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Gene Delivery with Organic Electronic Biomaterials

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Abstract: Gene therapy may be capable of treating a variety of diseases, a prerequisite of which is the successful delivery of polynucleic acids (e.g., DNA, RNA) to a patient's cells. Delivery can be achieved technologically (e.g., using electroporation), using viruses (natural gene delivery vectors) or non-viral vectors (e.g., lipids, nanoparticles, polymers). This article aims to give the reader an overview of the use of organic electronic materials (i.e., fullerenes, graphenes and conjugated polymers) as non-viral gene delivery vectors.

Keywords: organic electronics, carbon nanotubes, fullerene, graphene, conjugated polymer, gene delivery, gene therapy, biodegradable.

1. INTRODUCTION

Gene delivery has become a well-established field of science [1-4]. While viruses are Nature's protein-based gene delivery vectors, various other vectors have been investigated for their ability to deliver deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), including lipids, nanoparticles, polymers (e.g. polyethyleneimine (PEI) or polyamidoamine (PAMAM) dendrimers, depicted in Fig. **1**), and the bountiful literature is discussed in some interesting reviews [1-4]. Gene therapy was first approved for use by the European Commission (a viral gene vector, Glybera®, to treat lipoprotein lipase deficiency that can cause pancreatitis) [5-8], and recent clinical trials for the use of gene therapy to treat a variety of conditions including leukemia, myeloma and Parkinson's disease have been promising [9-13].

Organic electronic materials (OEMs) are of interest for technical and biomedical applications [14-20]. OEMs are typically comprised of fullerenes (bucky balls or nanotubes), graphene/graphene oxide, or conjugated polymers (e.g. polyaniline, polypyrrole or polythiophene), examples of which are depicted in Fig. **2**. Importantly, derivatives of these are commercially available allowing researchers to tailor the properties of the OEMs either through chemical modification or the generation of composites, with a view to their use for technical applications (e.g. diodes, solar cells, transistors) and medical applications (e.g., drug delivery, electrodes for the nervous system, theranostics) [14-20]. The optical properties (e.g., high fluorescence yield, high photostability) of organic electronic nanoparticles allows them to be imaged, and chemical modification of the nanoparticles facilitates complex formation with their therapeutic payload and targeting to specific cells, potentially yielding particles capable of simultaneous diagnostic, imaging and therapeutic activity [21].

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The focus of this article is gene delivery systems that are based on nanoscale OEMs, highlighting examples of each class of nanoscale OEMs in a systematic fashion to give the reader an overview of the topic.

2. FULLERENE-BASED NON-VIRAL VECTORS FOR GENE DELIVERY

Fullerenes are carbon-based nanomaterials, that are either spherical (bucky balls) or ellipsoids/tubes (commonly known as carbon nanotubes) depicted in Fig. **2**, and for which the Nobel Prize in Chemistry was awarded to Curl, Kroto and Smalley in 1996.

2.1. Bucky balls

Unmodified bucky balls are hydrophobic rendering them poorly soluble in aqueous media, and interesting fundamental studies show that they interact with amphiphilic cell membranes prior to uptake [22-25], they are relatively quickly cleared from blood (accumulating in the liver and spleen [25]), and they exhibit dose-dependent toxicity *in vivo* (low toxicity at low concentrations in mice, and high toxicity at high concentrations with potential for mutagenic/teratogenic activity) [25].

Bucky balls functionalized with hydrophilic anionic/cationic species (Fig. **3**) improves their solubility in water and renders them capable of forming complexes with calf thymus DNA as demonstrated by Nakamura and coworkers [26]. Bucky balls displaying four amines transfect vector plasmids (pGreen LANTERN-1) into fibroblast-like monkey kidney tissue cells, COS-1 cells [26]; and interestingly, the presence of serum plasma may assist dispersion of bucky ball-DNA/RNA complexes and their effective uptake [27]. Various derivatives of bucky balls have been described [28-32], including bucky ball derivatives displaying polymers such as PAMAM dendrimers that were capable of delivering DNA to the

MCF-7 human-derived breast cancer cell line or human-derived cervical cancer HeLa cells [33], and bucky ball derivatives displaying polyethyleneimine (PEI) and poly(ethylene glycol) (PEG) that were capable of delivering DNA to human embryonic kidney (HEK293) cells [34]. An elegant diversity-oriented study showed that tetra(piperazino)fullerene epoxide (Fig. **3**) was more effective and less toxic than the commercially available lipid-based transfection reagent Lipofectin® [35], and this was also demonstrated to effectively deliver the plasmids (encoding GFP) *in vivo* in the ICR strain of mice [36], and siRNA to EGFP-overexpressing C57BL/6 mice [37].

2.2. Carbon nanotubes

Studies of the biological fates of carbon nanotubes with different dimensions (i.e. diameter and length) are important, particularly for uncovering differences between single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs). The fates of intact MWNTs (with diameters of 20-30 nm and lengths of up to 1000 nM) were compared to shorter oxidized nanotubes [38]; both intact and oxidised nanotubes were taken up by a combination of endocytosis and phagocytosis; and the intact nanotubes were present in both intracellular and extracellular domains whereas the oxidised versions were detected preferentially in intracellular vesicles with limited amounts in extravesicular cytoplasm or brain parenchymal areas. The surface chemistry appeared to play a role in the inflammatory response to the nanotubes implanted in the brain of mice; with astrocyte and microglia activation in the vicinity of the injections, with slightly greater inflammatory response to the oxidized than the intact nanotubes after 30 days [38]. MWNTs (with diameters of $\geq$ 20 nm) were shown to induce p53-dependent responses in fetal development, moving across the blood-placenta barrier, restricting the development of foetuses and inducing brain deformity (i.e. teratogenicity), whereas smaller MWNTs (with diameters of 8 nm) showed markedly less fetotoxicity and SWNTs showed no fetotoxicity relative to controls, suggesting that MWNTs damaged the DNA, thereby inducing cell cycle arrest and apoptosis [39]. MWNTs (with diameters of 20-50 nm) used to transfect DNA into *Escherichia coli* were shown to damage the DNA (i.e. they were genotoxic), which resulted in mutation of the bacteria [40], and the results of these studies have given useful insight that will hopefully inform future research [41].

Akin to unmodified bucky balls, unmodified carbon nanotubes are hydrophobic which makes surface functionalization with hydrophilic moieties capable of forming electrostatic complexes with DNA/RNA commonplace [42, 43]. Nanotube functionalization via covalent and non-covalent methodologies [43, 44] is straightforward, and cell-specific targeting of nanotubes can be achieved with cell-specific ligands [43-45], or the application of external stimuli such as magnetic fields to magnetic derivatives of carbon nanotubes [46]. Interestingly, amine [47] or carboxylate [48] functionalized nanotubes can be degraded enzymatically with horseradish peroxidase or fluids that mimic the phagolysosomal fluid of macrophages has encouraged the development of carbon nanotube-based gene delivery vectors, and is discussed in excellent reviews [49-52].

Molecular modeling and experimental data indicates that complex mixture of supramolecular interactions, including electrostatic, hydrogen bonding, π-stacking and van der Waals interactions play a role in the binding of nanotubes to DNA [53-61], and RNA [57, 62-65]. An elegant study including computational simulations and in vitro cell culture studies with keratinocytes highlighted the role of the electronic structure of nanotubes on RNA binding and delivery, with metallic SWNTs delivering siRNA into the nucleus of keratinocytes, whereas semiconducting SWNTs transported siRNA only to the cytoplasm [66]. Interestingly, hydrophobic interactions that facilitate DNA binding to anionic carboxy-functionalized MWNTs yield complexes that were shown to transfect the DNA more effectively into Nile Tilapia (*Oreochromis niloticus*) spermatogonial stem cells than either electroporation or Lipofectamine® 2000 [67]. It is noteworthy that while cationic lipids can be effective non-viral vectors for gene delivery [68, 69], their formulation with nanotubes may increase the amount of DNA carried in otherwise equivalent formulations, improve their stability in the presence of serum (in analogy to the effect observed for bucky balls [27]) and improve their transfection efficiencies relative to commercially available Lipofectamine® 2000 [70]. Complexes of SWNTs, PEGylated phospholipids, poly(allyamine hydrochloride) and siRNA were capable of targeting the mutant K-Ras gene in human pancreatic carcinoma epithelial-like PANC-1 cells, and diminishing gene expression levels of mutant K-Ras mRNA by ca. 30% *in vitro* [71]. Complexes of amine functionalized SWNTs with cationic liposomes and siRNA (capable of targeting the luciferase gene in human lung cancer A549-Luc cells) were effective in silencing the luciferase gene, and a synergistic pro-apoptotic effect was obtained when delivering siRNA (siPLK1) and doxorubicin from the complexes in A549 cells *in vitro* [72], and moreover in Calu6 tumor xenografts [73]. Furthermore, complexes of nanotubes with cationic lipids and glyceraldehyde 3-phosphate dehydrogenase siRNA function *in vivo* in CD-1 mice, effectively mediating gene silencing [74].

Functionalization of nanotubes with naturally occurring amines (e.g. spermidine, spermine) yields bottle brush-like structures that are analogous to dendrimers with high binding affinities due to multivalency effects [75-80]. If nanoparticle-DNA or nanoparticle-RNA complexes are stuck in endocytic vesicles (which fuse with early endosomes, mature into lysozomes, and then degrade biomolecules trapped inside), treatment with chloroquine assists their escape from the vesicles [57, 76]. However, the generation of stimuli-responsive nanotubes potentially offers additional control of the location/time of payload delivery, and as such attaching cationic moieties via bioreducible disulphide bonds [81-83] facilitates the delivery of their therapeutic payload

siRNA (that suppresses tumor activity through interfering with MDM2 protein binding to p53 protein [84]), to breast carcinoma B-CAP-37 cells [85]. Complexes of amine-functionalized SWNTs and DNA effectively delivered the oncogene suppressor p53 gene to human breast cancer MCF-7 cells [85]; complexes of other amine-functionalized SWNTs have successfully transfected plasmid DNA (encoding the vp7 gene) to fish (grass carp) *in vivo* [86-89]. Interesting studies directed towards diminishing brain damage after stroke and traumatic brain injury by silencing caspase-3 expression (activation of which results in cell death) via carbon nanotube-mediated delivery of caspase-3 siRNA was shown to reduce neurodegeneration and promote functional preservation before and after focal ischemic damage *in vivo* in rats [47].

Functionalization of nanotubes with synthetic polyamines (e.g. PEI [90, 91] or polyamidoamine (PAMAM) dendrimers [92, 93]) is popular as the synthetic polyamines are effective non-viral gene delivery vectors, and conjugated to nanotubes they enable gene transfection both *in vitro* and *in vivo*, enabling transfection of microRNA regulating angiogenesis [94].

PEI-functionalized SWNTs delivered anti-luciferase siRNA into human lung cancer cell line H1299 (which expresses firefly luciferase), and were found to less effective than either PEI or Lipofectamine® 2000 and more cytotoxic than either PEI or Lipofectamine® 2000 [95]. Interestingly, analogously functionalized SWNTs [96] or MWNTs [97] effectively transfect DNA plasmids encoding luciferase into mouse neuroblastoma Neuro-2a cells *in vitro*, and for the SWNTs *in vivo* studies delivering the nanotube-DNA complexes via intravenous injection into the tail vein of rats showed the highest levels of transfection to the lungs [96].

First generation (G1) PAMAM-functionalized MWNTs were shown to transfect the pGL3 vector (encoding luciferase) into HeLa cervical cancer cells and the monkey kidney fibroblast-like COS-7 cell line, with greater efficiency and lower toxicity than the nanotubes, G1 PAMAM (1.4 kDa) or 25 kDa PEI alone [98]; by comparison, fourth generation (G4) PAMAM-functionalized MWNTs were more effective at transfection of DNA (encoding GFP) into the HeLa cells than the nanotubes or PAMAM alone yet somewhat less effective than Lipofectamine® 2000, and importantly, G4 PAMAM-functionalized nanotubes were less cytotoxic than either G4 PAMAM or Lipofectamine® 2000 [99]. An analogous study using first to third generation (G1-G3) PAMAMs showed that G2 was the optimal for transfection (nanotube-G2: 6.8 % vs nanotube-G1 2.2% or nanotube-G3 4.1%), albeit slightly more toxic than the G1 derivative [100]. Functionalization of the surface of MWNTs with G1 or G2 PAMAMs facilitated the transfection of a fluorescently labelled siRNA [101, 102], whereas functionalization with G1 to G5 PAMAMs facilitated the transfection of antisense c-myc oligonucleotides into human breast cancer cells (MCF-7 and MDA-MB-435 cells) and human liver cancer HepG2 cells down regulating the expression of the C-Myc gene and protein, and in this case the G5-functionalized nanotubes were most effective [103]. Carbon nanohorns functionalized with G4 or G6 PAMAM were shown to be effective at delivering siRNA that diminished levels of house-keeping GAPDH mRNA or p42-MAPK mRNA *in vitro* [104].

Functionalization of nanotubes with ligands that target specific receptors displayed on cells is one method of targeting vectors to specific cell populations, for example folate-functionalization to target cancer cells that overexpress folate receptors [105]. Indeed, folate-functionalized chitosan conjugated to MWNTs effectively transfected pEGFP DNA into the HeLa cervical cancer cells *in vitro*. Importantly, the nanotubes displayed dimension-dependent transfection efficiency and toxicity, with shorter nanotubes (100-400 nm in length and external diameters of 10-20 nm) being the most effective at transfection yet also the most toxic, whereas longer nanotubes (800 nm to 3 μm in length and external diameters of 10-20 nm) were somewhat less efficient but markedly less toxic. Furthermore, the surface functionalization of MWNTs (with folate-functionalized chitosan) improves the transfection efficiency (of pEGFP DNA) to 1.5 times that of unfunctionalized MWNTs, and decreases their cytotoxicity relative to unfunctionalized MWNTs [106].

Aptamer-functionalized SWNTs enable targeted delivery of DNA/RNA to various cell lines. For example, SWNTs functionalized with 5 TR1 aptamers (targeting MUC1) enabled the delivery of Bcl-xL-specific short hairpin shRNA to MUC1 positive breast cancer cells *in vitro* [107]; likewise, SWNTs functionalized with AS1411 aptamers (targeting nucleolin receptors) enable the delivery of Bcl-xL-specific short hairpin shRNA to human gastric cancer AGS (+nucleolin) cells and achieve shRNA-mediated gene-silencing strategy [108].

Peptide-functionalization of nanotubes can markedly improve their solubility in aqueous media, which may in certain cases (e.g. $(\text{-Lys-Trp-Lys-Gly-})_7$) also improve transfection ability [109,110]. Alternatively, functionalization of SWNTs with the tumor targeting NGR peptide (Cys-Asn-Gly-Arg-Cys) enabled the effective transfection of siRNA to human prostate cancer (PC-3) cells that induced severe apoptosis and suppressed proliferation of the cells *in vitro*, and moreover, *in vivo* in tumor-bearing mice [111]. Interestingly, complexes of plasmid DNA (encoding GFP) with estradiol functionalized MWNTs enhances their transfection efficacy towards cells that overexpress estrogen receptors over Lipofectamine® 2000, both *in vitro* (to estrogen positive MCF-7 cells) and *in vivo* in rats [112].

The use of external stimuli such as light or magnetic fields may enable relatively high levels of spatiotemporal control of gene delivery. Indeed, complexes of SWNTs with cholesterol-functionalized PEI and pTP53 plasmid DNA enhanced apoptosis and necrosis of HeLa cells *in vitro*, and achieved a higher tumor-growth inhibition *in vivo*, when enhanced by near infrared (NIR) laser-mediated

photothermal transfection (Fig. **4**) [113]. This was demonstrated by a variety of studies. The pTP53 containing the p53 gene (a cancer suppressor gene that may induce tumor cell apoptosis and arrest the cell cycle at the G1/S phase) was used as the therapeutic plasmid DNA, optionally in combination with SWNTs with cholesterol-functionalized PEI attached. The population of HeLa cells treated with naked pTP53 increased in the G0/G1 (Quiescence/Growth) phase, and a slight decrease in the G2/M (Growth/Mitotic) phase. The cells treated with the complexes of DNA and functionalized SWNTs showed a small population increase in the G0/G1 phase, and a larger decrease in the G2/M phase which was pronounced when exposed to NIR laser irradiation (3 W cm−2, 3 min) to approximately the same as Lipofectamine® 2000 (see histograms and graph bars of cell cycle in Figure 4A and 4B, respectively). It was observed that the treatment with the complexes of DNA and functionalized SWNTs and NIR laser irradiation induced significantly more necrosis and apoptosis of the HeLa cells, when compared to treatment with pTP53, Lipofectamine® 2000, or the functionalized SWNTs in the absence of NIR irradiation (see bar charts for apoptosis/necrosis in Figure 4C and the results of flow cytometry studies in 4D). These results were confirmed by observing the nucleus morphology with Hoechst 33342 staining of the cells after 72 h with various treatments, where the highest number of bright dots (which indicate nucleus damage) was observed for cells after the treatment with the complexes of DNA and functionalized SWNTs and NIR laser irradiation (Figure 4E). Suggesting that SWNTs have promise for photothermal transfection that functions by increasing membrane permeability, facilitating photoactive chemicals to escape from endosomes by generating reactive oxygen species, and thereby promoting the release of therapeutic genes [113].

MWNTs displaying both magnetic iron oxide and radio labels (99mTc) enabled simultaneous magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) as demonstrated *in vivo* in mice [114]. MWNTs coated with magnetite nanoparticles and mesoporous silica were shown to facilitate efficient loading and delivery of gentamicin, cytochrome C and siRNA to MC3T3-E1 cells *in vitro*, and imaging *in vivo* in mice [115, 116]. MWNTs in electric fields are known to amplify the electric field at their ends by a factor of 10-100 [117] which was used to permeabilize cell membranes *in vitro* in gram negative bacteria (*Acidothiobacillus ferrooxidans*) and NIH/3T3 cells [117, 118], and excitingly *in vivo* in mice via electromagnetic field-induced intracerebral delivery of plasmid DNA encoding the Bcl-2 gene using microwave radiation 8-12 GHz, 5 W, 20 seconds [117].

3. GRAPHENE-BASED NON-VIRAL VECTORS FOR GENE DELIVERY

Graphene derivatives (Fig. **2**) have the thickness of a single layer of graphite, and display interesting electronic, magnetic and optical properties and for which the Nobel Prize in Physics was awarded to Geim and Novoselov in 2010. Their properties are attractive for a number of applications [18, 119], and their degradability *in vivo* [120] makes them of particular interest for biomedical applications, as discussed in a number of recent reviews [121-126].

Akin to unmodified bucky balls, nanohorns and nanotubes, unmodified graphene is hydrophobic and insoluble in aqueous media, and it is frequently converted to the more hydrophilic graphene oxide (which is moderately soluble in aqueous media), and the hydrophobicity of graphene and graphene oxide enable interactions with the hydrophobic parts of DNA and RNA [53, 127]. Indeed, complexes of graphene oxide with either plasmid DNA (encoding GFP) or siRNA (targeting glyceraldehyde-3-phosphate dehydrogenase, GAPDH) are capable of transfection of human-derived cervical cancer HeLa cells and human umbilical vein endothelial cells (HUVECs) *in vitro* [128].

Strategies for their functionalization are analogous to nanotubes, typically covalent/non-covalent functionalization with cationic moieties, and the functionalization of graphene derivatives with various low and high molecular weight cations has been reported in the literature. Complexes of graphene oxide functionalized with octaarginine with DNA plasmid (encoding GFP) capable of transfection of human embryonic kidney (HEK293) cells *in vitro* [129]; or indeed transfection of Cell death siRNA to MCF-7 breast cancer cells transfection *in vitro* [130]. Complexes of ethidium bromide functionalized graphene oxide with plasmid DNA (encoding GFP) were markedly less toxic than ethidium bromide, and more effective at transfection to human gastric adenocarcinoma AGS cells than complexes with Lipofectamine® 2000 *in vitro* [131].

The functionalization of graphene quantum dots with poly(L-lactide)-PEG diminished the cytotoxicity of the graphene and enhanced the photoluminescence of the graphene over a broad pH (useful for imaging) and the conjugation of both miRNA-21-targeting and survivin-targeting agents improved the inhibition of cancer cell growth and apoptosis of cancer cells *in vitro* in HeLa cells [132]. Functionalization of graphene with poly(2-dimethylamino)ethylmethacrylate (PDMAEMA) by bioreducible disulphide bonds enabled successful transfection of plasmid DNA (encoding luciferase) into monkey kidney fibroblast-like COS-7 cells and human liver cancer HepG2 cells *in vitro* [133]. Likewise, complexes of graphene oxide functionalized with PEG and PEI by bioreducible disulphide bonds enabled successful transfection of plasmid DNA (encoding GFP) into human prostate cancer PC3 cells *in vitro*, which could be further enhanced by photothermal excitation upon exposure to NIR laser irradiation [134].

A comparison of complexes of graphene oxide functionalized with PAMAMs, PEI or polypropyleneimine (PPI) with plasmid DNA (encoding GFP) showed the PEI conjugates to be the most effective at transfection to mouse neuroblastoma Neuro-2a cells than complexes with either PAMAM or PPI *in vitro* [135]. Consequently, functionalization of graphene with PEI derivatives is popular, with complexes of linear PEI, anionic carboxy-

functionalized graphene oxide and plasmid DNA enables transfection to HeLa cells [119], although the complexes were prone to aggregation in the presence of serum. Replacement of the linear PEI with branched PEI enhanced the stability of their complexes with DNA in serum containing media, thereby enabling light-controlled delivery of DNA plasmids into the NIH3T3 fibroblast line and human prostate cancer PC-3 cells [136], and siRNA delivery to human mammary MDA-MB-435S melanocytes upon exposure to NIR laser irradiation [137].

Complexes of graphene oxide and PEI were capable of delivering siRNA (targeting the C-X-C chemokine receptor type 4 (CXCR4), siCXCR4) and suppressing gene expression and the metastatic potential of MDA-MB-231 cells *in vitro* [138]. Complexes of graphene oxide functionalized with PEI and PEG with plasmid-based Stat3 siRNA were effective at transfection and gene silencing of malignant melanoma B16 cells *in vitro* [139]. Interestingly, complexes of graphene oxide functionalized with PEI, PEG and chitosan with short hairpin shRNA were shown to be pH responsive (releasing their payload of doxorubicin and RNA at pH <6.5) and to successfully deliver their payload to human liver cancer HepG2 cells *in vitro* efficiently silencing ABCG2 expression and making the tumor cells more sensitive to the anticancer drug doxorubicin [140].

Excitingly, complexes of PEI-functionalized graphene oxide with mRNA (for reprogramming transcription factors) successfully generated rat and human induced pluripotent stem cells (iPSCs) from adult adipose tissue-derived fibroblasts (ADFs) *in vitro* in a gene integration-free fashion (Fig. **5**) [141]. The upper panel of Fig. 5A depicts a schematic diagram of the procedure for the preparation of human iPSCs by means of PEI-functionalized graphene oxide-mediated mRNA delivery into human ADFs, whereas the lower panel of Fig. 5 depicts bright-field images of the human iPSCs derived from the human ADFs; the former formed early iPSC-like colonies (day 18), and mature iPSC clones appeared after mechanical picking (day 24). The pluripotent properties of the iPSC clones generated from human ADFs were confirmed by immunocytochemical analysis with the iPSCs being positive for Oct4 expression (Fig. 5B). Furthermore, the expression of the endogenous pluripotency marker genes in iPSC clones (stemness marker genes: SSEA-4, Lin28A, Rex1, Nanog, and TRA 1-60), were well expressed in the iPSCs (Fig. 5C) but not in control hADFs. Reprogramming into iPSCs is accompanied with demethylation of promoters of critical pluripotency genes. The degree of epigenetic reprogramming was analyzed by studying the methylation patterns of the promoter region of a key pluripotency gene, Nanog. Bisulfite genomic sequencing of a 299-bp large region of the Nanog promoter which contains eight CpG sites was carried out. Although CpG sites of ADFs were methylated, none or only one CpG site was methylated in the PEI-functionalized graphene oxide-mRNA treated iPSCs (Fig. 7D), demonstrating that the pluripotent potential of the PEI-functionalized graphene oxide-mRNA treated iPSCs was similar to that of ES cell lines [141].

Furthermore, embedding complexes of PEI-coated graphene particles and DNA (encoding VEGF165) inside injectable hydrogels enabled their delivery to the site of acute myocardial infarction *in vivo* in rats, resulting in a significant increase in myocardial capillary density and reduction in scarring in the injected infarct region, and thereby improved cardiac performance [142].

Complexes of graphene oxide functionalized with PAMAMs and PEG with plasmid-based antisense oligonucleotides capable of antagonizing microRNA function were more effective at transfection to human lung cancer A549 cells than complexes with either Lipofectamine® 2000 or PAMAMs *in vitro* [143]. Complexes of graphene oxide functionalized with PAMAM with DNA plasmid (encoding GFP) capable of transfection of human-derived cervical cancer HeLa cells *in vitro* [144]. Complexes of carboxy-functionalized graphene, PAMAMs and plasmid DNA (encoding GFP) effectively transfected human cervical cancer HeLa cells or human osteosarcoma MG-63 cells, the efficiency of which could be markedly improved through the conjugation of oleate to the PAMAM [145], and folate-displaying graphene derivatives that target cancer cells were shown to be efficiently internalized through endocytosis and non-toxic towards human cervical cancer HeLa cells and human lung cancer A549 cells [146]. Complexes of carboxy-functionalized graphene, PAMAMs, epirubicin (an anticancer drug), amine-functionalized diethylene triamine pentaacetic acid loaded with Gd (a contrast agent), and either plasmid DNA (encoding GFP) or Let-7g targeting microRNA, were effective at the delivery of both the chemotherapeutic drug and therapeutic genetic material, and moreover simultaneous imaging, as demonstrated *in vitro* in human glioblastoma (U87) cells, and *in vivo* in the brains of mice, highlighting the potential of graphene-based theranostics [147].

4. CONJUGATED POLYMER-BASED NON-VIRAL VECTORS FOR GENE DELIVERY

The history of conjugated polymers is longer than for other classes of OEMs. The unintentional synthesis of polyaniline (Fig. **2**) first reported by Letheby in 1862 [148], and Bolto and Weiss reported the first intentional syntheses of analogous polymers in a series of papers in 1963 and 1964 [149-154], it was however the more widely publicized work of Heeger, MacDiarmid and Shirakawa in the late 1970s [155-158] that led to an explosion of academic and industrial interest in the synthesis and applications of electroactive polymers (EAPs) [159, 160] and ultimately their award of the Nobel Prize in Chemistry in 2000. However, the development of conjugated polymers for gene delivery is still at a relatively nascent stage by comparison with the other classes of OEMs [161].

In common with fullerenes and graphenes [53], EAPs interact with DNA and RNA through non-covalent interactions, including van der Waals interactions, π-stacking interactions, hydrogen-bonding interactions and ionic interactions [162-166]. Their chemistry is well described in the literature, and similar to other OEMs used for gene therapy frequently involves functionalization with cationic species, for example, complexes of PEI-functionalized polythiophene (Fig. **6A**) with siRNA (targeting luciferase) transfected human lung cancer A549-luc cells and successfully knocked down luciferase expression *in vitro* [167].

Complexes of cationic derivatives of poly(fluorenylene phenylene) displaying lipids (Fig. **6B**) with plasmid DNA (encoding GFP) were capable of transfecting human lung cancer A549 cells [168], human cervical cancer HeLa cells and human breast cancer MCF7/ADR cells with greater efficiency *in vitro* than both Lipofectamine® 2000 and PEI [169], and their high fluorescence facilitated real-time tracking of their location. Likewise, complexes of cationic oligofluorenes (Fig. **6C**) with transrenal DNA (TR-T5) delivered their payload to human lung cancer A549 cells concomitant with visualization *in vitro* [170], and hyperbranched polyfluorene derivatives displaying cationic PEI transfected plasmid DNA (encoding luciferase) into monkey kidney fibroblast cell-like cells *in vitro* [171].

Complexes of cationic poly(phenylene ethynylene) derivatives (Fig. **6D**) with siRNA (targeting specific genes in the cellulose biosynthesis pathway, NtCesA-1a and NtCesA-1b) successfully transfected tobacco BY-2 protoplasts *in vitro* [172], or siRNA (against actin B) to human cervical cancer HeLa cells *in vitro* successfully down regulating the target gene expression by 94% [173]. Interestingly, complexes of cationic poly(*p*-phenylene vinylene) derivatives (Fig. **6E**) with siRNA (targeting luciferase) successfully transfected human cervical cancer HeLa-Luc cells and diminished luciferase expression *in vitro* and this effect was enhanced photothemally upon exposure to white light [174].

Importantly, cationic derivatives of conjugated polymers can bind DNA/RNA and release it in response to electrochemical triggers, for example a cationic derivative of polycyclopentadithiophene (Fig. **6F**) can release DNA using voltammetry scans of -0.3 to +0.5 V versus a saturated calomel electrode [175] or polythiophene (Fig. **6G**) can release DNA using voltammetry scans of -0.5 to -2.4 V versus a saturated calomel electrode [176], suggesting the potential for electrochemically induced DNA/RNA delivery. We believe that biodegradable conjugated polymers [177, 178] such as those depicted in (Fig. **6, H, I and J**) may have an important role to play in their translation from the bench to the clinic.

CONCLUSION

The delivery of DNA/RNA as a pharmaceutical means to treat various diseases (i.e., gene therapy) is now a well-established field of science. While a variety of vectors have been investigated (including viruses, nanoparticles, etc.), the use of organic electronic material-based vectors was the focus of this review; touching on their chemical structures (Fig. **7**), surface modification, interactions with DNA/RNA, and their efficacy as gene delivery vectors both *in vitro* and *in vivo*. Their greater efficacy relative to current commercially available non-viral vectors and their beneficial theranostic properties make them incredibly attractive for further investigation, particularly in light of the evidence that they are biodegradable, and it is likely that the first clinical trials for such materials will be in the near future.

CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest regarding this review article.

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FIGURE LEGENDS

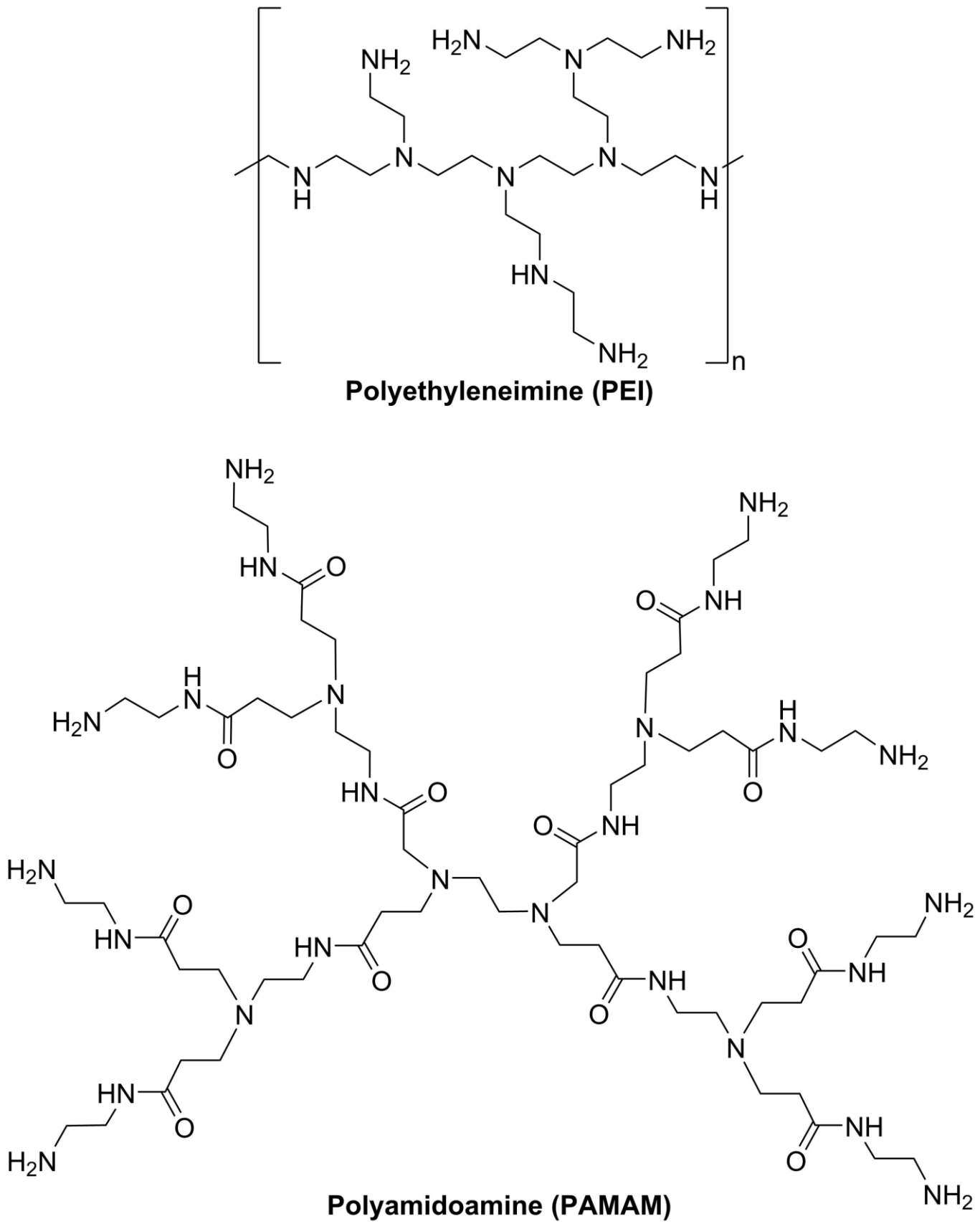


Fig. (1). Examples of the chemical structures of derivatives of polyethyleneimine (PEI) or polyamidoamine (PAMAM) dendrimer.

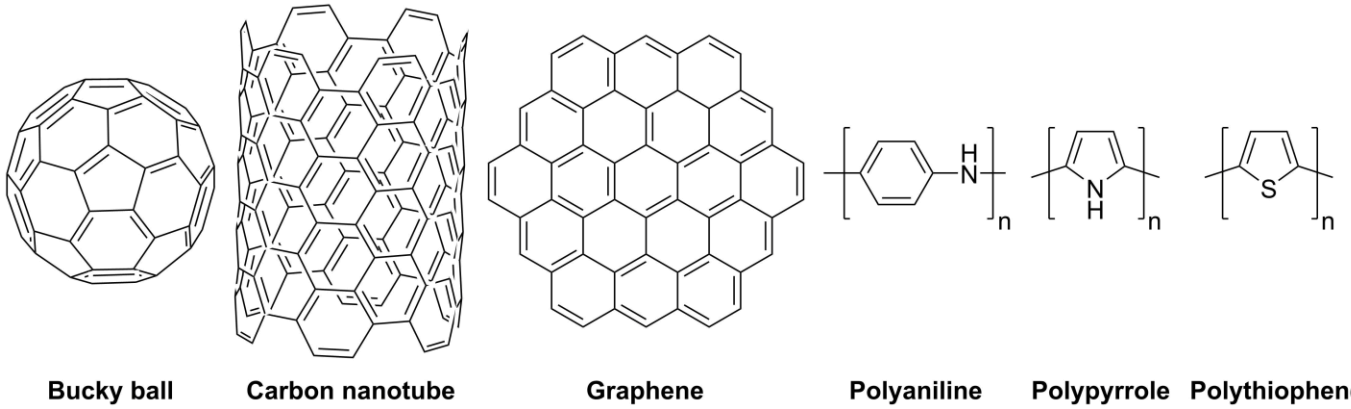
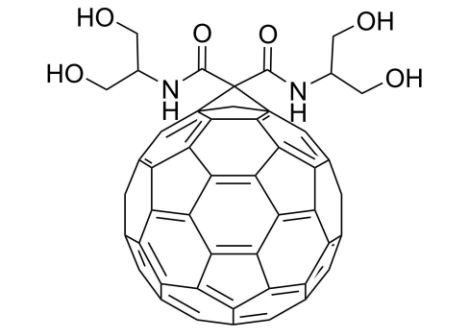
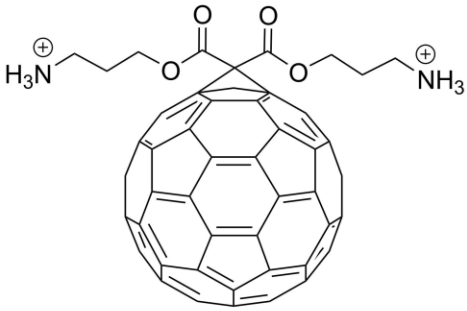


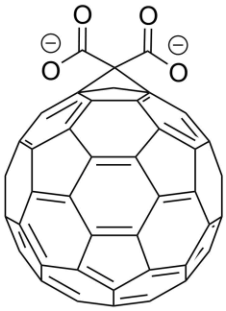
Fig. (2). Examples of the chemical structures of derivatives of fullerenes (bucky balls or nanotubes), graphene, or conjugated polymers (e.g. polyaniline, polypyrrole or polythiophene).



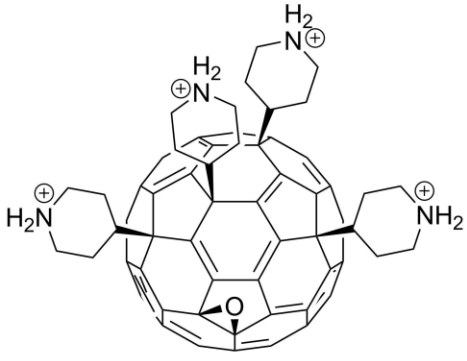
Neutral



Cationic



Anionic



Tetra(piperazino)fullerene epoxide

Fig. (3). Examples of the chemical structures of neutral, cationic, anionic and tetra(piperazino)fullerene epoxide derivatives of bucky balls.

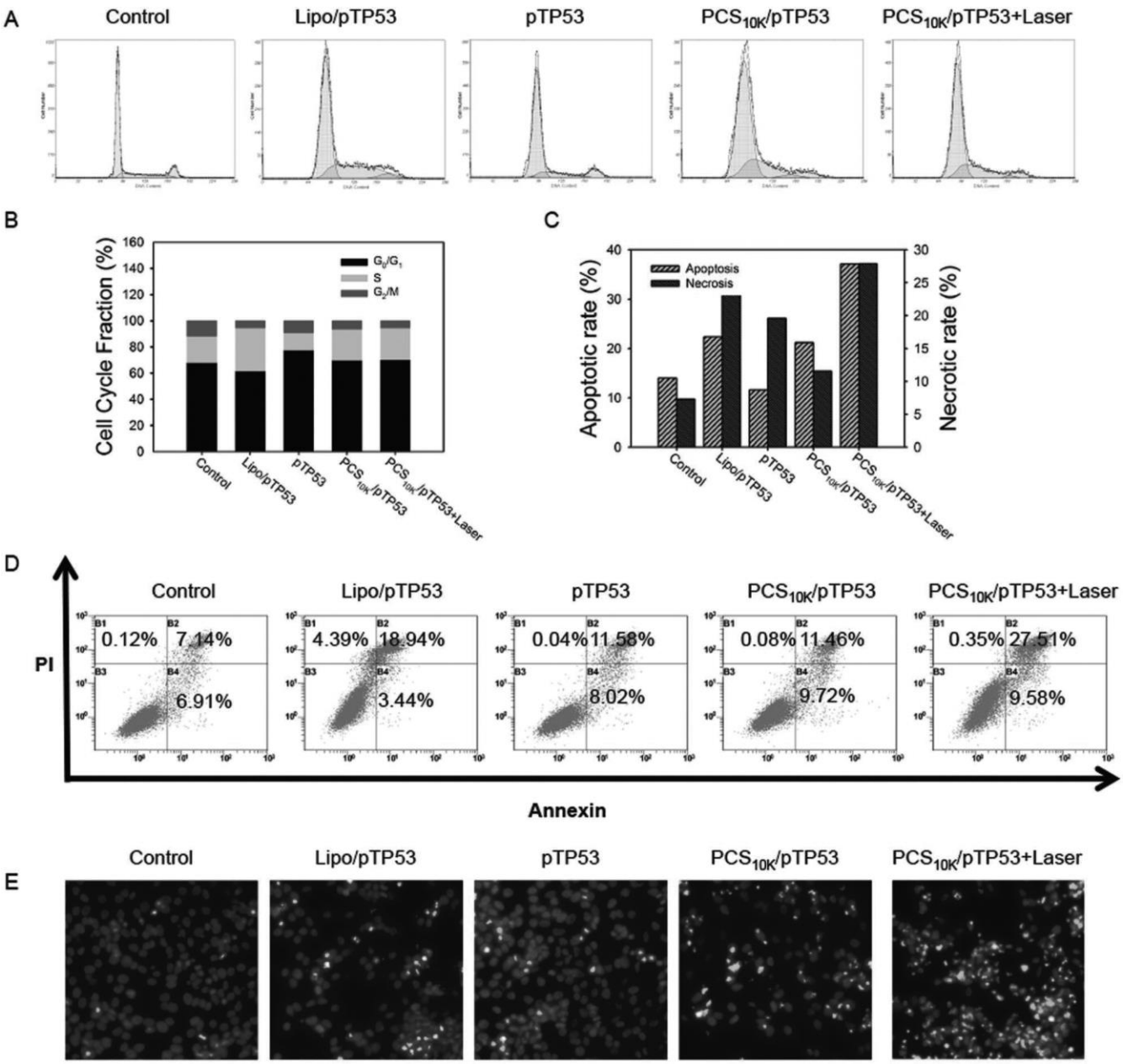


Fig. (4). Cell cycle fraction and apoptosis assay after pTP53 transfection in HeLa cells. A) Histograms and B) graph bar of cell cycle in the G0/G1, S, and G2/M population. Annexin V-FITC/PI co-staining assay by D) FCM and C) graph bar for apoptosis and necrosis rates. E) Nuclei fragment by Hoechst 33342 staining in HeLa cells. This figure is reproduced from reference 113. Reprinted by permission of John Wiley & Sons, Inc.

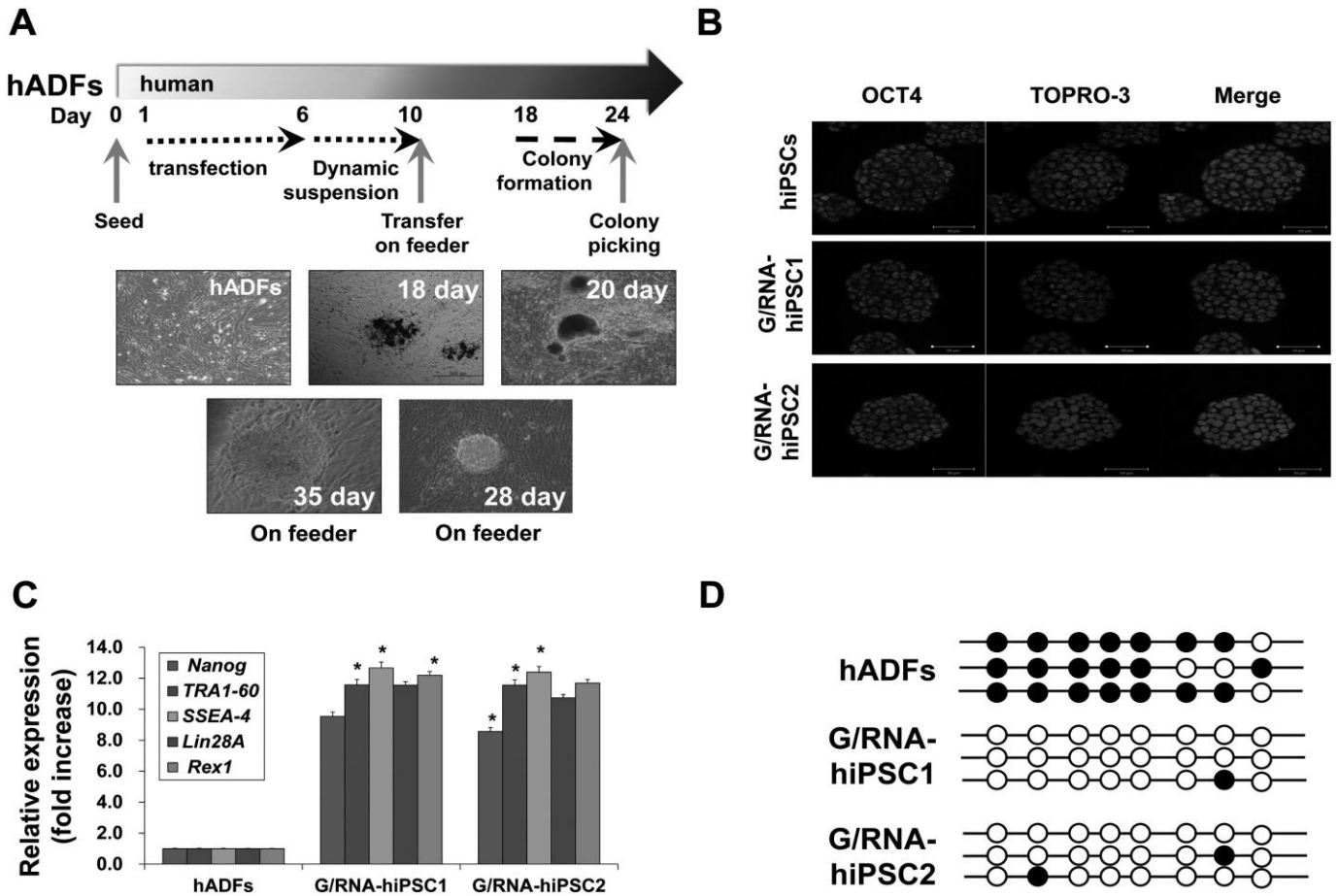


Fig. (5). GO-PEI-RNA-mediated generation of iPSCs (G/RNA-iPSCs) from ADFs. (A) Upper panel; a schematic diagram of the procedure for the preparation of hiPSCs by means of GO-PEI-mediated RNA delivery into hADFs. Lower panel; bright-field images of G/RNA-hiPSCs derived from hADFs; the former formed early iPSC-like colonies (day 18 for hiPSCs), and mature iPSC clones appeared after mechanical picking (day 24 for hiPSCs). (B) Immunocytochemical analysis OCT4 expression in G/RNA-hiPSCs. The nuclei were stained with TOPRO-3. Scale bar: 50 μm. (C) Quantitative real-time RT-PCR analysis of the expression of endogenous pluripotency markers. Expression of the stemness markers such as SSEA-4, Lin28A, Rex1, Nanog, or TRA 1-60, was analyzed in hADFs. The housekeeping gene Gapdh was used as a loading control; *$p < 0.05$. (D) Bisulfite genomic sequencing of human Nanog promoter region. Open and closed circles indicate unmethylated and methylated CpG dinucleotides, respectively. Three representative sequenced subclones from hADFs and from the above-mentioned iPSC clones are shown. This figure is reproduced from reference 141. Reprinted by permission of Elsevier.

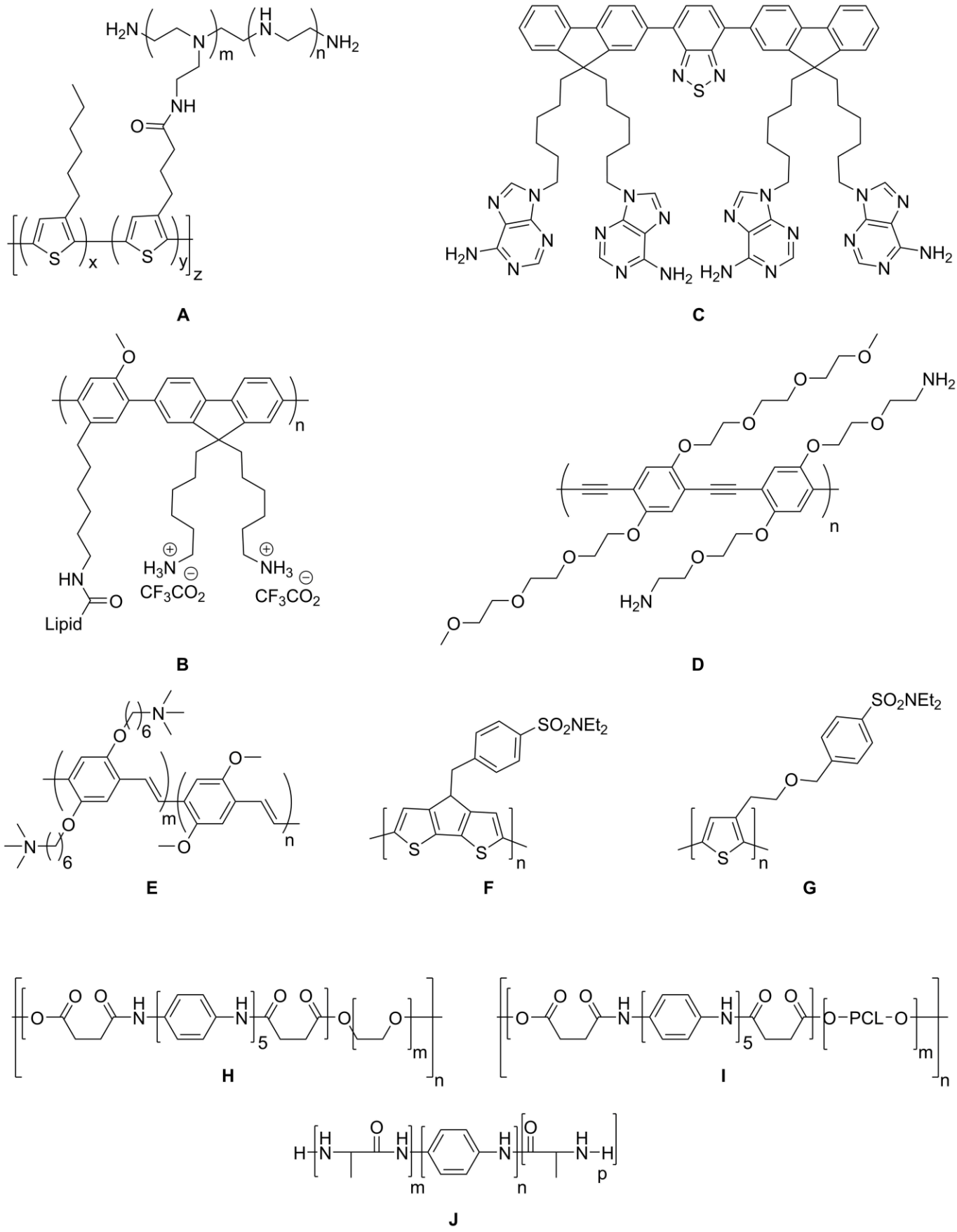


Fig. (6). Examples of the chemical structures of conjugated polymers.

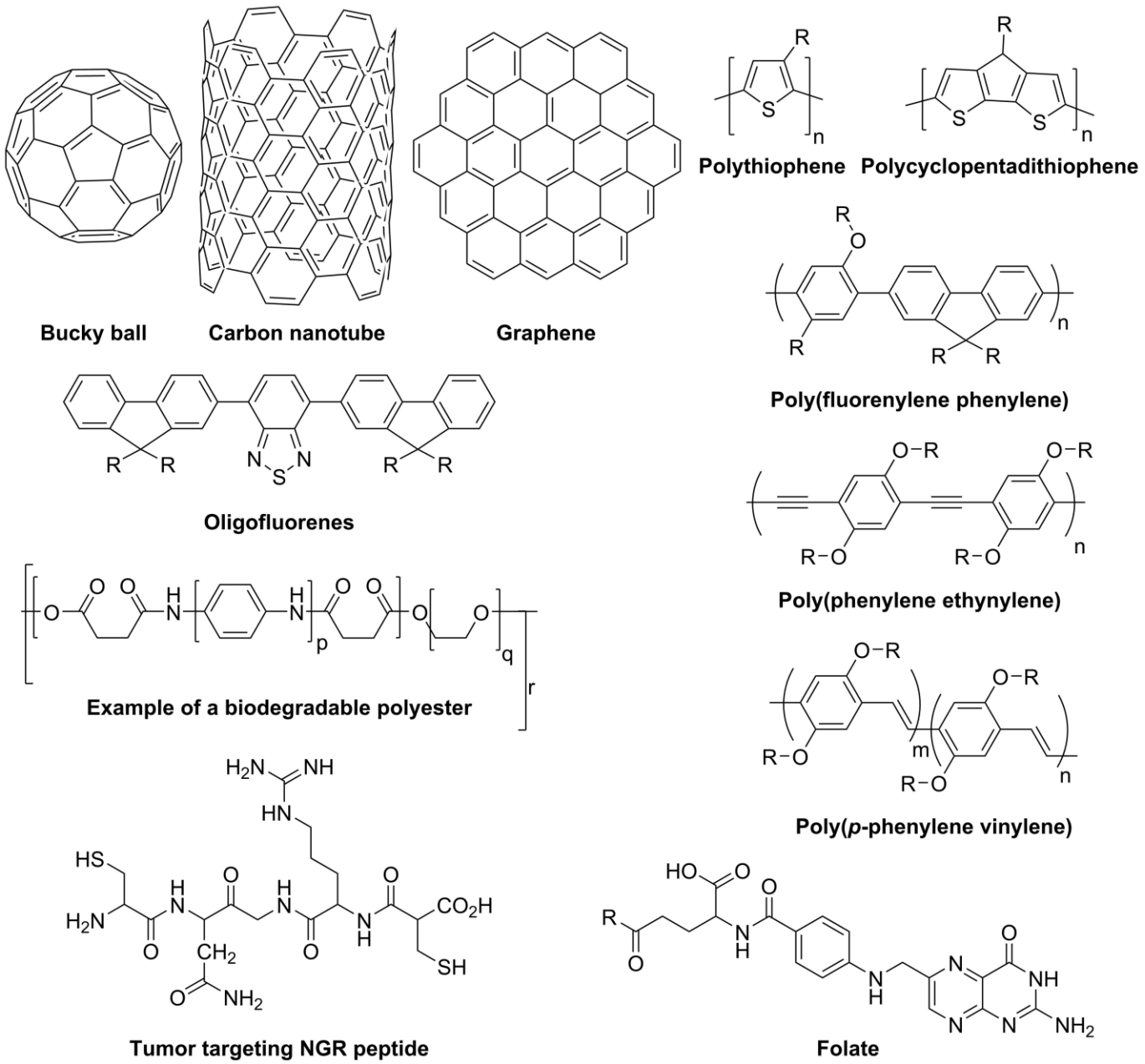


Fig. (7). Examples of the chemical structures of organic electronic biomaterials and targeting units.

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