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Organelle-targeting surface-enhanced Raman scattering
(SERS) nanosensors for subcellular pH sensing

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Supramolecular chemistry of carbon nano-onions

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Carbon nano-onions (CNOs) are concentric multi-layered fullerenes. Their shape, size and layer count depends on the method of preparation. Their low cytotoxicity allows for high applicability in the biomedical field, in particular, nanomedicine. However, an adequate dispersion of particles in aqueous media is required for the most effective use in this application. Given the hydrophobic nature of pristine CNOs, as is the case with most carbon nanomaterials, they show poor water solubility. Non-covalent functionalisation can be utilised to alter their dispersibility properties, without affecting the intrinsic properties of the sp^2 nanomaterial. The use of CNOs in the field of nanomedicine also requires consideration of drug release at the target site. As covalent bonds are inadequate for this purpose, attention is brought towards non-covalent interactions as a viable option for targeted release. This minireview outlines the different methods and approaches for non-covalent modifications of CNOs reported in the literature.

1 Introduction

Nanomaterials are structures where at least 50% of the material has one of their dimensions in the 1 to 100 nm range; as defined under the 2011/696/EU directive[1]. Carbon nanomaterials (CNMs) are one of the most researched types of nanomaterials, given their wide range of applications in biology, chemistry, physics and engineering. One of the more widely researched CNMs is graphene; a 2-dimensional monolayer of carbon atoms in a hexagonal *honeycomb-like* arrangement, where all carbon atoms are sp^2 hybridized[2]. It has long been theorised to exist, but experimentally isolated and characterised by Novoselov *et al.* only in 2004[3]. There are many other types of CNMs, including carbon nanotubes[4], carbon nano-horns[5], fullerenes[6], carbon dots[7], and nanodiamonds[8]. Although this list is non-exhaustive, all of these materials have unique properties and applications. Carbon nano-onions (CNOs) are another type of CNM that have amassed considerable academic and industrial interest, given their versatility and a high potential for different applications.

CNOs are zero-dimensional carbonaceous nanoparticles characterised by their multi-layered closed shells enveloping one-another (Fig. 1) – a structure like that of an onion. The diameter of CNOs typically lies in the range of 1.4 and 50 nm, they have an interlayer distance of approximately 3.4 Å, and usually have a C_{60} or C_{80} fullerene at their core[10]. However, the specific dimensions and structure of CNOs can vary severely, and largely depends on the method of preparation[11]. Many issues and challenges exist in regards to reproducibly preparing CNOs

of well-defined size and structure. Presently, there are a vast number of preparation methods for CNOs of various shapes and sizes (Fig. 1). DC arc-discharge deposition of graphitic particles on negative electrode results in non-spherical, faceted, concentric graphitic particles of varying size with a 3-10 nm central hollow-space[12]. Curling and closure of graphitic networks by electron beam irradiation results in CNOs that are 47 nm (70 shells) to several micrometres in diameter, where the sphericity decreases with size[13]. Underwater arc discharge between two graphite electrodes results in CNOs 4-36 nm in diameter; other CNMs are side-products of this method[14]. Thermal annealing of DNDs at 1500°C under high vacuum in quasi-spherical and polyhedral CNOs 3-10 nm in diameter[15]. Thermal annealing of DNDs at 1650°C under a He atmosphere results in CNOs 5-6 nm (6-8 shells) in diameter[16]. Catalyst-free synthesis through thermolysis of $NaN_3-C_6Cl_6$ under Ar or air results in CNOs 50-100 nm in diameter with large 20-25 nm hallow-cores[17]. Thermal reduction of glycerin with magnesium powder at 650°C over 12 h results in a high yield of CNOs 60-90 nm in diameter connected through their outermost shells[18]. Fe/NaCl catalysed decomposition of acetylene at 420°C and heated to 1100°C results in CNOs 15-50 nm in diameter (mainly 15-35 nm) with metallic (Fe_3C) cores[19]. KrF laser vaporisation of carbon targets (40 wt% fullerene C_{60} with 60 wt% of carbon black or carbon nanofibres or carbon nanofibres with $LaNi_5$ catalyst) under a low-pressure (0.1 to 200 Torr) He atmosphere results CNOs as small as 1.4-2 nm (2-3 shells) in diameter[20,21]. Currently, thermal annealing of DNDs is arguably the best method for CNO preparation; it shows the highest potential for industrial mass-production, as this relatively inexpensive method results in a narrow-distribution of highly pure CNOs[22].

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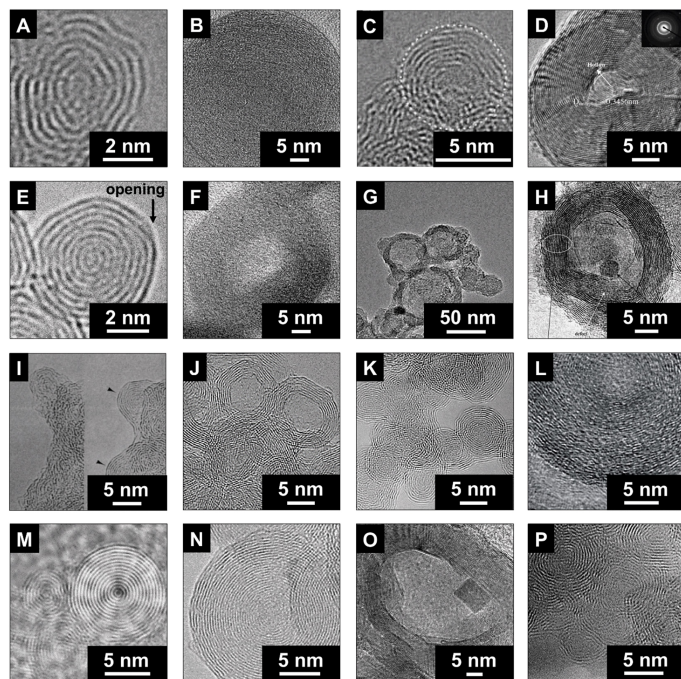Corresponding Author E-mail: silvia.giordani@dcu.ie

Fig. 1 A - P HRTEM micrographs of CNOs as synthesised through various methods. This figure is reprinted from ref. 9 with permission from the Royal Society of Chemistry.

Like many other CNMs, pristine CNOs (p-CNOs) produced through these methods are hydrophobic. This causes them to aggregate in aqueous and organic solvents, even after sonication. *Ipso facto*, p-CNOs exhibit low solubility. This lack of solubility and dispersibility can be ameliorated through modification of the nanomaterial itself, as can be achieved by covalent and non-covalent surface modification. Covalent functionalisation methods have been highly reported in literature[23]. Of the many covalent approaches reported, oxidation of CNOs exhibits particular popularity; justified by the properties of the resulting oxidised CNOs (oxi-CNOs) which show good water dispersibility, and also allow for further amidation and esterification reactions. One efficient and commonly utilised approach to the oxidation of p-CNOs is through the reaction with 3 M HNO_3 under reflux conditions for 48 hours[11,24]. In terms of stability, covalent bonding is superior to non-covalent binding as an effect of load-transfer from the attached group to the CNM; however, the drawback of the covalent approach is the disruption of sp^2-hybridized structure with sp^3-hybridized carbons at the point of covalent bond formation. Disrupting this regular structure affects the intrinsic properties of CNOs, such as their reactivity, mechanical toughness, and conductivity[25]. In consequence, this minireview explores the current understanding and developments in the non-covalent approach to surface modification of CNOs.

Non-covalent surface modification is also of particular interest to biomedical applications. In general, CNOs show low-cytotoxicity and great biocompatibility across many biological systems. *In vitro* assays of various functionalised CNOs

(f-CNOs) have been carried out on various cell lines, showing good results – these included cytotoxicity assays of MCF-7 cells[26], HeLa cells[27–30], HeLa Kyoto cells[31], 4T1 cells[32], and KB cells[27]. Moreover, f-CNOs have also shown good biocompatibility with fresh-water polyps (*Hydra vulgaris*)[33], common fruit flies (*Drosophila melanogaster*)[34], and zebrafish (*Danio rerio*)[35,36]. This biocompatibility and low-cytotoxicity gives rise to a high potential for CNOs to be engineered for the use in nanomedicine as drug carriers. The development of non-covalent surface modification of CNOs to create multifuncitonalised hybrids would allow for many applications in the nanomedicine field. Some possible applications include the coupling with targeting peptides & fluorophores for bioimaging applications[27], coupling with targeting peptides & drug molecules for drug delivery applications, coupling with targeting peptides & sensors for diagnostic applications[37], and coupling with targeting peptides & nano-robots for cell repair applications[38]. However, if CNOs are to be used for targeted drug delivery, the mode of drug attachment to the CNOs needs consideration. It is not enough for the system to reach the target-site if the drug does not release. As such, non-covalent interactions are preferred, as they are weak and reversible.

A plethora of non-covalent interactions have been observed, measured and defined; ranging from weak interactions such as the Casimir force[39], to those more moderate in strength, such as interactions of ionic character. To quote Hans-Jörg Schneider:

> With courageous simplification, one might assert that the chemistry of the last century was largely the chemistry of co-valent bonding, whereas that of the present century is more likely to be the chemistry of noncovalent binding[40].

Non-covalent interactions that can be utilised in the creation of CNO-based supramolecular systems include electrostatic interactions, van der Waal forces, and π interactions (Fig. 2). More specifically, these can be divided into the following: the charge-charge interaction (Fig. 2A); also called an ionic interaction, it is a repulsion/attraction between two formal charges[41]. Halogen bonding (Fig. 2B); a type of σ-hole interaction that allows covalently bonded halogens to bind nucleophiles and electrophiles alike[42]. Hydrogen bonding (Fig. 2C); a proton transfer reaction between a proton donor (Fig. 2C R−H) and a proton acceptor (Fig. 2C A)[43]. The charge-dipole interaction (Fig. 2D); an attraction/repulsion of a formal charge and the point dipole charge of a dipole moment[44]. The dipole-dipole interaction (Fig. 2E); an attraction/repulsion of two point dipole charges[44]. The dipole-induced dipole interaction (Fig. 2F); an interaction that occurs when a polar molecule induces a dipole moment in a polarisable molecule through electric field induced separation of HOMO-LUMO energies. An attractive interaction then occurs between the permanent dipole moment of the first molecule, and the dipole moment of the polarised molecule[44]. The π-π interactions (Fig. 2G); often referred to as π-π stacking, these are interactions occurring between two π-electron rich systems[45]. The charge-π interaction (Fig. 2H); an interaction between the formal charge of a molecule and π-orbitals. The
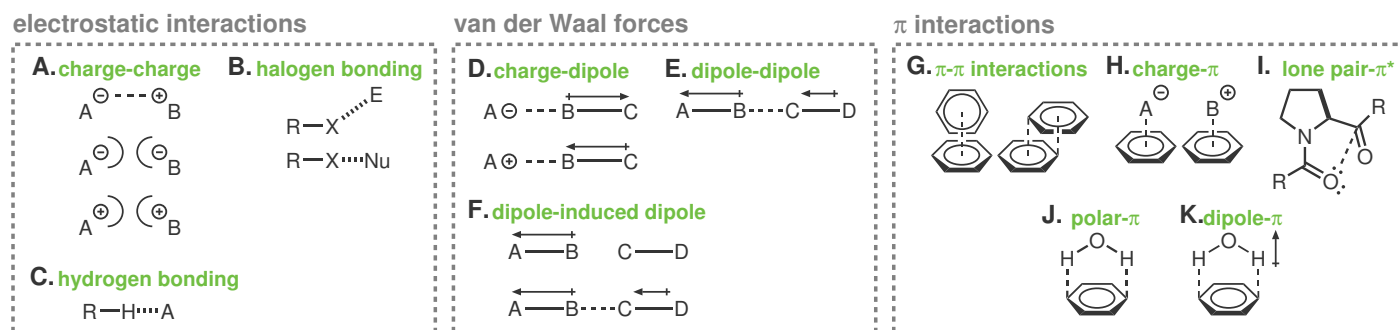
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Fig. 2 A-K Common non-covalent interactions that may be utilised in the non-covalent functionalisation of CNOs[41–46]. This list is non-exhaustive in terms of various non-covalent interactions; interactions which are not applicable to this review, such as metallic bonding and London forces, have been omitted.

lone pair-π interaction (Fig. 2I); also called a $n \rightarrow \pi^*$ interaction, this is an interaction between an electron lone pair and a π^* orbital[46]. The hydrophobic interaction; an entropy driven tendency of non-polar solutes to aggregate in polar solvents[44].

2 Non-covalent surface modification of CNOs

The first supramolecular complexes of CNOs have been reported by Echegoyen *et al.* in 2008. Their approach involved the attachment of pyridyl ligands to the CNO surface. This was achieved through a multistep method; the CNOs were first oxidised by reaction with a 3:1 ratio of H_2SO_4/HNO_3 for 10 minutes. The resulting oxi-CNOs were then reacted with 4-aminopyridine at 170°C for 24 hours. This resulting pyridyl functionalised CNOs (py-CNOs) could then undergo a complexation reaction with transition metals. They demonstrated such a complexation with the use of zinc tetra-phenyl porphorin (ZnTPP). When reacted with the py-CNOs, the Zn underwent axial ligation, binding to the pyridyl groups. This resulted in the formation of a py-CNO/ZnTPP supramolecular system (Fig. 3), with possible applications in catalysis and hydrogen storage. The results suggest that similar nanohybrids can also be synthesised with the use of platinum and palladium porphyrins[47].
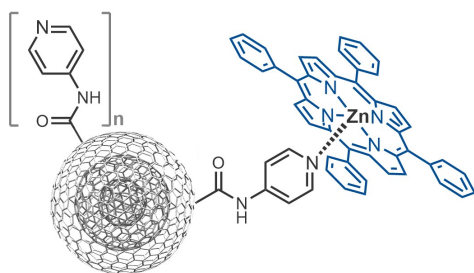

Fig. 3 Schematic of the first CNO-based supramolecular system; the py-CNO/ZnTPP complex designed by Echegoyen *et al.*[47].

In 2012, Plonska-Brzezinska, Echegoyen *et al.* investigated a strategy for improving the conductivity of poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS);

a highly-conjugated electrode material. Their approach involved the incorporation of CNOs into the polymers through non-covalent interactions. The group created the supramolecular composites by wrapping p-CNOs and oxi-CNOs with PEDOT:PSS at various mass ratios relative to the CNOs. This was achieved by dispersing PEDOT:PSS and CNOs in water and sonicating for 2 hours, followed by a filtration, washing and drying process. The CNO/PEDOT:PSS composites were then used to prepare films for electrode purposes. These were prepared by redispersing the composites in ethanol through sonication, followed by the drop-casting methods. Electrochemical studies of these materials suggested that the non-covalent incorporation of CNOs into PEDOT:PSS is a viable approach for creating materials suitable for electrode and supercapacitor applications[48].

The same year, Plonska-Brzezinska, Echegoyen *et al.* decorated oxi-CNOs and p-CNOs with *p*-phenylenediamine (*p*-PDA) and 4-aminobenzoic acid (4-ABAc) respectively. The group found that this modification considerably increased the solubility of the nanomaterials in protic solvents and increased dispersibility in aqueous solutions with no agglomeration being observed. The surface residues of the two nanomaterials were then polymerised *in situ* with aniline, resulting in CNO/poly-*p*-PDA/PANI and CNO/4-ABAc/PANI. These final polymer-wrapped systems showed good solubility in water, methanol and THF[49]. Although this example does not involve a non-covalent surface modification, the polymer wrapping which envelops the CNOs contains hydrogen bond acceptors (HBA), which can be utilised to non-covalently bind molecules of interest. Further cases where CNOs have been covalently polymer-wrapped exist[24,50–52], though, the concept that molecules of interest can be non-covalently incorporated into these polymer networks remains largely the same.

Also in 2012, Overbury *et al.* studied the microscopic diffusivity dynamics of phenanthrenequinone (PQ) on the surface of CNOs using quasielastic neutron scattering (QENS) as a function of PQ surface coverage and temperature. They prepared two PQ-modified CNO supramolecular complexes, one of high PQ surface coverage (0.60 PQ/nm^2) and one of low PQ surface coverage (0.23 PQ/nm^2). They achieved this by dispersing

various concentrations of PQ in methanol and mixing with CNOs for 20 minutes. They then vacuum-filtered the samples and oven-dried the material, thereby obtaining supramolecular complexes where PQ was π-π stacked onto the CNO surface. Their QENS study unexpectedly revealed that PQ molecules on CNO surface exhibit similar dynamic behaviour to that of water on oxide surfaces [53].

In 2013, Plonska-Brzezinska, Echegoyen *et al.* explored non-covalent polymer-wrapping of CNOs with poly(ethylene glycol)/polyscorbate 20 (PEG/P20) and poly(4-vinylpyridine-*co*-styrene) (PVPS). For this purpose, oxi-CNOs and p-CNOs were polymer-wrapped with PEG/P20 and PVPS respectively. PVPS-wrapped CNOs (CNO/PVPS) were also further functionalised with two thiol derivatives; 3-mercaptopropionic acid (MPA) and 2-mercapto-4-methyl-5-thiazoleacetic acid (MMTA). Overall, the resulting CNO/PEG/P20, CNO/PVPS, CNO/PVPS-MPA & CNO/PVPS-MMTA supramolecular systems showed enhanced water solubility and dispersibility. The specific use of the PVPS & PEG/P20 polymers also allowed for further functionalisation through thiol chemistry. These supramolecular systems revealed that non-covalent polymer-wrapping is a viable approach to increasing solubility and dispersibility of CNOs. The flavonoid biomolecule, quercetin, was then hydrogen bonded onto the polymers in CNO/PEG/P20, CNO/PVPS-MPA & CNO/PVPS-MMTA through sonication of the aqueous dispersions. The successful incorporation of quercetin indicated the promising potential of applying these supramolecular CNO-based systems in the fields of biosensing and targeted drug delivery [54].

In 2014, Echegoyen, Fragoso *et al.* created CNO-based supramolecular structures which involved host-guest non-covalent interactions. They prepared and oxidised small CNOs (6-12 shells), and covalently functionalised the surface with β-cyclodextrin (βCDs). The βCDs would then act as a host to ferrocene grafted dextran polymers (Fc-Dex). The resulting Fc-Dex wrapped CNOs-βCDs (Fig. 4) were highly soluble as a result of inclusion complexes between Fc and βCDs moieties [55].
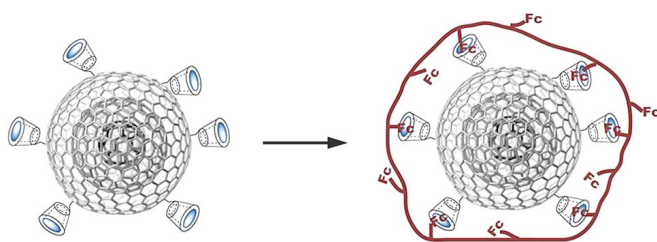

Fig. 4 Schematic representation of the host-guest attachment of Fc-Dex to CNOs-βCDs, resulting in a water soluble supramolecular system. This figure is adapted from ref. 55 with permission from ACS.

In 2015, our group reported a non-covalent functionalisation of p-CNOs through π-π interactions. The aim of our research was cellular imaging and cell internalisation pathway elucidation. For this purpose, we prepared a soluble CNO-based supramolecular system with fluorescent properties – we reacted p-CNOs with a pyrene-BODIPY dyad, forming a non-covalent assembly, whereby the aromatic part of the dyad was π-π stacked onto the p-CNO surface (Fig. 5); a similar approach to that carried out by Erbas *et al* on CNTs [56]. The resulting system showed good cellular uptake by HeLa cells through an endocytosis pathway, and low cytotoxicity [29], opening up the possibility of using non-covalently functionalised CNOs as efficient shuttles for targeted hydrophobic drug delivery.
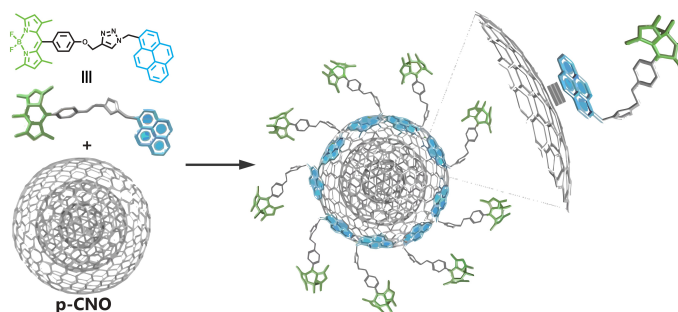

Fig. 5 Schematic diagram for the non-covalent π-π stacking interaction of the aromatic rings on the pyrene-BODIPY dyad with the p-CNO surface. This figure is adapted from ref. 29 with permission from the Royal Society of Chemistry.

In 2016, Tripathi *et al.* researched the use of CNOs as selective tunable photoluminescent sensors for glucose. In their approach, carbon nanoparticles were prepared through pyrolysis of vegetable ghee, and then oxidised through the standard method [11,24]. The most fluorescent fraction was isolated through high-speed centrifugation, followed by gel filtration. When excited from 400 to 660 nm, the oxidised nanoparticle exhibited photoluminescence across the 550 to 800 nm range. When coupled with methylene blue, the compound enveloped the negatively-charged surface of the nanomaterial through non-covalent surficial charge transfer and hydrophilic interactions, resulting in the quenching of photoluminescence. When glucose was introduced into the system, glucose molecules abstracted methylene blue from the nanoparticle surface through hydrogen-bonding, turning the photoluminescence back on (Fig. 6). The selective detection limit of glucose for this system was measured at 1.3×10^{-2} M [57].

Also in 2016, Plonska-Brzezinska, Echegoyen *et al.* explored the use of surfactants to disperse CNOs for biomedical applications. They investigated surfactants of cationic, anionic and non-ionic character to non-covalently modify the surface of CNOs. These included: sodium dodecyl sulfate (SDS), sodium dodecyl benzene sulfonate (SDBS), hexadecyltrimethylammonium bromide (CTAB), 4-(1,1,3,3-tetramethylbutyl)phenyl-polyethylene glycol (Triton X-100), and polyethylene glycol sorbitan monolaurate (Tween 20). Their study revealed that these surfactants adsorb onto the CNO surface, resulting in stable and well dispersed CNO/surfactant composites. Moreover, *in vitro* antimicrobial assays of these CNO/surfactant composites on a strain of *Escherichia coli* revealed that only the CNO/CTAB composite decreased cell viability, as an effect of composite dissociation in
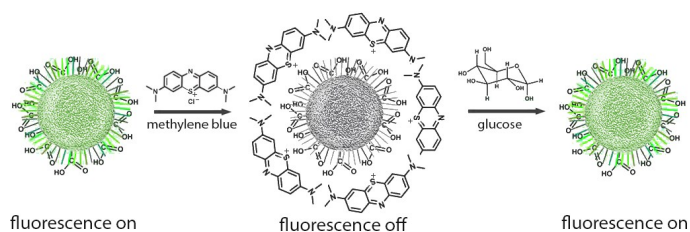
Fig. 6 Schematic diagram for the glucose mediated *on/off* switching of photoluminescence. As methylene blue non-covalently binds into the surface of the nanoparticle, the photoluminescence is switched *off* (middle). In the presence of glucose, methylene blue is abstracted from the surface, switching the photoluminescence back *on* (right). This figure is adapted from ref. 57 with permission from the Royal Society of Chemistry.

water[58].

In 2017, Sarkar *et al.* oxidised CNOs through the standard method[11,24], and reacted the resulting oxi-CNOs with double-strand calf-thymus DNA (dsDNA) in water. They observed that oxi-CNOs facilitate the unzipping of dsDNA into single-strand DNA (ssDNA), followed by the macromolecular aggregation of ssDNA with oxi-CNOs. The aggregation progressed over a 16 h period, resulting in the formation of various shapes of increasing complexity; rod → triangle → hexagon → 6-petal flower → flower assortments (Fig. 7). Sarkar interpreted the aggregation as a polymer-wrapping of the ssDNA around oxi-CNOs through hydrogen-bonding interactions[59].
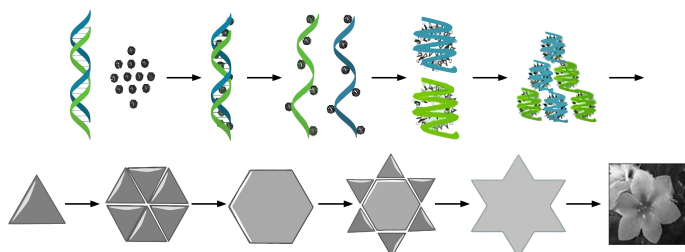

Fig. 7 Formation of supramolecular structures of increasing complexity through aggregation of ssDNA with oxi-CNOs (depicted as black-balls). This figure is adapted from ref. 59 with permission from Springer under Creative Commons Attribution 4.0.

In 2018, Revuri *et al.* created a white-light emitting CNO-based supramolecular system for the detection of glutathione (GSH); a cancer biomarker. They used sodium deoxycholate (DOCA) to prepare WCNOs (white-light emitting CNOs) through the pyrolysis method (heated at 400°C for 90 min). These WCNOs had a broad distribution of hydroxyl and carboxyl groups on their surface, which were responsible for the emission properties of the nanomaterial. They then coated the WCNOs in a MnO$_2$ nanosheet through the addition of KMnO$_4$. The resulting MnO$_2$ nanosheet-coated WCNO supramolecular system showed good water-solubility and no fluorescence; an effect of the FRET-mediated fluorescence quenching of MnO$_2$. The material was then evaluated as a possible biosensor for the detection of GSH

in vitro (on 4T1 metastatic breast cancer cells) and *in vivo* (in Balb/C mice). When the system was exposed to cancer-cells, the MnO$_2$ nanosheet coating of the WCNOs has been shown to be selectively abstracted by GSH. This etching of the metallic coating thus restored the WCNOs fluorescence properties. The results of this study indicated that WCNOs non-covalently coated in metallic nanosheets have the potential for use in biosensing and nanomedicine[32].
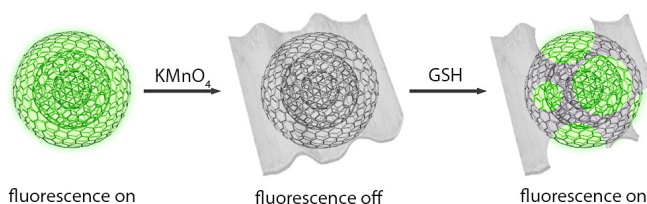

Fig. 8 Schematic diagram for the GSH-selective fluorescence-based manganese oxide coated WCNO biosensor. The surface coverage of WCNOs with a metallic coating quenches their fluorescence. GSH, a cancer biomarker, has shown to selectively etch the MnO$_2$ coating from WCNOs, allowing them to regain their multichannel fluorescence.

Also in 2018, Fragoso *et al.* explored the use of crown ethers and aminated, biocompatible polymers to create a dispersible supramolecular, CNO-based system. Onto the surface of p-CNOs, the group covalently functionalised 4-aminobenzo-18-crown-6 crown ethers through a reaction with diazonium salts. The nanoconstructs were then dispersed in a 2% w/v aminated carboxymethyl cellulose solution. The amine groups in the resulting supramolecular system coordinated to the crown ethers through a non-covalent interaction between the positively charged ammonium groups and the crown ether oxygen atoms (Fig. 9), resulting in a stable aqueous dispersion. It was also discovered that the system is sensitive to pH increase and potassium competition for crown ether coordination[60].

In 2020, our group reported the use of hydrophobic interactions to non-covalently functionalise p-CNOs with a conjugate consisting of hyaluronic acid (HA) covalently linked to a 1,2-dimyristoyl-*sn*-glycerol-3-phosphoethanolamine (DMPE) phospholypid. When p-CNOs were reacted with the conjugate HA-DMPE, a hybrid material was formed. In this material, the hydrophobic chains of the phospholipid non-covalently interacted with the p-CNO surface, while the hydrophilic chains of HA increased water solubility (Fig. 10). This approach worked well, as the hybrid nanomaterial remained well-dispersed in water after 30 days. HA-DMPE with a fluoresceinamine tag (Fl-HA-DMPE) was also reacted with p-CNOs. This reaction yielded similar results, as well as fluorescent properties, which allowed for *in vitro* cellular uptake and *in vivo* biodistrubution studies on zebra fish. Our results indicated that the use of HA provided the supramolecular system with hyaluronate (CD44$^+$) receptor targetability. Moreover, the nanoconjugates showed no toxic effects in zebrafish during development from embryo to larvae[61].
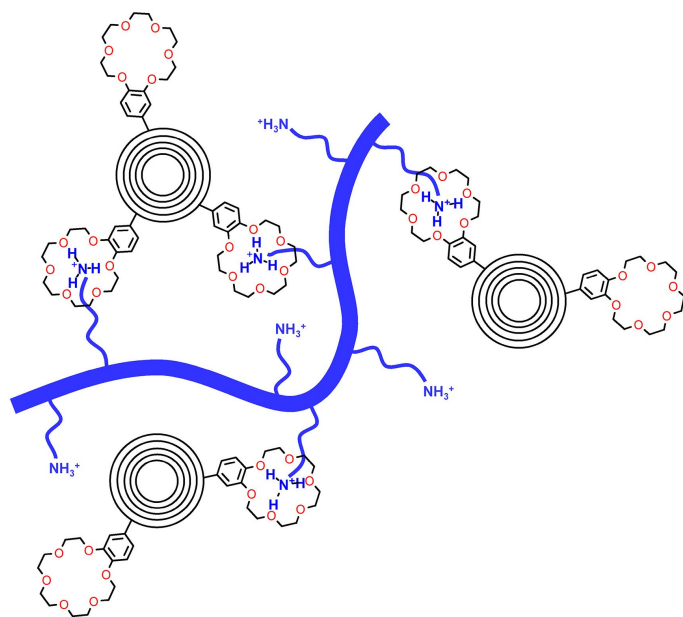
Fig. 9 Supramolecular dispersion of CNOs via the capturing of ammonium cations on an aminated carboxymethyl cellulose polymer by the oxygen atoms of crown ethers covalently functionalised onto the CNO surface. This figure is adapted in part from ref. 60 with permission from Elsevier.
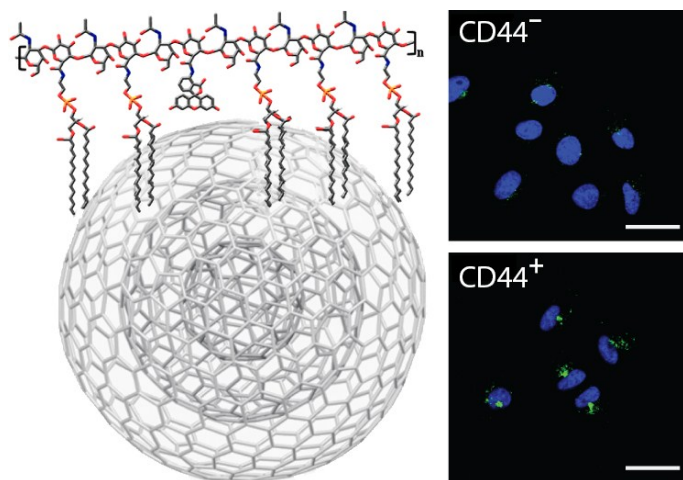

Fig. 10 Schematic for the non-covalent hydrophobic interaction between the HA-DMPE chains and the p-CNO surface (left), and the receptor targetability of the supramolecular nanoconstruct demonstrated on cells overexpressing the HA receptor (CD44+; green fluorescence, vs. CD44-; negligible green fluorescence). Scale bars are equal to 10 μm. This figure is adapted from ref. 61 with permission from Elsevier.

3 Conclusions

Discovered by Ugarte in 1992, carbon nano-onions (CNOs) are concentric multi-layer fullerenes with a regular sp^2 hybridised surface. Their mechanical, chemical and biological properties contribute to many applicabilities, particularly in the nanomedical field. However, CNOs share an unfavourable property with many other carbon nanomaterials (CNMs); they have a very hydrophobic nature. This lends to the difficulty in dispersibility and solubilisation of the material, and so the surface needs

to be altered prior to the application of CNOs to biological systems. Conventionally, this has been achieved through covalent chemistry, which comes with a disadvantage – covalent modification of CNOs disrupts the regular sp^2 structure, altering the nanomaterials intrinsic properties. As such, attention is slowly shifting to non-covalent surface modification approaches as an alternative. As of writing, examples of these approaches are sparse in literature. These include complexation with metal ligands, various polymer-wrapping approaches, charge-charge interactions with oxi-CNOs, and π-π stacking interactions with pristine CNOs. It can be speculated that non-covalent functionalisation reported for other sp^2 CNMs can be drawn at to similarly functionalise CNOs, given their similar chemistry.

Conflicts of interest

There are no conflicts to declare.
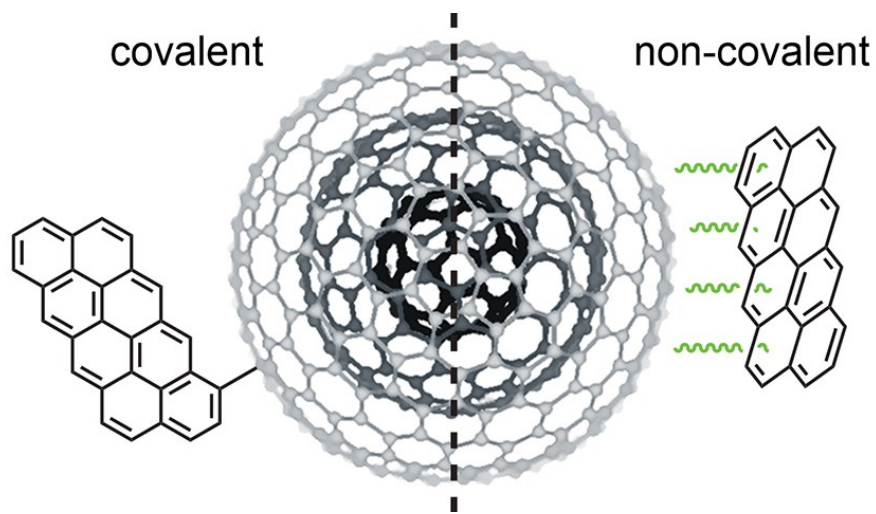
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An exhaustive and succinct minireview of the various reported approaches to the non-covalent surface modification of carbon nano-onions (CNOs).

80x39mm (300 x 300 DPI)