state gives the longer-lived (up to milli-second scale) triplet state, T^1, which is subsequently quenched. In the case of molecular oxygen, quenching by energy transfer leads to the formation of a highly reactive and cytotoxic ROS, singlet oxygen.The effectiveness of PDT relies on the evolution of singlet oxygen in areas with a high density of cancerous cells.

Functionalized fullerenes have shown interesting biomedical applications as potential phototherapeutic agents. The hydrophobic carbon sphere of fullerene C_{60} can be substituted by cationic groups to obtain amphiphilic structures. These compounds absorb mainly UV light, but absorption in the visible region can be enhanced by anchoring light-harvesting antennas to the C_{60} core. Upon photoexcitation, fullerenes act as spin converters by effective intersystem crossing. From this excited state, they can react with ground state molecular oxygen and other substrates to form reactive oxygen species. This process leads to the formation of singlet molecular oxygen by energy transfer or superoxide anion radical by electron transfer.

Hepatocellular carcinoma has become one of the most prevalent cancers, with a high mortality rate. Accurate diagnosis at an earlier stage is regarded as an effective measure to reduce the disease-related mortality of liver cancer. Magnetic resonance imaging (MRI) as a non-invasive checking mode has become a powerful tool in medical diagnosis. However, MRI contrast agents for liver-specific imaging either have some side effects or the imaging effect is not ideal. Thus, development of more efficient and security MRI contrast agents for the early diagnosis of hepatocellular carcinoma is urgent. Herein, a kind of water-soluble gadofullerene nanoparticle (GFNP) with high efficiency and security has been successfully used to achieve *in situ* liver cancer imaging. By comparing GFNPs with different functional groups, $Gd@C_{82}$ modified by a hydroxyl group (GF-OH) presents the highest contrast efficiency both *in vitro* and *in vivo*. Notably, the smallest tumor with a diameter of only 0.5 mm could be clearly observed by GF-OH using MRI. Moreover, the imaging window of GF-OH is more than 3–6 hours. In addition, GF-OH can be mostly excreted from the living body and causes no serious toxicity. These results demonstrate that GF-OH is a safe, efficient MRI contrast agent for the diagnosis of early orthotopic hepatocellular carcinoma.

Photodynamic inactivation experiments indicate that cationic fullerenes are highly effective photosensitizers with applications as broad-spectrum **antimicrobial agents**. In these structures, the hydrophobic character of C_{60} improves membrane penetration, while the presence of positive charges increases the binding of the fullerene derivatives with microbial cells.

Magnetic resonance imaging (MRI) is a molecular imaging technology that has been widely adopted in biomedical and clinical diagnostics fields owing to its capability of deep tissue imaging with high spatiotemporal resolution. Responsive small molecule MRI contrast agents, known as MRI probes, are of particular interest for the detection and visualisation of target analytes *in vitro* and *in vivo*, thus expanding MRI's capability into the molecular imaging regime. Each of the responsive MRI probe selectively responds to corresponding target analyte and then gives the magnetic resonance (MR) signal change for this analyte detection.

II. CONCLUSION

The structure of C_{60} has truncated icosahedrons made up of 20 hexagonal rings located at the center of the icosahedral faces and 12 pentagons located around the apexes. It is the most symmetric molecule with 2-fold, 3-fold and 5-fold rotational symmetry. Fullerene molecules can exist as a spherical, ellipsoid, tubular shapes consisting hexagonal, pentagonal and sometimes heptagonal rings. C_{60}belongs to the spherical fullerene class which looks like a soccer ball, while C_{70} belongs to the ellipsoidal class which looks like rugby ball. In 1990, a method was discovered for producing macroscopic amounts of this distinctive material and this allowed scientists to understand its chemistry and explore its properties.

For more complexation, carbon atoms can exist with other hybridization states called intermediate hybridizations with different degrees. The degree of hybridization in this case caused by the curvature of the sp^2 hybridized structure, leading to produce strained C–C bonds. Usually, carbon atoms with pure sp^2 hybridization state shows an ideal flat structure. While in the case of atoms with curved structure, their hybridization degree should be >2 as in the case of fullerene carbon.

Usually, carbon atoms in sp^2 hybridization state arrange themselves in hexagonal rings as well as in a various other polygonal rings. The non-hexagonal rings can leads to curving the flat sheet or keeping its flatness if the polygon arrangement fulfils certain symmetry rules. The pentagon rings induce a positive curvature while heptagon or octagon rings induce a negative curvature. Therefore, carbon materials with sp^2 hybridization state can exist into three types: positive curved fullerene-type, which includes carbon atoms with hexagonal and pentagonal rings and negative curved schwarzite-type, this type includes carbon atoms with hexagonal and either heptagonal or octagonal rings and the last one called zero-curvature graphene-type which includes carbon atoms with hexagonal rings only.

Nanoscale carbon-cage can be easily modified with various given chemical groups for desired biomedical functions. Among all the spherical fullerene variants, the C_{60} variant and its derivatives have been widely studied. Metallofullerenes, the complexes of metal-containing fullerenes, are also very important fullerene variants. Endohedral metallofullerenes, with encapsulated metal atom inside fullerene offer a bright prospect for medicine and pharmaceutics because they present a unique motif with "super chelation" due to entrapment of metal ions in the fullerene interior space.

Endohedral Fullerenes as medical radio diagnostics

Gadolinium-containing fullerenes can serve as a platform for developing future biomarker targeting contrast agents.

Gadolinium endohedral fullerene-based MRI contrast agents can be functionalized to specifically target atherosclerotic plaques.

Endohedral Fullerenes as theranostics

Specifically engineered gadolinium endohedral fullerene MRI contrast agents can cross the blood-brain barrier to selectively target and deliver a therapeutic payload to cancerous glioblastoma cells.

To sum up, the endohedral fullerenes are a well established class of carbon nanostructures. The interplay of carbon cages and encaged species results in new nanomaterials with exciting electronic states and properties. Prospective applications of endohedral fullerenes in biomedicine including MRI contrasting agents, X-ray contrasting agents, radiotracers and radiopharmaceuticals, antitumour agents, antimicrobial agents, provide a strong motivation for further active work in this field.

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