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Hybrid Nanosystems for Biomedical Applications

Joshua Seaberg[1,#], **Hossein Montazerian**[3,4,5,#], **Md Nazir Hossen**[1,2,#], **Resham Bhattacharya**[6], **Ali Khademhosseini**[5,*], **Priyabrata Mukherjee**[1,2,*]

[1]Department of Pathology, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma 73104, USA.

[2]Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104, USA.

[3]Department of Bioengineering, University of California-Los Angeles, Los Angeles, CA 90095, USA

[4]Center for Minimally Invasive Therapeutics (C-MIT), University of California-Los Angeles, Los Angeles, CA 90095, USA

[5]Terasaki Institute for Biomedical Innovation (TIBI), Los Angeles, CA 90024, USA

[6]Department of Obstetrics and Gynecology, University of Oklahoma Health Science Center, Oklahoma City, OK 73104, USA

Abstract

Inorganic/organic hybrid nanosystems have been increasingly developed for their versatility and efficacy at overcoming obstacles not readily surmounted by non-hybridized counterparts. Currently, hybrid nanosystems are implemented for gene therapy, drug delivery, and phototherapy in addition to tissue regeneration, vaccines, antibacterials, biomolecule detection, imaging probes, and theranostics. Though diverse, these nanosystems can be classified according to foundational inorganic/organic components, accessory moieties, and architecture of hybridization. Within this review, we begin by providing a historical context for the development of biomedical hybrid nanosystems before describing the properties, synthesis, and characterization of their component building blocks. Afterward, we introduce the architectures of hybridization and highlight recent biomedical nanosystem developments by area of application, emphasizing hybrids of distinctive utility and innovation. Finally, we draw attention to ongoing clinical trials before recapping our discussion of hybrid nanosystems and providing a perspective on the future of the field.

Graphical Abstract

[*]Correspondence to: Priyabrata Mukherjee, Professor of Pathology, Priyabrata-Mukherjee@ouhsc.edu; Phone: 405-271-1133; Ali Khademhosseini, Professor and Director, Khademh@terasaki.org.

[#]Equal contribution

Author contributions

PM conceived the concept for the manuscript. JS and HM compiled and analyzed the literature. JS created the figures. JS, MNH, HM, and PM contributed to discussion and perspectives. JS, MNH, HM, RB, AK, and PM contributed to the editing process.

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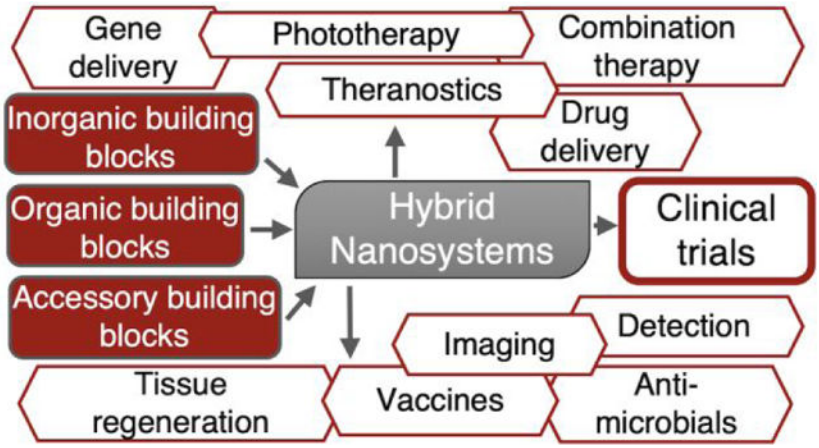

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Inorganic/organic hybrid nanosystems present attractive solutions to current challenges in drug and gene delivery, tissue regeneration, phototherapy, vaccine development, biosensing and detection, and theranostics. Although the development of such nanosystems has occurred only recently, the term “hybrid” appeared in the English lexicon in the 17th Century and is derived from the Latin “hybrida,” the offspring of a domesticated sow and a wild boar. The scientific study of hybridization exploded when Gregor Mendel published *Experiments in Plant Hybridization (1865)*, in which he described how progeny inherit and express characteristics of their progenitors.[1] The term shed its biological restraints over time and was increasingly used to describe something derived from two or more distinct sources. Under this broader definition, hybrid systems stepped into the public spotlight in 1997 with the release of the Toyota Prius hybrid electric vehicle.[2]

The earliest mention of a hybrid nanosystem in the biomedical field occurred the same year, with Elghanian *et al.* publishing a colorimetric polynucleotide detection system using nucleotide-hybridized gold nanoparticles (AuNPs) in *Science*.[3] True hybrid nanosystems containing inorganic and organic structural components were introduced in 1998 when Caruso *et al.* reported a synthesis of nanoscale silica-polymer hybrid spheres.[4] Around the turn of the 21st Century, the development of hybrid nanosystems expanded greatly through the hybridization of silica with micelles,[5] liposomes,[6] and polymers[7] along with the introduction of polymer-functionalized metallic nanoparticles.[8, 9] By 2003, interest in these systems was rapidly growing, and review articles started to appear.[10] This growth has continued steadily over the past two decades, with the search “hybrid nanoparticle” producing nearly 2,000 matches in the National Library of Medicine last year in comparison to only 42 in 2003 (Figure 1).

Here, we give an overview of recent reports of inorganic/organic hybrid nanosystems in the biomedical field. As it was impossible to include all relevant contributions within this

article, we instead report findings of diverse applications and distinct utility and reference reviews for more general topics. Furthermore, we focus on “true” hybrid nanosystems incorporating organics and inorganics as structural components rather than as therapeutics or accessory moieties. As such, we hope that this paper may provide broad information on biomedical hybrid nanosystems that the interested reader can utilize as a starting point for a more thorough investigation.

We start by introducing the primary inorganic and organic building blocks utilized by hybrid nanosystem architects, with emphasis placed on biomedically-relevant properties, synthesis, and characterization. Once each building block has been discussed, standard architectures are presented to provide a framework for understanding hybrid nanosystem design. Afterward, we present select hybrid nanosystems by application, starting with gene and drug delivery before discussing phototherapy, tissue regeneration, antimicrobials, vaccine development, detection and imaging, and theranostics. Finally, we mention the active clinical trials utilizing hybrid nanosystems before concluding with a discussion of the state of the field and providing a perspective on the continued development of hybrid nanosystems.

Characterization of hybrid nanosystems

Hybrid nanosystems are composed of inorganic and organic building blocks, each displaying distinct properties that determine practical applications and characterization methods (Figure 2). Widely-utilized inorganic building blocks include metals such as gold and iron oxide nanoparticles (AuNPs and IONPs, respectively), inorganic compounds including zinc oxide (ZnO) nanoparticles (ZONPs) and calcium phosphate (CaP) nanoparticles (CPNPs), and porous structures like mesoporous silica nanoparticles (MSNs) and metal-organic frameworks (MOFs). Organic building blocks include polymers and copolymers, lipids, dendrimers, and isolated cell membranes. Carbon derivatives such as graphene oxide (GO), fullerene (C60), carbon nanotubes (CNTs), and graphene quantum dots (GQDs) can display properties similar to both organic and inorganic systems; consequently, we have included carbon-based materials as inorganic building blocks even though they can also function as organic building blocks. From these materials, nearly limitless hybrid nanosystems have been designed to overcome challenges in the biomedical field.

Inorganic building blocks

Gold nanoparticles (AuNPs)—Nanoscale gold is the most frequently-utilized inorganic building block due to its biocompatibility, ease of synthesis, low polydispersity, self-therapeutic properties, and tunable plasmonic properties.[11] Several of these properties are geometry-dependent; consequently, AuNPs,[12] gold nanorods (AuNRs),[13] gold nanoshells (AuNSs),[14, 15] gold nanoclusters (AuNCs),[16] and nanocages[17] are all observed in the literature. Variation of nanoscale gold geometry has been shown to affect its optical properties, the available surface area, and transport properties.[18] Gold nanostructures display self-therapeutic properties to fight cancers, including inhibition of tumoral angiogenesis,[19, 20] inhibition of MAPK-signaling to reverse epithelial-mesenchymal transition in cancer,[21] and alteration of non-viral gene delivery uptake pathways to avoid

lysosomal degradation.[22] Alternatively, nanoscale gold is readily modified by electrostatic interactions or gold-thiol (Au-S) bonds, allowing facile functionalization with a variety of therapeutics, polymers, and targeting ligands.[23] While Au-S bonds are relatively strong (30–40 kJ/mol), the weaker interactions between gold and nucleic acids allow adsorption and release for gene delivery applications.[22] Electrostatic interactions can also facilitate the coating of anionic AuNPs with cationic polymers to promote cellular transfection and provide hybrid systems with simple conjugation chemistries.[24] Through these functionalization techniques, AuNPs can be adapted for use as either a core or surface-adjacent structure in hybrid nanosystems.

The optical properties of gold nanostructures include localized surface plasmon resonance (LSPR), in which incident light induces a collective oscillation in the surface electrons of a nanomaterial.[25] This oscillation can be exploited in several ways: plasmon generation and decay can increase the nanoparticle temperature for hyperthermal therapy, promote electrons to antibonding orbitals for photocatalysis, produce acoustic waves for photoacoustic imaging, or fluoresce by scattering differentially energized photons.[26] LSPR can be tuned *via* geometry variation,[27] *i.e.*, AuNRs may be tuned by varying the aspect ratio, allowing AuNRs to specifically absorb and scatter light within the biological windows for photodynamic/photothermal therapy and photo-triggered therapeutic release.[28–30] Additionally, the size, geometry, and concentration of nanoscale gold alters its absorbance in solution, resulting in color variation.[27] Spectrophotometric characterization has been utilized in biodetection systems by coupling aggregation to the presence of a target molecule in solution.[31,32]

Gold nanostructures have been synthesized through several physical, chemical, and biological methods, though chemical methods are standard for hybrid nanosystems.[33] Chemical synthesis of gold nanostructures requires a source of oxidized gold, a reducing agent, and a capping or stabilizing surfactant to prevent irreversible nanoparticle aggregation; variation in the identity and concentrations of these reagents will affect the size and morphology of the final nanostructure.[34] AuNPs have been synthesized through the reduction of chloroauric acid ($HAuCl_4$) with citric acid as a stabilizing and reducing agent where the gold-to-citrate ratio controls nanoparticle size.[35] AuNPs can also be formed through top-down processes such as laser ablation[36] or through “green” syntheses utilizing plant-derived reducing agents.[37] Hollow AuNSs can be synthesized by reducing gold ions on the surface of cobalt nanoparticles while simultaneously oxidizing the core to cobalt oxide.[38] AuNRs can be synthesized from AuNP seeds incubated with silver nitrate ($AgNO_3$), while other non-spherical geometries utilized in hybrid nanosystems have been synthesized through seed-growth approaches utilizing sodium borohydride ($NaBH_4$) and zwitterionic surfactants,[39] acetic acid and $AgNO_3$,[40] and dilute peptide solutions.[16, 29] As such, geometry and synthesis method can be selected on an application-specific basis.

AuNPs can be characterized by several methods. Dynamic light scattering (DLS) and electrophoretic light scattering (ELS) provide information on AuNP size, polydispersity index (PDI), and ζ-potential. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) show AuNP size, morphology, size distribution, surface properties, and position within a hybrid nanosystem. Fourier transform

infrared (FTIR) and UV-Vis spectroscopy (UV-Vis) measure AuNP optical properties, and surface plasmon spectroscopy allows the characterization of LSPR. Finally, X-ray diffraction (XRD) can describe the structure of the AuNP on an atomic scale and inductively coupled plasma-mass spectrometry (ICP-MS) allows detection of elemental gold at low concentrations.[41] Figure 3 displays geometries and properties of AuNPs in addition to synthesis and characterization techniques. For further reading, we recommend reviews by Yeh *et al.*, Elahi *et al.*, and Dreaden *et al.* on general biomedical applications for AuNPs,[11, 27, 35] Grzelczak *et al.* on shape control in nanoscale gold,[42] Pérez-Juste *et al.* and Cao *et al.* on AuNRs,[43, 44] Amendola *et al.* on AuNP LSPR,[25] and Vines *et al.* on AuNPs in photothermal cancer therapy.[45] Due to the aforementioned characteristics, nanoscale gold is utilized in nearly every biomedical application of hybrid nanosystems.

Iron oxide nanoparticles (IONPs)—IONPs are another common inorganic material in hybrid nanosystems. Both forms of IONPs (maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4)) are attractive in biomedical applications for their biocompatibility and low toxicity.[47] IONPs have been synthesized in many geometries including spheres, hexes, triangular prisms, cubes, stars, rings, clusters, and shells.[48] IONP geometry is related to available surface area, carrying capacity, and interactions with electromagnetic radiation. For example, varying geometries of IONP have shown similar biocompatibility despite varying SA/V ratios, while hollow IONPs can act as drug carriers and IONP rings absorb microwave radiation.[48] Notably, 10–20 nm IONPs exhibit superparamagnetism, making them responsive to an applied magnetic field while otherwise displaying non-magnetic properties.[47] Superparamagnetic IONPs can confer magnetic targeting properties to nanotherapeutics, act as contrast agents for magnetic resonance imaging (MRI), and be utilized for magnetic hyperthermal therapy.[49–51] Biomedical application of IONPs is further expanded by their ability to induce ferroptosis in cancer cells,[52] and additional studies have shown that IONPs exhibit antibacterial activity[53] as well as photoluminescence.[54] As such, this breadth of properties makes IONPs attractive as nanosystem building blocks.

Chemical, physical, and biological methods have been employed in IONP synthesis, with chemical methods being most popular in hybrid nanosystems.[47] IONPs display facile synthesis through basic coprecipitation of iron salts, with variations in particle size being attained through pH control.[50] Alternatively, IONPs can be synthesized through a microemulsion technique in which iron salts combine to form IONPs within a surfactant-stabilized oil and water mixture.[47] Like AuNPs, IONPs are frequently characterized by DLS, ELS, UV-Vis, FTIR, ICP-MS, XRD, and electron microscopy.[55] Ansari *et al.* and Ali *et al.* provide more complete reviews of IONPs for the interested reader.[55, 56] IONPs are the second-most widely employed inorganic building blocks and are used primarily for their superparamagnetic properties.

Other metallic components—Other metallic nanoparticles have also been incorporated into hybrid nanosystems for therapeutic effect. Platinum nanoparticles (PtNPs) kill cancer cells through ion leaching,[57] while silver nanoparticles (AgNPs) and copper nanoparticles (CuNPs) are recognized along with PtNPs for their antibacterial properties and are commonly incorporated into systems for treatment or prevention of bacterial infection.[58, 59]

PtNPs exhibit a variety of geometries including spherical, baton, and cubic. They are constructed through chemical processes such as chemical vapor deposition, physical methods including laser ablation, and biological methods utilizing yeast and bacteria.[60] Similarly, AgNPs display distinctive physical and optical properties in addition to strong antimicrobial properties that have been exploited for drug delivery, tissue regeneration, imaging, and diagnostic applications.[61] As with other metallic nanoparticles, AgNPs may be formed *via* top-down methodologies to break down silver (Ag) macrostructures or through bottom-up chemical and biological methods.[61] Finally, CuNPs exhibit properties similar to AgNPs, though their propensity to oxidation makes them less biocompatible than the noble metals.[62] Each of these nanoparticles has been shown to exhibit some form of fluorescence/photoluminescence, plasmonic properties, and catalytic activity. As with the other metallic nanoparticles, PtNPs, AgNPs, and CuNPs are characterized by DLS, ELS, UV-Vis, FTIR, ICP-MS, XRD, SEM, TEM, AFM, and/or x-ray absorption spectroscopy.[60–62] Sim *et al.* and Lee *et al.* provide thorough reviews on AgNPs in biomedical applications,[61, 63] while Jeyaraj *et al.* reviewed the synthesis, characterization, and biomedical use of PtNPs[60] and Al-Hakkani recently published a review of CuNPs of value to the curious reader.[64] These building blocks are less prevalent in the literature than their AuNP and IONP counterparts, but they are commonly utilized in antimicrobial applications along with sporadic use throughout other areas.

Inorganic compounds—Several inorganic compounds have been used in hybrid nanosystems. CPNPs exhibit low toxicity and high stability in a range of geometries, including rods, spheres, and needles, and the crystallinity of the structure may be tuned to accommodate specific loading and release profile requirements.[65] Moreover, CPNPs have shown antibacterial effects and fluorescence/photoluminescence in addition to pH-responsive properties for enhanced lysosomal escape.[66, 67] CPNPs are most frequently formed through chemical precipitation processes that can be tuned for use in hybrid nanosystems.[65] For example, therapeutic-loaded CPNPs can be synthesized by coprecipitation from calcium nitrate and diammonium hydrogen phosphate in the presence of a therapeutic.[65, 68] CPNPs can be characterized by DLS, UV-Vis, ICP-MS, XRD, nitrogen adsorption/desorption isotherms, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), FTIR, and electron microscopy.[65, 69] Though already heavily referenced, the review by Levingstone *et al.* further describes methods for synthesis and characterization of therapeutic CPNPs.[65] CPNPs are most commonly used in gene delivery applications.

Similarly, ZONPs have been employed in biomedical applications for their antibacterial and antifungal activity. Moreover, ZONPs exhibit anti-cancer self-therapeutic properties which have been attributed to the release of zinc ions and the catalytic accumulation of reactive oxygen species (ROS).[70] ZONPs have been synthesized through physical, chemical, and biological mechanisms and demonstrate distinctive optical and semiconducting properties that have led to their use in bioimaging,[71] antimicrobial food packaging,[72], and sunscreen.[71] Furthermore, ZONPs show anti-inflammatory effects that have been harnessed in wound dressings and plasmonic properties that have been optimized for photocatalysis.[73] Wurtzite, which contains zinc and oxygen atoms arranged in tetrahedral formation, is the most stable zinc oxide structure and is consequently the most prevalent form in hybrid nanosystems.[74]

ZONPs can be characterized by DLS, ELS, FTIR, UV-Vis, TEM, SEM, XRD, ICP-MS, TGA, and DSC.[70] Further understanding of ZONPs can be obtained from relevant reviews by Sirelkhatim *et al.*[75] and Jiang, Pi, & Cai.[73] Based on the aforementioned properties, ZONPs find use in several applications, including combination therapy, antimicrobials, detection and imaging, and vaccines.

Mesoporous nanostructures—Mesoporous nanostructures are attractive building blocks primarily for their biomolecule adsorption/desorption capabilities.[76] Mesoporous silica has been incorporated into hybrid nanosystems as MSNs or coatings. MSNs introduced in 1968 were noticed for their high surface area and tunable pore size.[77, 78] Current sol-gel synthesis processes utilize polymers and surfactants that are later removed *via* solvent extraction to control pore size and orientation.[79] MSN pore size ranges from 2 to 50 nm and is frequently gated to retain encapsulated therapeutics until a stimulus triggers gate opening.[77, 80] Hollow MSNs are synthesized through soft templating around micelles or by hard templating around the polymer or metallic nanoparticles, with the mesoporous shell conforming to the surface of the degradable template.[79] Mesoporous silica can also coat a core nanoparticle or form a loose outer shell surrounding a cluster of inner core nanoparticles in a “rattle-type” system.[81] MSNs can be characterized by methods similar to other inorganic building blocks, including DLS, ELS, UV-Vis, FTIR, XRD, and TEM. Additional reading on MSN synthesis and advances can be obtained from Wu *et al.* and Narayan *et al.*[77, 79] MSNs are found in hybrid nanosystems throughout the biomedical field, with widespread use in gene/drug delivery and combination therapy as well as in nanovaccines and theranostics.

MOFs form similarly porous structures of metal ions surrounded by organic ligands. Whereas MSNs display few intrinsic therapeutic properties, MOFs can exhibit antibacterial properties along with fluorescence/photoluminescence, pH-responsivity, and catalytic activity. MOFs are regularly synthesized through solvothermal processes featuring a metal salt and organic linker in a poorly volatile solvent, though alternative electrochemical, mechanochemical, and sonochemical processes also exist.[82] Following synthesis, MOFs are activated by removing excess linkers and solvent.[83] Characterization techniques include powder XRD, nitrogen adsorption/desorption, TGA, SEM, ICP-MS, optical emission spectroscopy, nuclear magnetic resonance (NMR), and FTIR, which provide information on the crystallinity, stability, porosity, symmetry, and morphology of MOFs.[82] Zeolitic imidazolate frameworks (ZIFs) are MOFs containing transition metals connected by imidazolate linkers and are attractive for their loading capacity and stimulus-responsive degradation.[84] Moreover, MOFs can acquire additional therapeutic properties by incorporating alternative metal nanoparticles through replacement reactions,[58] and polymer hybridization can improve MOF surface characteristics.[85] Reviews of MOFs by Safaei *et al.*,[83] and Wang, Zheng, & Xie provide content not covered in this overview.[86] MOFs are ubiquitous in hybrid nanosystem applications throughout the biomedical field.

Nanoclays—Nanoclays are layered silicates that originate from the clay minerals constituting sedimentary rocks and soils.[87] The general chemical formula of (Ca, Na, H)(Al, Mg, Fe, Zn)$_2$(Si, Al)$_4$O$_{10}$(OH)$_2$ characterize these clay aluminosilicates.[88] Nanoclays are

primarily formed of the repeated units of alternating octahedral AlO_6 and tetrahedral SiO_2 sheets with different AlO_6:SiO_2 ratios where the metallic cations are substituted in between the silicate layers.[89] Clay nanomaterials are often available in the form of synthetic and natural platelets that may rearrange structurally to develop few-nanometer-scale nanotubes and nanofibers.[90] The biocompatibility of nanoclays has made them suitable for a wide range of biomedical applications. Among the different nanoclay types, montmorillonite (MMT),[91] Laponite,[92] and whitlockite[93] are some of the most frequently used fillers in biopolymer matrices to enable different functions. Nanoclays such as halloysite have been used as mechanical reinforcements for bone cements in polymer composites. Other examples such as MMT have been served as crosslinking points to endow toughness to hydrogels matrices.[94] Tissue engineering applications have taken advantage of the ability of nanoclays to promote cell adhesion and proliferation. This effect is shown in multiple material compositions, *e.g.*, a gellan/manuka honey-based hydrogel incorporated with MSNs and bentonite clays where the scaffolds supported chondrogenesis and controlled immune response.[95] Nanoclays have been further utilized for immobilizing enzymes particularly in biosensor devices for monitoring biomolecules such as glyphosate.[96] As such, the potential for drug delivery applications have been demonstrated.[97] The antimicrobial protein lysozyme incorporated into the halloysite nanotubes as an example, resulted in poly(lactic acid) (PLA)-based hybrid composites for the delivery of lysozyme.[98] The strong negative charges on the surface of Laponite and its water uptake capability has enabled their use in hemostatic agents for rapid coagulation and control of hemorrhage.[99] Many studies have confirmed promoted wound healing by using nanoclays such as nontronite.[100] The rheological effects of nanoclays in aqueous solutions have opened up their application to injectable shear-thinning biomaterials[101] *e.g.*, for treating aneurysms or delivering biomolecules in the body.[102] Further developments are still in progress as the different aspects of nanoclay-based composites are uncovered.

The natural formation of clay occurs under geologic conditions, most frequently where rocks are in contact with water or air and form sedimentations. Synthetic approaches, however, involve low- and high-temperature techniques through hydrothermal techniques. Nanoclay characterization techniques include but are not limited to powder XRD, small-angle neutron scattering (SANS), TGA, FTIR, DLS, UV-Vis, and TEM.[103] Further readings are available in the literature on synthesis and application of nanoclay-based nanocomposites by Gup *et al.*[104] Rafiee *et al.*[105] have reviewed the mechanical properties of the nanoclay-based nanocomposites. A detailed overview of the nanoclays biomedical applications was also presented by Peña-Parás *et al.*[106] The current trends show that nanoclays hold a tremendous promise for future developments in functional materials.

Carbon-based materials—Carbon has been introduced into hybrid nanosystems as GO,[107] GQDs (semiconductor particles <100 nm in diameter),[108] CNTs,[109] C60,[110] and diamond nanocrystals.[111] Carbon building blocks exhibit biocompatibility and are widely utilized in phototheranostics for their tunable photoluminescence[112] and ability to couple with metallic nanoparticles for enhanced imaging contrast.[107, 113] The geometry and conductivity of carbon materials lend them additional functionality for use in biosensors,[114, 115] as exemplified by Lee *et al.*'s nanosystem for DNA detection through

measurement of conductivity changes between AuNPs, iron nanoparticles (FeNPs), and CNTs.[109] As such, nanoscale carbon can confer distinct properties to hybrid nanosystems for diverse applications.

The breadth of existing carbon nanostructures requires an equally-exhaustive set of synthesis and characterization processes. Nanoscale graphene (sheets of sp^2-hybridized carbon) can be formed from either atomic carbon in bottom-up approaches or through top-down approaches starting from macro-scale graphite.[116] Graphene is oxidized to GO in protonated solvents, and the presence of oxygen-based functional groups provides enhanced versatility to GO nanocomposites and GQDs.[116] C60 can be synthesized through graphite vaporization *via* laser pulsation in helium flow,[117] while CNTs are produced through chemical vapor deposition, laser ablation, or carbon arc-discharge techniques.[118] These nanostructures can be characterized by TEM, SEM, DLS, UV-Vis, mass spectrometry, XRD, DSC, and adsorption/desorption isotherms, in addition to X-ray photoemission spectroscopy, Raman spectroscopy, flow field flow fractionation, near-edge X-ray absorption fine structure, and electron energy loss spectroscopy.[117, 119] For further reading, Dasari Shareena *et al.* expound upon graphene-based nanomaterials in the biomedical field,[120] Astefanei *et al.* provide insight on C60 characterization,[117] Tian *et al.* summarize the synthesis and some applications of GQDs,[121] and Anzar *et al.* and Eatemadi *et al.* further explain the properties and biomedical applications of CNTs.[118, 122] Carbon-based materials are especially suited for use in nanosystems designed for detection and monitoring, phototheranostics, and combination therapy, and consequently, show up disproportionately in those areas of application. Figure 4 displays the inorganic building blocks of hybrid nanosystems along with their characteristics and methods of characterization.

Organic building blocks

Lipids/liposomes—Liposomes, spherical bilayers of lipids encapsulating an inner aqueous space, represent the predominant organic building block of hybrid nanosystems. Lipid-based nanosystems exhibit biocompatibility, self-assembly, facile synthesis, high loading capacity, and trans-membrane delivery capability.[123] Liposomes are frequently constructed from a combination of lipids for ζ-potential (surface charge) control, with cationic liposomes displaying enhanced cellular uptake but poor serum stability and neutral/anionic liposomes displaying poor uptake and varying serum stability.[22] Cationic lipids like *N*-[1-(2,3-dioleoyloxy)propyl]-*N,N,N*-trimethylammonium (DOTAP) can be combined with anionic lipids, cholesterol, or zwitterionic lipids to tune the liposome ζ-potential to 20–25 mV.[124, 125] Furthermore, lipids are occasionally conjugated with hydrophilic polymers such as polyethylene glycol (PEG) or zwitterionic polymers to reduce *in vivo* clearance.[126] Finally, lipids can be functionalized with targeting ligands to improve specific accumulation of liposomes in targeted environments.[127]

Liposome construction requires both synthesis/isolation of constituent lipids and the formation of liposomal structure. Natural lipids and cholesterol can be isolated from biological systems, whereas other lipids are synthesized *de novo* from chemical building blocks.[128, 129] Liposome formation can be accomplished in several ways. In thin-film rehydration, lipids dissolved in an organic solvent or organic/aqueous emulsion form a

film through lyophilization or evaporation that is subsequently rehydrated and formed into liposomes through vortexing, extrusion, or sonication.[130] Alternatively, liposomes can be formed through solvent vaporization, ethanol injection, or reverse-phase evaporation.[131] Liposomes are characterized *via* DLS, ELS, TEM, UV-Vis, FTIR, high-performance liquid chromatography (HPLC), and gel filtration.[132, 133] Has and Sunthar provide a comprehensive review on liposomal preparation,[134] while reviews from Akbarzadeh *et al.* explain liposome classification and preparation[131] and Pattni, Chupin & Torchilin review liposomal drug delivery systems.[135] Liposomes are prevalent throughout the biomedical field with exception of the areas of antimicrobials and vaccines.

Polymers—Polymers form the second class of organic building blocks. Cationic polymers such as chitosan, poly(ethylene imine) (PEI), and poly(L-lysine) (PLL) enhance cellular uptake through electrostatic interactions with anionic cell membranes. These polymers facilitate electrostatic loading of nucleic acids and conjugation with stimulus-responsive and/or active targeting ligands.[24, 38, 136, 137] Alternatively, stimulus-responsive polymers display conformational changes in response to exogenous or endogenous stimuli, including temperature,[138] redox,[139] and pH.[140] Some polymers such as polydopamine (PDA) convert incident light into thermal energy, allowing them to be used as LSPR-independent photoabsorbers.[141] Regularly, two or more polymers are combined into the block or grafted copolymers like poly(lactic-co-glycolic acid) (PLGA) to combine the functionalities of constituent polymers and introduce previously unrealized functionality.[142]

The method of polymer synthesis for a hybrid nanosystem is both material and system dependent. For example, the natural polymer chitosan is isolated from the shells of crustaceans,[143] whereas synthetic polymers such as PEI are formed through addition or condensation reactions.[144] Poly-amino acids can be synthesized by polymerization initiation in the presence of monomer, with the degree of polymerization controlled by tuning the initiator, reactant concentrations, and reaction conditions.[145] In contrast, PDA can be synthesized through dopamine oxidation followed by cyclization and polymerization.[146] Copolymer grafting can be accomplished by *n*-hydroxysuccinimide (NHS) or maleimide chemistries,[147] whereas block copolymers are typically synthesized through sequential polymerization reactions.[148] Polymer characterization can be accomplished *via* NMR, FTIR, UV-Vis, XRD, SANS, DSC, Raman spectroscopy, and matrix-assisted laser desorption ionization time-of-flight mass spectroscopy, whereas characterization of polymer nanoparticles is commonly accomplished by DLS, ELS, SEM, TEM and AFM.[149] Several relevant reviews exist on biomedical applications of PEI[150–152] as well as PLL,[153] PLGA,[154] poly(*N*-isopropylacrylamide) (PNIPAM),[155] and poly(methyl methacrylate) (PMMA).[156] Polymer building blocks are pervasive and can be found in hybrid nanosystems in every area of biomedical application.

Dendrimers—The third organic building blocks are dendrimers, which are branching, radially-symmetric star-shaped biomolecules made up of repetitive units dispersing from an origin.[157] Dendrimers are especially suited for biomedical applications because of their monodispersity, non-toxicity, solubility, self-assembly, and stability.[157] Polyamidoamine (PAMAM) is the standard dendrimer used in hybrid nanosystems and has been useful for

gene delivery,[158] chemotherapy,[159] and *in vivo* imaging.[160] Ligand-functionalized PAMAM has shown active targeting capabilities,[158, 161] while selective dendrimer crosslinking can control the release profile of an entrapped therapeutic.[159]

Dendrimer synthesis can take several forms. Divergent PAMAM synthesis is carried out by sequential addition of methyl acrylate and ethylene diamine branching away from a functional core. Each pair of reactions adds a new layer (generation) to the dendrimer, and the extent of the reaction may be monitored spectrophotometrically *via* copper sulfate chelation reactions.[162] Alternatively, convergent synthesis involves the creation of the branches before final connection to a core structure, and some have experimented with combined divergent/convergent processes in which branches and microbranched cores are formed separately before combination.[163] Several notable biomedical hybrid nanosystems utilize divergently-synthesized fifth-generation (G5) PAMAM.[158, 164, 165] Dendrimer can be characterized through gel permeation chromatography (GPC), HPLC, potentiometric titration, and electrospray ionization mass spectroscopy (EI-MS) in addition to SEM, FTIR, UV-Vis, ELS, and DLS.[166–168] Reviews by de Araújo *et al.*[169] and Abbasi *et al.*[157] provide additional insight into the biomedical application of dendrimers. As with liposomes, dendrimers are found in all areas of the biomedical field inhabited by hybrid nanosystems except antimicrobials and vaccines.

Cell membranes—Several groups have begun coopting the membranes from cells to encapsulate nanoparticles. These cell membranes provide high serum stability in addition to cell-specific properties. The membranes of several types of cells have been incorporated into nanotherapeutics, including platelets, red blood cells (RBCs), white blood cells (WBCs), cancer cells, mesenchymal stem cells (MSCs), and bacteria.[170] Cell selection heavily influences the properties of membrane-bound nanosystems. For instance, nanoparticles coated in cancer cell membranes can present antigens to activate anticancer immunity,[171] whereas RBC membranes promote long circulation and trans-epithelial transport, MSC membranes target cancers, and platelet membranes target damaged blood vessels and pathogens.[170, 172] Cell membranes have encapsulated organic materials such as polymer nanoparticles,[171] gelatin, liposomes, and proteins,[172] and inorganics including MOFs,[173] MSNs,[174] gold nanocages,[175] upconversion nanoparticles,[176] IONPs,[177] and quantum dots.[178] These hybrids have been applied for purposes ranging from targeted delivery of small interfering RNA (siRNA) and chemotherapeutics[173, 179] to imaging-guided phototherapy[180] and vaccine development.[174]

The formation of membrane-based nanosystems requires initial membrane isolation followed by encapsulation of a desired core. Organelles can be separated from membrane components through sonication, extrusion, freeze/thaw cycling, hypotonic lysis buffer, or Dounce homogenization followed by differential ultracentrifugation.[172] The isolated membrane can then encapsulate nanoparticles *via* coincubation in conjunction with sonication, extrusion, electroporation, or microfluidic techniques.[170, 172] The resultant nanohybrids are commonly characterized by DLS, ELS, TEM, SEM, and UV-Vis.[171, 174, 175] Several recent reviews from Xuan, Shao & Li[170] and Vijayan, Uthaman, & Park[172] provide useful supplementary information on synthesis, characterization, and application of cell membrane-based biomedical nanosystems. Cell membrane building blocks are found in

hybrid nanosystems used in gene and drug delivery, phototherapy, combination therapy, vaccines, and theranostics.

Accessory building blocks—Along with the aforementioned inorganic and organic building blocks, accessory building blocks are often included in hybrid architectures. Accessory building blocks are chemical groups or molecules included in the structure of the hybrid nanosystem that confer additional properties to the system without contributing as a major structural component. The major accessory building blocks include hydrophilic polymers, targeting ligands, and stimulus-responsive moieties (Figure 5E). Hydrophilic polymers such as PEG or zwitterionic polymers confer stealth properties to a nanosystem by forming a hydration shell.[39, 181] This hydration shell creates an energy barrier that must be overcome to contact the polymer, thus reducing non-specific protein interactions and extending circulation time *in vivo*.[182] Furthermore, PEG can selectively adsorb proteins that improve nanosystem retention, whereas select zwitterionic polymers have shown complete elimination of the protein corona.[181, 183, 184] As serum stability and low *in vivo* clearance are prerequisites for many nanotherapeutic applications, hydrophilic polymers are included in a notable portion of hybrid nanosystems. For additional information, we recommend several reviews on PEG hydrogels[185–187] as well as Erfani *et al*. on zwitterionic moieties.[181] Hydrophilic polymers can be expected to be found throughout the biomedical field.

Active targeting moieties such as antibodies and ligands for upregulated receptors can enhance the accumulation of a hybrid nanosystem to a specific environment. The tumor microenvironment of several cancers has been reported to disproportionately express folate receptors, CD44 receptors, and integrins α5β3 and αvβ3, which can be actively targeted by folic acid (FA), hyaluronic acid (HA), and arginine-glycine-aspartic (RGD) peptides respectively.[14, 24, 188] Cyclic targeting ligand iRGD utilizes a two-step process to sequentially target αv integrins and neuropilin-1 *via* a CendR interaction following proteolytic cleavage.[189] Finally, nanosystems can be modified with redox/pH-sensitive moieties, crosslinked to control therapeutic loading and release profiles, or functionalized to alter nucleic acid condensation.[142, 190] Reviews on active targeting in biomedical nanosystems can be obtained from Muhamad, Plengsuriyakarn, & Na-Banchang[191] and Bazak *et al*.[192] Targeting ligands and antibodies have been included in hybrid nanosystems throughout the biomedical field. Figure 5 describes the organic and accessory building blocks for hybrid nanosystems.

Hybrid architectures—Hybrid nanosystems consistently take one of several forms. Hybridization of inorganic nanoparticles with lipids creates nanoparticle-functionalized liposomes boasting liposomal loading and delivery along with nanoparticle targeting, transfection, transport, and/or plasmonic properties (Figure 6A).[125, 193–195] Similarly, cell membrane-encapsulated nanoparticles combine the properties of the inorganic core with serum stability and biospecific targeting (Figure 6B). Alternatively, metal nanoparticles can be bound to the surface of liposomes for stimulus-responsive release of encapsulated components (Figure 6C).[28] Utilizing polymers or dendrimers instead of lipids allows inorganic nanoparticles to be encased in a shell to create core/shell nanosystems (Figure 6D,E,F);[196, 197] inversely, polymer nanoparticles can also be functionalized with

surface-associated inorganic components (Figure 6G).[198] The layer-by-layer architecture involves sequential coating of metallic nanoparticles by polymer and therapeutic to create nanosystems with tunable release profiles (Figure 6H).[199] Finally, the rattle-type architecture consists of a solid core nanoparticle surrounded by an unattached porous shell (Figure 6I).[200] The hybrid architectures in the mixtures and dispersions of nanoparticles in polymer networks and prepolymers are governed by the surface energies and the molecular interactions between media and the nanoparticles. For instance, shear-thinning gelation in the aqueous solutions of Laponite-based hybrid nanoclays stems from the synergistic contribution of negative and positive charges present on the Laponite nanoplatelets which is responsible for the so-called “house of cards” hybrid architectures.[201] These architectures play an important role in determining the physical properties of the hybrid nanosystems and explains gelation in the absence of shear forces (shear-thinning property). Though not every biomedical hybrid nanosystem will fit these classifications, they can be used as a reference for architectures present in the field.

Biomedical applications

Having discussed their components and architectures, we will now describe current hybrid nanosystems in various biomedical applications. Gene and drug delivery commonly utilize hybridization to marry the carrying capacity of organic materials with the self-therapeutic, biocompatible, and imaging properties inherent to inorganic materials. Hybridization in phototherapy alone and in combination with gene and/or drug delivery offers coupling of photo-responsive properties with carrying capacity, stimulus-responsivity, and targeted therapeutic delivery. In tissue engineering, hybridization confers additional properties over pure organic or inorganic systems, including improved wound healing, enhanced cellular adhesion and remodeling, and reduced inflammation. In the context of antimicrobials, hybrid nanosystems offer the opportunity to selectively eliminate bacterial targets, reverse antibiotic resistance, and couple antibacterial properties with phototherapy. Hybrid vaccines have shown improved thermostability over non-hybridized counterparts. For imaging and detection applications, hybrid nanosystems offer altered imaging/visual properties based on the local microenvironment detectable through changes in conductivity, absorption, fluorescence, and/or T_1 relaxation time. Finally, theranostics integrate imaging properties with gene delivery, drug delivery, and/or phototherapy, a task better suited for hybrid nanosystems in comparison to non-hybridized parallels. As such, hybrid nanosystems offer advantages over non-hybridized systems in each of these applications.

Gene delivery

Some of the most notable advances in hybrid nanosystem technologies have come in the field of gene therapy, which seeks to treat disease through the transfer of genetic material to enhance, augment, or inhibit gene expression. Current gene delivery strategies include viral and non-viral techniques, the former utilizing the natural transduction efficacy of viral particles while the latter relies upon the transfection properties of engineered vectors. Some challenges facing viral gene delivery efforts include reduced carrying capacity, tropism, and inflammation, while non-viral vectors show better carrying capacity but face major challenges in transfection efficiency and gene modulation efficacy.[207] Hybrid inorganic/

organic vectors offer enhanced transfection efficacy over either material alone, which has resulted in notable growth in hybrid vector development in recent years.

Liposome hybridizations for gene delivery

Liposomes offer effective gene transfection exemplified by commercial liposome-based transfection reagents such as Lipofectamine™ and HiPerfect™. Liposomal systems overcome gene transfection challenges by providing a positive surface charge and lipid shell to prevent charge repulsion and allow membrane fusion for gene delivery. Nevertheless, several studies have shown that liposome transfection is improved through AuNP hybridization, as nucleic acids can be adsorbed to the AuNP surface and subsequently loaded into liposomes (Figure 6A). Gold-functionalized liposomes have been synthesized to deliver siRNA, with the uptake pathway determined by the AuNP-liposome composition.[208] Similarly, we recently reported the development of an AuNP-liposome siRNA delivery system that significantly improved knockdown of a glycolytic switch in ovarian cancer by shifting the uptake pathway to avoid lysosomal degradation.[22] These findings suggest that AuNP-hybridized liposome delivery systems can provide dramatic improvements to non-hybridized vectors.[22]

AuNP-liposomal delivery of siRNA can be enhanced by active targeting. Du *et al.* presented an AuNP-liposome containing FA that showed improved transfection efficiency in folate-receptor positive cells.[209] Moreover, active targeting combined with liposome-AuNP hybridization can permit delivery to traditionally hard-to-treat locations.[210] AuNP-liposomes can also deliver a combined gene/protein payload such as that required for CRISPR/Cas9 therapy. The Jiang lab reported that a gold/lipid-based vector successfully knocked down PIk1 expression in A375 cells *in vitro* through the delivery of Cas9 protein and sgRNA.[211] A follow-up study showed that the plasmonic properties of AuNPs allowed for the targeted release of Cas9-sgPlk-1 plasmids in response to laser radiation to better control gene-editing practices *in vivo*.[212] As such, AuNP-liposome hybrids appear poised to deliver next-generation gene-editing technologies in upcoming years.

Polymer hybridizations for gene delivery

Polymer nanosystems commonly utilize a cationic polymer to complex with nucleic acids and overcome charge repulsion from anionic cell membranes in conjunction with a metal nanoparticle containing self-therapeutic or magnetic properties. The combination of AuNPs and biocompatible polymers as gene vectors typically take one of two forms: the core-shell morphology includes an AuNP within a functionalized shell of polymer and therapeutic,[196] while the “layer-by-layer” approach consists of an AuNP sequentially coated in cationic polymer and nucleic acid.[199] In core-shell architectures, AuNPs have been functionalized with PEI to deliver DNA and RNA for pre-clinical treatment of prostate cancer,[24, 213] breast cancer,[214] liver cancer,[215] melanoma,[216] and glioblastoma.[217] Furthermore, AuNPs enhance the permeability of lipid bilayers, which has been exploited by AuNP-PEI hybrids in transdermal gene delivery.[216] AuNP-PEI vectors have also been functionalized with FA and other ligands to improve their target-specific transfection efficiency.[213, 218] Lastly, gold-PEI vectors can display photo-responsive delivery properties through absorption of near-infrared (NIR) radiation.[38] Like PEI, PLL is a cationic polymer effective for gene transfection, and

gold-PLL vectors have been developed to deliver RNA to treat breast cancer[39, 219, 220] and liver cancer *via* the RNA interference (RNAi) regulatory system.[40] Others have applied AuNP-chitosan hybrids in applications from liver and breast cancer treatment to iontophoretic melanoma therapy and osseointegration of dental implants.[137, 221, 222] Gold-polymer vectors can also display redox-responsivity, allowing them to selectively release nucleic acids in environments of elevated glutathione.[198, 223] This evidence suggests that gold-polymer nanosystems present an effective hybridization for gene delivery applications.

Other inorganic building blocks applied in hybrid polymer gene vectors include IONPs and mesoporous structures. IONP-cationic polymer nanosystems have been employed to deliver siRNA and plasmid DNA and have shown enhanced transfection over non-magnetic vectors.[224, 225] Alternatively, Salah *et al.* used nanozeolite MOF-polymer nanosystems to deliver miR-34a to hepatocellular carcinoma,[226] and polyelectrolyte-conjugated MSNs have served as siRNA vectors for the treatment of H1N1.[227] Finally, CaP and PEI have been hybridized to deliver mcDNA to T-cells for cancer immunotherapy, resulting in rapid T-cell-induced apoptosis of hepG2 cells.[228] As such, inorganic-polymer vectors show breadth in application, with an emphasis on cancer therapy and versatility to treat viral disease.

Dendrimer and cell membrane hybridizations for gene delivery

Thirdly, inorganic-dendrimer nanosystems have been investigated as non-viral vectors. As with cationic polymers, dendrimers conjugated to inorganics overcomes charge repulsion with cell membranes and facilitates delivery of nucleic acids. The Shi lab among others has published several recent articles on PAMAM-entrapped AuNP nanosystems as non-viral vectors, where AuNPs confer biocompatibility and structural integrity while PAMAM conveys enhanced loading and transfection capabilities.[164] Furthermore, AuNP-PAMAM hybrids have been functionalized with an array of surface moieties ranging from zwitterions for stealth to β-cyclodextrin for improved nucleic acid condensation,[158, 164, 190] and FA, HA, or RGD-peptides augment gene delivery efficacy for inhibition of tumor growth.[158, 161, 165] Consequently, AuNP-PAMAM hybridization shows notable potential for gene delivery. Alternatively, cell membranes can encapsulate inorganic nanoparticles loaded with siRNA to create biocompatible nanovectors; these nanovectors offer distinct advantages over other organic components in that they more closely replicate the endogenous tissues. For example, Zhuang *et al.* incorporated an siRNA-loaded ZIF-8 MOF into a platelet cell membrane for targeted gene silencing in mammary adenocarcinoma.[173] These approaches signify the diversity and effect of hybrid nonviral vectors.

The building blocks and architectures utilized in gene delivery applications allow us to make several observations about hybrid vectors. Unsurprisingly, nanoscale gold is the most utilized building block for its myriad beneficial properties, including biocompatibility, cell membrane destabilization, nucleic acid adsorption/desorption, self-therapeutic properties, and ease of synthesis. AuNPs hybridized with liposomes, polymers, or dendrimers form the largest group of hybrid gene delivery systems, and the organic building blocks seem to represent comparable alternatives with minimal differences observed in the efficacy of one over another. Intriguingly, few of these systems display magnetic targeting or photoresponsive gene release, though this is likely due to vectors with those properties

also displaying phototherapeutic or imaging properties. As such, hybrid gene vectors with nanoscale gold are among the most promising and effective non-viral vectors for future gene therapies.

Drug delivery

Drug delivery systems (DDSs) seek to increase the local concentration of a drug in a specified environment to reduce side effects and improve efficiency, and hybrid nanosystems show potential to overcome drug delivery barriers like rapid *in vivo* clearance and selective drug encapsulation/release.[229] In the following section, we summarize notable strides made by hybrid DDSs within recent years.

Liposome hybridizations for drug delivery

Inorganic-liposome hybridizations are distinctively suited for small molecule drug delivery applications. The lipid bilayer of liposomes is practical for drug loading and can isolate encapsulated therapeutics from the surroundings, while inorganic components may provide magnetic targeting, imaging, biocompatibility, and photothermal drug release capabilities. Chemotherapeutic agents such as doxorubicin (DOX) and paclitaxel (PTX) have been widely encapsulated within gold-liposome hybrids for drug delivery applications.[230, 231] NIR-triggered DOX release has been achieved by coating liposomes in gold shells or nanocages that rupture the lipid bilayer *via* thermal decay or CO_2 bubble generation.[14, 17, 28] Other gold-liposome DDSs respond to endogenous stimuli; *e.g.* several AuNP-liposome hybrids have been designed to degrade in the mildly acidic tumor microenvironment.[193, 232]

The superparamagnetic properties of IONPs provide active drug targeting capabilities to liposomes by application of an external magnetic field, and these “magnetoliposomes” are widely successful as DDSs.[126] Magnetic targeting improves magnetoliposomal DOX delivery efficacy in comparison to both liposomal and free DOX.[233–235] Magnetoliposomes have also been utilized to delivered curcumin, docetaxel, gemcitabine, cisplatin, and cuphen, and have been reported effective for radical scavenging as well as treatment of diverse cancers.[202, 236–238] Magnetoliposome-mediated chemotherapy can be further enhanced through active targeting ligands and moieties with endogenous stimulus sensitivity.[127, 194, 239, 240] Finally, one report describes a IONP/liposome-based docetaxel delivery system that displayed drug release in response to both an external magnetic field as well as NIR.[241] As such, the development of magnetoliposomes has been a boon for targeted drug delivery.

Aside from AuNPs and IONPs, few inorganic materials have been hybridized in liposomal DDSs. Liposome-encapsulated MOFs can codeliver several drugs simultaneously[195] and display self-therapeutic properties against cancer through ion leaching.[242] Si-O-Si networks have been incorporated into thermosensitive liposomes to improve their stability for room temperature storage,[243] and nickel-bis(dithiolene) display gold-like NIR absorption properties to induce drug release under NIR.[244] Finally, incorporation of AgNPs into liposomes has been shown to alter the loading capability and partition coefficient of encapsulated curcumin, suggesting that metal nanoparticles can relocate hydrophobic drugs

closer to the liposome surface.[245] As such, liposome-encapsulated metal nanoparticles form effective platforms for the delivery of small molecule drugs to a variety of targets.

Polymer hybridizations for drug delivery

Inorganic-polymer DDSs have been investigated with less intensity as have inorganic-liposome hybrids. The biocompatibility of AuNPs has been applied in conjunction with chitosan, polyvinylpyrrolidone (PVP), and polypeptides to deliver drugs including 5-fluorouracil, DOX, curcumin, and sunitinib malate.[21, 246, 247] Moreover, polymers conjugated to AuNP DDS hybrids can be readily modified with pH-responsive moieties and targeting ligands.[197] Additionally, inorganic compounds and MSNs can form the core of hybrid polymer DDSs, while others have designed systems including ZIFs, and PtNPs to release chemotherapeutics in response to reduced pH.[57, 85, 248] For example, Dong *et al.* utilized a CaP shell around a phosphatidylserine-PEG core to confer pH-responsivity to co-delivery of verapamil and novantrone to treat multidrug-resistant breast cancer.[66] Finally, inclusion of AgNPs can confer hybrid polymer DDSs with antibacterial properties, allowing them to be used in combination antibacterial/chemotherapeutic capacity.[249]

Alternative hybridizations for drug delivery

Inorganic-dendrimer hybrids are also effective for chemotherapeutic delivery.[159] In one example, Parlanti *et al.* designed an IONP-PAMAM nanosystem exhibiting magnetic targeting and pH-responsive DOX release for the treatment of pancreatic cancer.[250] This system is noteworthy for its uptake mechanism in which the dendrimer is cleaved and taken into the cell while the inorganic core remains outside.[250] Alternatively, ruthenium-modified carbosilane dendrimers exhibit low toxicity to non-cancerous cells while inhibiting leukemia cell viability.[251] Membrane-coated inorganics show potential as DDSs as well. MSC and RBC membranes have been used to encapsulate MOFs for targeted protein delivery,[252] while DOX has been delivered *via* AuNCs encapsulated within 4T1 breast cancer cell membranes,[175] and therapeutic antibodies have been delivered with platelet membrane-coated IONPs.[253] Conversely, some DDSs have utilized nucleic acids for structural purposes. Wang *et al.* developed a fascinating system for the delivery of anticancer drugs by encapsulating ZONPs in DNAzyme (a short catalytic sequence of DNA)-substrate scaffolds. When the ZONPs responded to reduced pH by producing Zn^{2+}, a DNAzyme cofactor, the DNAzyme broke down the scaffold for therapeutic release.[67] Finally, several forms of carbon have been utilized as pseudo-organic components in hybrid DDSs. Cyclic carbon (C18) has been employed as a shell surrounding IONPs for benzamide loading. The hybrid nanosystem prevented biofilm generation by *C. albicans* while exhibiting biocompatibility, suggesting potential for infection treatment.[254] Lastly, MSNs conjugated with GO and functionalized with aspartic acid show low cytotoxicity alone but enhanced cell death and apoptosis in MCF-7 cells when loaded with curcumin.[255] Though the building blocks may vary, hybridization offers a distinct and effective approach to constructing DDSs.

Hybrid DDSs take advantage of the carrying capacity of liposome, polymer, dendrimer, and cell membrane components to deliver a variety of small molecule therapeutics to diverse targets. AuNP- and IONP-liposome hybridizations are among the most effective systems due to their ability to carry both hydrophilic and hydrophobic drugs in an isolated

environment and respond to exogenous stimuli, which allows selective delivery and release of encapsulated therapeutics. Aside from these popular architectures, the diversity expressed by hybrid DDSs is astounding. Porous materials allow facile adsorption/desorption of small molecules, which are ideal properties for DDSs, and hybridization within organic building blocks facilitates tuning of the release profile. Drug delivery is also where we initially encounter carbon-based materials, and they make a minor but not insignificant contribution to our understanding of hybrid DDSs. All considered, hybrid nanosystems represent a noticeable improvement over nonhybridized DDSs by allowing drug delivery to correspond with external targeting and photo-responsive drug release.

Phototherapy

Phototherapy harnesses external radiation for therapeutic purposes. The first NIR window (wavelength 700–1000 nm, NIR-I) is characterized by reduced absorption by biological tissues, allowing deep its penetration into the body.[256] A second biological window (NIR-II) has been reported above 1000 nm, and some sources indicate that a third biological window exists above 1500 nm, though others have designated it a subset of NIR-II.[257, 258] Semantics aside, compounds incorporated into nanosystems that absorb in these biological windows can allow NIR activation of therapeutics. Phototherapy can be split into two categories. Photothermal therapy (PTT) harnesses the increase in temperature experienced by photoabsorbing nanoparticles to kill adjacent cells,[259] whereas photodynamic therapy (PDT) utilizes electrons excited by photons interacting with photosensitizers to generate active therapeutics such as singlet oxygen ($^1O_2$) and other ROS.[260] Several recent advances in the application of hybrid nanosystems to phototherapy are outlined in the following section (Figure 7).

The absorption spectra of photothermal nanosystems are heavily influenced by the material and geometry of the inorganic component. AuNRs and AuNPs can be engineered to exhibit an absorption peak within the NIR range (See Figure 3). Additionally, absorptive LSPR decay is readily employed for hyperthermic therapy, and as a result, several groups have developed gold-based hybrid nanosystems for PTT.[45] AuNPs have been incorporated into liposomes to improve tumor targeting and deep phototherapy by exploiting the NIR-II window.[261, 262] As with gene and drug delivery, these AuNP-liposome systems can be modified with ligands and magnetic components to allow both endogenous and exogenous targeting.[262, 263] Similarly, AuNRs have been utilized as the core of NIR-I-responsive core-shell poly(o-methoxyaniline) hybrids displaying morphology control through polymer concentration variation.[13] In one geometry, gold-capped polymer janus particles encapsulated in cell membranes exhibited photothermal effects resulting in enhanced motile behavior along with PTT.[204, 264] As a gold alternative, aniline-based polymers have been applied to PTT in coordination with lanthanide-based upconversion nanoparticles (which absorb two photons at low energy and emit a single photon at higher energy). This nanosystem was shown to effectively photoablate tumors *in vivo* with NIR radiation but to be non-toxic in its absence.[265] While most photothermal hybrid nanosystems are developed for cancer treatment, other applications exist. For instance, Zhou *et al.* designed a nanocomposite capable of PTT simultaneously displaying non-NIR-coupled effectivity against bacterial infection and applications in wound healing,[141] which

exemplifies how photothermal hybrid nanosystems can be designed for several applications simultaneously.

Unlike PTT, PDT harnesses incident light to initiate a chemical reaction. In these systems, metal nanoparticles are frequently included for their non-optical properties, and additional photosensitizers are included to facilitate the therapeutic process. For example, liposomes carrying the photosensitizer chlorin e6 (Ce6) were modified with AuNCs, where the AuNCs inhibited thioredoxin reductase to improve the efficacy of $^1O_2$ produced by Ce6.[16] Liposomes have also been modified with IONPs to provide magnetic targeting capabilities for protoporphyrin delivery.[266] Likewise, MOFs have been conjugated with photosensitizers and nanozymes for two-step PDT in which the nanozymes generate O_2 from H_2O_2 before photosensitizer radiation converts O_2 to $^1O_2$, overcoming the PDT limiting factor of tumor hypoxia.[267] A similar approach to alleviate tumor hypoxia prior to PDT was exploited by Zuo *et al.* in constructing a platelet membrane-encapsulated $W_{18}O_{49}$ and metformin nanosystem.[268] Other membrane-based PDT nanosystems have employed platelet membranes in conjunction with photodynamic cores to improve PDT efficacy and reduce skin damage,[269] and macrophage membrane-encased IONPs for magnetic responsivity.[203] Additional PDT hybridizations have utilized TiO_2, SiO_2, phosphorus quantum dots, iridium nanocrystals, PtNPs, and AgNPs along with photosensitizers to kill cancers and bacteria.[270–273]

Though both PTT and PDT exploit the biological windows for therapeutic purposes, differences in exploitation mechanisms highlight a distinction between them in hybrid nanosystem building block selection. Those employing PTT commonly utilize inorganic nanoparticles for photoabsorption while organic components are included for biodistribution, targeting, and stability purposes. Consequently, PTT *via* hybrid nanosystems allows for improved efficacy over non-hybridized systems through improved accumulation in the desired environment and reduced *in vivo* clearance. In contrast, transferring the onus of PDT to a photosensitizer allows for the selection of inorganic building blocks based on non-optical properties, which provides versatility to overcome common PDT obstacles such as tumor hypoxia and photosensitizer loading/delivery. As such, hybrid nanosystems offer advantages over current therapies for both PTT and PDT through differing means.

Combination therapy

While the aforementioned examples show the benefits of hybridization in gene and drug delivery as well as phototherapy, hybrid nanosystems excel in combination therapies utilizing multiple strategies (*i.e.* combined chemo/phototherapy, gene/drug codelivery, *etc.*) to more effectively treat malignancies. In the following section, we summarize the current work in combination therapy using hybrid nanosystems. From an architecture perspective, gold-functionalized liposomes are well-suited for chemo-phototherapy and co-delivery of genes and small molecule drugs, as this combines the loading capacity and transfection of liposomes with the optical and self-therapeutic properties of nanoscale gold. Polymer-functionalized gold of varying geometries has been proven effective for gene/drug codelivery, gene-PTT, and chemo-phototherapy, with cationic polymers enhancing transfection capability and facilitating drug loading while gold cores provide tunable optical

and self-therapeutic properties. Moreover, as the majority of these systems discussed thus far have been cancer therapies, Table 1 displays notable hybrid nanosystems developed for cancer treatment.

Gene and drug codelivery

Codelivery of nucleic acids and small molecule drugs have the potential to exceed the most effective monotherapies. Through careful drug and gene selection, the therapeutic effect of one can enhance the efficacy of the other. For example, interfering RNA (RNAi) therapy can downregulate nonspecific cellular efflux pumps responsible for clearing the cytoplasm of chemotherapeutics, improving the efficacy of drugs co-delivered by the hybrid system.[274, 275] One popular hybridization for gene/drug codelivery is nanoscale gold and liposomes, and these systems have been further modified for magnetic targeting and photo-triggered release of encapsulated therapeutics.[276, 277] Alternatively, Han *et al.* developed an AuNP-PEI nanosystem capable of re-educating stellate cells in pancreatic ductal adenocarcinoma through the co-delivery of all-trans retinoic acid and siRNA to knockdown heat shock protein 47.[278] AuNRs have been combined with PEI to co-deliver DOX and short hairpin RNA (shRNA) to metastatic breast cancer (MBC) and inhibited tumor growth and metastasis.[279] Another MBC therapy was developed from AuNPs incorporated into hydrogels for co-delivery of miRNA and cisplatin.[280] AuNPs have also been decorated with DOX and siRNA-loaded proteins for ovarian cancer therapy,[281] conjugated with DNAzymes, and ZnO quantum dots for miR-21 and DOX delivery,[282] and even trapped within a dendrimer for ultrasound-triggerable release of miR-21 and gemcitabine.[283] Finally, MSN-ZIFs have been designed for the pH-responsive delivery of DOX, DNA, and CRISPR-Cas9 components *via* subretinal injection *in vivo*.[205] As such, hybrid nanosystems make up an effective strategy for co-delivery of nucleic acids and small molecules.

Gene delivery and photothermal therapy

The biocompatible and self-therapeutic properties of nanoscale gold combined with tunable absorption properties make it unparalleled in combination gene-PTT. AuNPs, AuNRs, AuNSs, and gold nanoprisms have been combined with biocompatible polymers to create nanosystems to treat lung cancer, breast cancer, and gastric cancer.[29, 284–286] As with gene/drug codelivery, careful selection of therapeutics can produce synergistic effects. Liu *et al.* used a gold nanoflower-based hybrid to delivered siRNA to knock down heat-shock proteins prior to PTT.[287] Mesoporous PDA nanoparticles also display effective photothermal conversion. PDA has been coated with CaP to produce pH-responsive nanosystems exhibiting effective siRNA knockdown and PTT.[288] As such, gold and PDA provide effective means for harvesting NIR and converting it to thermal energy for PTT in combination with gene delivery.

Combination chemo-phototherapy

Chemo-phototherapy has recently emerged as a next-generation cancer treatment in which gold nanostructures are regularly employed to harvest NIR radiation and convert it to thermal energy. AuNS-coated liposomes containing chemotherapeutics can couple laser-activated drug release with PTT.[289, 290] In a similar approach, gold-coated $MnFe_2O_4$ nanoparticles have been encapsulated within liposomes to create photoresponsive and

superparamagnetic DDSs,[291] and Au nanocages have been encapsulated within cancer cell membranes to deliver DOX for selective combination chemo-PTT.[175] One study compared the efficacy of AuNPs and AuNSs within a thermo-responsive liposomal coating and determined that AuNSs displayed better LSPR tunability, allowing for more efficient absorption of NIR for PTT and drug release.[292, 293] Nevertheless, even less efficient AuNPs have displayed photoinduced PTX release and photothermal hypothermia when conjugated with PLL and loaded with PTX.[294]

Gold has also been hybridized with structural nucleic acids and mesoporous semiconductors for chemo-phototherapy. Song *et al.* developed AuNR-DNA nanostructures loaded with DOX through base-pair intercalation that showed increased cellular uptake of both the DOX and AuNRs.[295] Another AuNR-DNA nanoplatform was developed to release DOX in response to NIR through the photoacoustic effect in addition to mRNA-triggered release.[296] Finally, a rattle-type chemo-phototherapy hybrid nanosystem was constructed from Au@Cu2-xS mesoporous nanocrystals that exploited metal-semiconductor hybridization to deliver DOX with NIR activation and detect the presence of oncogenic RNA through adsorption of miRNA gene probes to the nanocrystal surface.[297]

Carbon-based inorganic building blocks find special use in chemo-phototherapy. Wang *et al.* detailed an intricate nanosystem containing a hollow, IONP-functionalized carbon core surrounded by a redox-responsive MnO_2 shell coated in PEI and RGD targeting peptides. Upon exposure to glutathione, the MnO_2 shell degraded and activated a ROS-generating chemodynamic drug that showed greater than 99% tumor suppression when coupled with NIR.[298] Furthermore, GO-polymer nanosystems have been designed to actively target tumors for methotrexate delivery in combination with PTT,[299], and chitosan-reduced GO can deliver DOX in conjunction with photodynamic $^1O_2$ generation.[300] Thus, hybrid nanosystems can readily combine delivery of small molecule therapeutics with phototherapy in addition to NIR-responsive drug release.

Gene and drug co-delivery in combination with phototherapy

As combination therapies have shown improvement over monotherapies, gene and drug co-delivery in coordination with phototherapy offers even greater opportunity for enhanced therapeutic efficacy. As such, Deng *et al.* designed an AuNP-liposome hybrid capable of X-ray-triggered gene and drug release. Moreover, the photosensitizer verteporfin was incorporated within the liposome to generate $^1O_2$ upon X-ray irradiation.[301] Similarly, AuNR-silica nanocapsules have been designed to deliver sorafenib and p53 to malignant hepatocellular carcinoma; this nanosystem displayed both NIR-triggered release of the encapsulated gene/drug and PTT from the AuNRs.[200] From these examples, we can conclude that hybridization provides a method by which nanosystems can effectively approach the challenges of combination therapies.

Hybridization in the context of combination therapy provides opportunities for synergy, with drugs, genes, and phototherapies selected to amplify the efficacy of the cotherapies of a given nanosystem. Though it is possible for synergistic effects to be observed in non-hybridized systems, hybridization offers improved methods for their inclusion in a single system. Based on this evidence, polymer-functionalized gold nanosystems are the

preeminent architecture in combination therapy applications. For alternatives to gold, carbon-based building blocks have shown promise in delivering chemotherapeutics in combination with both PDT and PTT, and PDA is also an effective photoabsorber. Table 1 displays recent hybrid nanosystems for gene, chemo, and phototherapy for cancer treatment.

Tissue regeneration and remodeling

Tissue engineering aims to recapitulate native tissue characteristics to develop biological substitutes for replacing damaged tissues.[311, 312] Hybrid nanosystems have led to significant advances in fabricating biomimetic tissue constructs. Both inorganic and organic building blocks have shown promise *via* regulating cell growth and differentiation as well as tuning the material properties of the extracellular matrices (ECM). These improvements are demonstrated for regeneration of the tissue types such as skin, bone and cartilage, nerve, cardiac, and vascular tissues. In the following sections, the recent advances made by hybrid nanosystems in tissue healing and regenerative areas are summarized.

Wound management

Hybrid nanosystems have facilitated wound healing in different capacities. In particular, metal nanoparticles incorporated with injectables and wound dressing patches can promote wound healing efficacy. This improvement stems from the active tissue regenerative and antimicrobial function of nanoparticle components during the stages of wound healing. AgNPs are one of the most widely used compounds for treating chronic ulcers and tissue burn infections.[313] The non-specific release of AgNPs which initially raised toxicity concerns was circumvented in the recent silver-based products such as Acticoat Flex 3 wound dressings.[313] AgNPs can facilitate wound epithelialization according to a study on human anorectal surgery wounds treated with AgNPs extracted from the *Delonix elata* leaf in which the wound fully disappeared after 17 days post-procedure.[314] AuNPs can accelerate wound healing in polymer-based hybrids because of their antioxidant and antimicrobial properties. AuNPs aid hemostasis and inflammatory phases of wound healing.[315] Skin wound healing capability of biopolymers such as collagen[316] and chitosan,[317] increased with the addition of AuNPs. One attractive feature of AuNPs is the possibility of surface functionalization through which their wound healing efficacy can be further enhanced. Cyclic lipopeptide surfactin functionalization of AuNPs further improved wound healing capability in AuNPs incorporated polymer as confirmed in a rodent wound model.[318] The plasmonic properties of AuNPs can also enable their wound healing capability, as the emitted heat in response to NIR light is known to reconfigure and interdigitate the tissues locally at the wound site.[319] Among the metal nanoparticles, CuNPs play a pivotal role in wound healing by inducing angiogenesis through enhancing the release of vascular endothelial growth factor (VEGF), upregulating the expression of integrin, and stabilizing the ECM proteins. A wound-healing agent based on chitosan and CuNPs studied by Gopal *et al.*[320] demonstrated a decrease in tumor necrosis factor-α (TNF-α) and an increase in interleukin-10 (IL-10) in the rat models.

ZONPs have also proved their excellent potential for wound healing applications. The addition of ZONPs to polymer matrices is associated with an increase in re-epithelialization,

tissue granulation, keratinocyte migration, as well as collagen deposition. The ZONPs synthesized from the *Trianthema portulacastrum Linn*. exhibited anti-inflammatory, antibacterial, and antioxidant properties based on which the wound healing characteristics are stemmed from.[321] The planar structure of GO sheets also enables grafting bio-functionalities required for wound healing. Recently, a reduced graphene oxide (rGO) embedded in isabgol was utilized for treating diabetic wounds.[322] Addition of rGO was associated with accelerated wound healing in Wistar rats. The rGO can favor re-epithelialization, promote the collagen concentration, as well as angiogenesis in the wound area. The use of silica in wound dressings can enhance the proliferation and migration of fibroblast cells.[323] The positively charged silica nanoparticles (SiNPs) can be dissolved in the wound media and thereby generate the silicic acid that has been shown to stimulate wound healing in dressings. Wound healing was escalated with the addition of SiNPs to the PVP polymers due to the sustained delivery of SiNPs at the wound site. Nanoparticles of titanium dioxide (TONPs) also demonstrated enhance in burn wound model *in vivo* which results in re-epithelialization, angiogenesis, and fibroblast migration.[324] Hybrid nanosystems led to a significant impact on the wound healing efficacy of the polymeric matrices.

In addition to the tissue regenerative properties, hybrid nanosystems have advanced wound management techniques by due to their hemostatic effects which facilitates blood coagulation in case of hemorrhage. The hemostatic properties in nanoparticles originate from their large surface charges and water absorbing capability. SiNPs coated with PDA is one example of additives that could shorten the time to hemostasis (by 150 seconds compared to a commercial Celox hemostatic agent).[325] The hemostatic effect was due to the activation of the extrinsic coagulation cascade by SiNPs and promoting platelet and erythrocytes aggregation. Nanoclays such as nanokaolin in combination with tannic acid was shown to act as FXII factor activator to trigger hemostasis in an adhesive hydrogel platform.[326] Laponite, the synthetic nanosilicate formed of nontoxic components (Na^+, Mg^{2+}, $Si(OH)_4$, Li^+) is known for its hemostatic properties due to its strong surface charges. Addition of Laponite to gelatin leads to a shear-thinning injectable biomaterial which can reduced the clotting time by ~50% (at 2 wt.% Laponite) by activating the intrinsic coagulation pathway through Factor XII.[99, 327] MMT can induce coagulation in blood. MMT particles were incorporated in a GO crosslinked composite could stop bleeding in a rabbit artery wound model within 84 seconds.[328] Rapid plasma absorption is an established mechanism of hemostasis in MMT based composites. The release of Ca^{2+}, Mg^{2+}, and PO_4^{3-} ions from nanowhitlockites ($Ca_{18}Mg_2(HPO_4)_2(PO_4)_{12}$) have accelerated activation of coagulation cascade and reduced bleeding time *in vitro* and blood loss *in vivo* by ~50% compared to a sham control.[93]

Bone and cartilage tissue engineering

Bone damage causes a large financial burden on the health care system. The lack of sufficient osteointegration in bone implants limits their lifetime and leads to revision surgeries that are often more costly and associated with more severe complications. Hybrid nanosystems have shown potential to enable nanoscale engineering of bone implants for more robust integration with the surrounding tissue. It is important to note that nanocrystalline hydroxyapatite (nHA), *i.e.*, $Ca_{10}(PO_4)_6(OH)_2$, forms the majority of the

bone matrix. Nano-phase ceramics, therefore, have received attention to address challenges at the bone-implant interface. Nanoscale nHA (*e.g.*, 67 nm grain size of nHA) provide a high surface fraction enhancing osteoblast activity due to the larger vitronectin adsorption.[329] Similarly, the ZONPs and titania, with 23 and 32 nm sizes, respectively, were reported to enhance calcium and collagen deposition. They also increased alkaline phosphatase activity compared to their microscale counterparts.[330] Self-assembly of organic helical rosette nanotubes based on DNA pairs in aqueous solution was characterized with osteogenic properties due to the structure of their peptide side chains (*e.g.*, RGD, KRSR for osteoblast adhesion, and lysine).[331] The nanostructured self-assemblies of peptides based on KLD-12 and Lys-Leu-Asp was proposed for cartilage repair application.[332] The hydrogels promoted chondrocyte differentiation and facilitated the deposition of the cartilage-like ECM.

Another rosette nanotube functionalized with lysine was reported for improvement in chondrogenic differentiation of adipose-derived mesenchymal stem cells (ADSCs).[333] The nanotubes were integrated with gelatin methacryloyl (GelMA) and poly(ethylene glycol) diacrylate (PEGDA) polymer matrices and 3D printed using a stereolithography printer. The addition of the nanotubes was associated with 34% increase in the ADSCs population. Carbon-based inorganic nanoparticles and their induced electrical conductivity have been frequently demonstrated to enhance osteogenic activities for bone tissue engineering applications. For instance, the incorporation of CNTs in polymers has increased the volume of bone formation by four times.[334]

Organic assemblies engineered in nanoscale such as nanofibrous polymers processed through electrospinning, particulate leaching, as well as phase separation are among the potential methods for bone tissue regeneration. Stem cell differentiation can be regulated by the organic hybrid nanosystems based on electrospun poly (ε-caprolactone) (PCL).[335] The electrospun nanofibers comprised of PLGA-tussah silk fibroin doped with GO aided MSC differentiation, accelerated the osteoblast differentiation as well as new bone formation.[336] Hybrid 3D porous scaffolds based on rGO and nHA was developed to fill in bone defects *in vivo* for circular calvarial defects in rabbit models.[337] Nanosphere metals, their oxides, and metallic alloys are three other classes of nanoparticles with osteoconductive properties. Titanium (Ti), the medical-grade titanium alloy (Ti6Al4V) and chrome alloys (CoCrMo) have been studied in their nanophase, and their enhanced osteoblast adhesion behavior was confirmed compared to their conventional solid counterparts.[338] To promote osteogenesis, nanofibers based on Zein PDA were developed to deliver TONPs conjugated with protein-2 (BMP-2). MSNs with cone-like pore shapes were also characterized for BMP-2 delivery.[339] The BMP-2 conjugates resulted in an increased expression of the osteoblast cells and its sustained delivery facilitated cell differentiation and adhesion due to their interconnected nanoscale matrix.[340] A 3D printed PCL scaffold was coated in a layer by layer fashion by PDA and AgNPs.[341] The findings were suggestive of improvement in both antibacterial and bone regeneration and demonstrated excellent performance in treating bone defects *in vivo*. Among other metal-based nanoparticles, the combination of zinc silicate and nHA with collagen has been associated with improved angiogenesis in bone scaffolds through p38 MAPK pathway in activated monocytes.[342] AuNPs in another study was conjugated with siRNA to activate both osteogenic as well as revascularization capabilities of the Ti

implants.[343] Nanoscale components can further improve in terms of their osteoactivity by chemical modifications at their surfaces.

Vascular tissue engineering

Vascular diseases and disorders due to coronary heart disease, or atherosclerosis have led to a large demand for vascular grafts. The vascular cell function is improved by incorporation of functional nanoscale components *via* preventing thrombosis and inflammation. Cell alignment in vascular cells (*i.e.*, smooth and endothelial muscle cells) play a key role in their function and have been paid particular attention in the literature. In this context, processing methods such as electrospinning have enabled directional deposition of nanofibers from hybrids that are capable of cell alignment. For instance, smooth muscle cell infiltration was reported in the case of nanofibrous scaffolds based on collagen/elastin/PLLA, 21 days post culture.[344] Vascular grafts were obtained by a combination of 3D printing and electrospinning.[345] A triple-layer PCL consisting of 3D printed inner layer-coated with aligned nanofibers were co-electrosprayed to form the third layer. In an *in vivo* study, the longitudinally aligned fibers facilitated migration of endothelial cells. Bilayered vascular grafts involving the inner layer of aligned PCL and collagen nanofibers with an outer layer from a randomly oriented PCL and silica nanofibers were fabricated by co-electrospinning.[346] In this vascular graft, the inner layer aimed to facilitate endothelial cell adhesion and migration while the outer layer provided strong mechanical support and enhanced fibroblast affinity. Shear-thinning biomaterials also have shown a great promise for endovascular embolization.[102, 347] The synthesized hybrids of nanosilicates (Laponite) with gelatin has been introduced an excellent candidate as they provide a biocompatible and injectable material platform as they could occlude blood vessels and promote connective tissue formation in the vessel lumen. Besides, they have shown excellent function for treatment of aneurysms as their injection at the aneurysm site can stop progression of disease and prevent damage to the blood vessels.

Cardiac tissue engineering

The complexity of the cardiac tissue structure and its regeneration process have led to major challenges in reproducing the cardiac tissue functions. Material selection, surface engineering, processing method (*e.g.*, electrospinning and 3D bioprinting) as well as the electrical coupling between the artificial scaffold and native tissue have been the main subjects in the study of cardiac scaffolds. Cardiac tissues have been enabled by the cell aligning effect of nanofibrous hybrids and the electrical conductivity offered by the carbon and metal-based systems.[348] Cardiac patches are aimed to host living cells (cardiomyocytes, bone marrow-derived stem cells *etc.*) and allow cell cultivation in presence of conductive components. Cardiac patches can be highly aligned in micro- and nanoscales to enhance synchronized contractions for instance, using the highly-aligned CNT sheets.[349] In the CNT-based hybrid systems, cardiomyocytes have shown similar electrical-impulse transmission behavior as the native myocardium and demonstrated lower cell-to-cell and beat-to-beat dispersion of the repolarization in the cultured cells with CNT content.[350] An engineered CNT embedded GelMA was characterized with 85% decrease in excitation threshold and 4 times larger synchronous beating rate due to the nanofibrous network of CNTs.[351] Functionalized CNT with hydrazine in pericardial matrix led to human-induced pluripotent

stem cell (hiPSC)-derived cardiomyocyte maturation. The cells demonstrated larger than 500% maturation on the conductive hydrogels and enhanced connexin 43 expression.[352] AuNPs deposited on decellularized omental matrix was proposed by Shevach *et al.*[353] for cardiac tissue engineering. The fabricated cardiac patches were characterized with Cx43 expression and increased contraction force and resulted in a larger calcium signal propagation. AuNPs incorporated in hydrogels can promote cardiomyogenic differentiation of stem cells. The electrical stimulation on the H9c2 cells in a porous polyurethane (PU)/AuNRs and AuNSs was investigated by Ganju *et al.*[354] The results suggested active expression of Nkx-2.5 antriuretic peptide precursor, and atrial natriuretic peptide. GelMA hydrogels containing AuNRs were also characterized by increased troponin I and sarcomeric actinin (cardiac markers).[355]

Neural tissue engineering

Hybrid nanosystems have had a notable contribution to improve healing disorders and injuries in the nervous system. The materials for neural tissue engineering are sought to be cytocompatible and should pose mechanical and electrical properties similar to that of native tissue to effectively direct neuron outgrowth and thereby bridge disordered nerve gaps. Nanofibrous electrospun PLLA incorporated in laminin (the protein that is known to promote neurite) was proposed for peripheral nerve repair.[356] A recent work demonstrated the aligned touch-spun PCL nanofibers could enhance neuron-specific class III β-tubulin expression along with bipolar elongation.[357] The excellent electrical properties of the carbon-based nanomaterials have made them an attractive candidate for nerve tissue regeneration. Manipulation of surface charges on the CNTs is an important factor as the neurite length, cone growth density, and branching improved by introducing positive charges.[358] Metallic nanoparticles such as AuNPs have been also able to endow electrical conductivity to the polymer matrices for regulation of neural cell differentiation. Hybrid nanocomposites based on AuNP complexes with polyaniline enabled electrical stimulation.[359] Particularly, microtubule-associated BMP-2 was prominently expressed and the stimulation process led the neurites to grow from the stem cells. Peripheral nerve regeneration can be also enabled by layered electrospun scaffolds based on Fe_3O_4 magnetic nanoparticles and melatonin.[360] The scaffolds were able to mitigate the oxidative stress and inflammation which eventually resulted in enhanced nerve regeneration performance.

Antimicrobials

We now direct our discussion towards antimicrobial hybrid nanosystems. Where gold is disproportionately employed in delivery applications, AgNPs are unequally exploited for antibacterial functions. While naked AgNPs are invaluable for disinfection, their shortcomings include cytotoxicity and ecosystem damage.[361] Hybridized AgNPs, in contrast, demonstrate applications ranging from water treatment to delivery of oral antibiotics. For example, silver-based nanosystems produced a 4-log reduction in waterborne *L. pneumophilia* and a 6-log reduction in *B. subtilis*, and the inclusion of magnetic components facilitated removal from solution for reduced ecotoxicity.[361] AgNPs can be incorporated into polymers for enhanced bacterial membrane damage,[306, 362] functionalized with photosensitizers for photodynamic antibacterial activity,[363] or incorporated into NIR-

responsive MOFs for photothermal-antibacterial activity.[58] Others have developed magnetic field-responsive antibacterials displaying enhanced penetration of bacterial biofilms through IONP hybridization.[364, 365] Finally, Ag/CuNPs have been conjugated with PDA and shown to exhibit both rapid and extended antibacterial activity through sequential burst/sustained ion release.[59]

AgNP hybridization has also heightened the efficacy of antibiotics. Ullah *et al.* conjugated tobramycin to graphene-coated AgNPs and reported severe cell wall damage among *E. coli*,[366], and Al-Obaidi *et al.* developed hybrid silver-chitosan-ciproflaxin nanoparticles to deliver antibiotics to the alveoli *via* inhalation.[367] AgNPs have also been the foundation for targeted antibiotic nanosystems, with one study reporting that selective wall binding domains allow for specific targeting of *B. anthracis* over *B. subtilis* or *S. aureus*, suggesting the ability to eliminate pathogen without compromising the gut microbiota.[368] As the extent of the influence of the gut microbiota is still poorly understood, the development of targeted antibiotic delivery systems are expected to be a growing area of research in upcoming years.

Though less prevalent than silver-based antimicrobial hybrid nanosystems, AuNPs can also form the basis for nanoparticle-like antibacterials. AuNPs have been conjugated with antimicrobial peptides to vastly improve the disinfection capability of the peptide alone[369] As such, this system utilizes the antimicrobial properties of an organic component with the delivery function of an inorganic component, whereas the previously discussed systems used the antimicrobial properties of AgNPs with delivery conferred by organic materials. AuNP hybrids have also been loaded with conventional antibiotics. Monti *et al.* performed a computational/experimental study and found that gentamicin release from an AuNP-chitosan core-shell nanoparticle can be controlled by varying the polymer to antibiotic ratio and the deposition pattern of the adsorbed layer.[370] An inverse architecture of chitosan-poly(acrylic acid) coated with AuNPs was developed as a photosensitive system capable of disinfection when exposed to NIR.[371] Alternatively, AuNRs have been incorporated into RBC and platelet membranes to create hybrid nanosystems capable of acoustic propulsion and removal of pathogenic bacteria and toxins.[372] Perhaps the most interesting application of gold in antibacterials is in reversing developed antibiotic resistance. When combined with ampicillin and daptomycin, AuNC hybrids have been shown to kill antibiotic-resistant bacteria.[373, 374] With the selection for superbugs a concern, the ability to kill antibiotic-resistant bacteria is an essential development in drug research.

Tertiary to silver and gold, copper has also formed the inorganic portion of antimicrobial hybrid nanosystems. Copper displays antibacterial properties similar to silver; it is thus unsurprising that copper-chitosan hybrids have shown efficacy in killing cariogenic *S. mutans*.[375] In another study, Elfeky *et al.* developed a cellulose nanocrystal loaded with copper/ZnO that displayed effective photo-induced efficacy against bacteria and *A. stephensi* larvae, a known vector for malaria.[376] Finally, atypical inorganic building blocks utilized in antibacterial hybrid nanosystems have included ZnO, cerium oxide, and silica.[377, 378]

Hybrid antimicrobials offer several advantages over their non-hybridized counterparts. AgNPs are highly effective antibacterials whose drawbacks can be negated by hybridization with polymers and other organics. Additionally, hybridization allows for targeted delivery

of antibiotics, which could become crucial as we continue to learn about the effect of the gut microbiota on human health. Furthermore, hybridization allows for combination phototherapy in addition to antimicrobial activity, providing heretofore unrealized control in clinical settings. Finally, the discovery that gold hybrids can reverse antibiotic resistance in bacterial strains could prove essential with current concerns about human selection for superbugs. As such, antimicrobial nanosystems are yet another area where hybridization can offer great strides forward over current practices.

Vaccines

Vaccines have saved approximately 40,000 lives per birth cohort, making them among the most vital contributions of modern medicine.[379] Despite our advances, we still face challenges in vaccine development such as vaccine efficacy and thermostability that can be addressed by hybrid nanosystems. The improved thermostability of hybrid nanovaccines is notable because vaccine stability greatly affects the efficacy of immunization programs across the world. Metal nanoparticles form the basis of several hybrid vaccines. As the size of a nanoparticle-based vaccine influences its efficacy, the high tunability and low PDI of AuNPs make them especially useful for vaccine hybrids.[380] AuNP-based vaccines have been developed against pathogen ranging from dengue virus to *Burkholderia mallei* and enterohemorrhagic *E. coli*.[381–383] Al-Deen *et al*. developed a DNA-based malaria vaccine from IONPs coated in PEI, claiming magnetic targeting and pH-responsive DNA condensation.[384] Others report that hybridized silica-PEI vaccines show improved thermostability and shelf-life over conventional vaccines[385] and that silica-cationic polymer hybridization can form the basis for oral vaccines.[386] Other mesoporous materials have been shown useful for codelivery of antigen and adjuvant. Yang *et al*. reported a redox-responsive hybrid vaccine based on a MOF (MIL-101-Fe-NH_2) nanoparticle to deliver antigen and adjuvant simultaneously, which suggests that MOFs can improve immune-response to vaccines through stabilization and co-delivery.[387]

Cancer immunotherapy is another area of rapid vaccine development. Hybrid nanosystems are useful cancer vaccines and have been constructed in a variety of materials and architectures. In one example, hollow MSNs hybridized with PEI have shown improved Th1 antitumor immunity and memory in comparison to hollow MSNs alone.[302] MSNs coated in dextran and encapsulated within cancer cell membranes have shown similar potential for cancer immunotherapy.[174] Others have designed zinc phosphate-lipid hybrids to induce immunity against melanoma[303] and ZnO nanowires complexed with poly-L-lactide microfibers to effectively deliver colorectal cancer antigen to dendritic cells.[304] As such, vaccine efficacy and clinical translation may be improved noticeably by hybrid nanosystems.

Vaccines based on hybridization show several benefits over alternatives. In addition to thermostability, hybrid nanosystems provide versatility to treat and prevent a variety of diseases, and it is here that we see MSNs and MOFs utilized widely for their carrying capacity and delivery capabilities. Interestingly, the range of maladies that can be addressed *via* hybrid nanovaccines is broad, yet the number of publications in this area is smaller than in other areas. Though this could be seen as a mark against hybridization, the success of the

published hybrid vaccines suggest rather that the field is young and that further development should be expected in coming years.

Detection and imaging

Hybrid nanoarchitectures can dramatically improve the existing technologies employed in biomedical detection and imaging. In these applications, inorganic building blocks typically provide responsivity to external radiation or magnetism while organic components contribute to biodistribution and functionality. As such, the following section provides an overview of current hybrid nanosystems used for MRI and photoimaging in addition to systems developed to detect and monitor specific biomolecules *in vivo*.

Imaging

MRI functions by aligning the protons in a tissue with magnetic field, knocking them out of alignment with the field *via* radio waves, and recording the image produced as the protons realign with the magnetic field. MRI contrast agents (probes) such as chelated gadolinium or IONPs assist proton realignment and decrease the longitudinal relaxation time (T_1), thus improving image clarity.[388] As such, gadolinium has been incorporated into a polymer-liposome system to allow the selective accumulation in the tumor microenvironment *via* the enhanced permeability and retention EPR effect.[389] Another design coated superparamagnetic IONPs with exopolysaccharide and reported dose-dependent T_1 decreases.[390] Where hybrid nanoprobes improve on non-hybrid contrast agents is in stimulus sensitivity. Through rational design, nanoprobes can alter contrast properties in response to endogenous stimuli. Kim *et al.* report a hybridization of an IONP coated in manganese oxide and polysorbate 80 that responds to intracellular glutathione to lower T_1 only in reductive environments.[391] Similarly, the Wang lab developed pH-responsive magnesium oxide/silica core/shell nanoparticle functionalized with FA to actively target the tumor microenvironment. As the manganese oxide was degraded in the acidic tumor, Mn^{2+} ions acted as T_1 contrast agents. As an additional measure, coumarin-545T was incorporated within the silica shell to allow fluorescence imaging as an alternative cancer visualization tool.[392]

Along with MRI, hybrid nanosystems exhibit advantages in both fluorescence and photoacoustic imaging. When AuNRs were encapsulated within liposomes containing indocyanine green, combination photoacoustic tomography and fluorescence imaging improved the detection and resolution of liver cancer *in vivo* ten-fold.[393] Lipid-encapsulated AuNPs can also improve the detection of biological autoluminescence by penetrating the mitochondrial membrane and enhancing ROS production, greatly improving the utility of biological autoluminescence as a diagnostic tool.[394] Furthermore, dendrimer-entrapped cubic IONPs have been conjugated with HSP90α mRNA attached to a quenched fluorophore; when the nanoparticles were taken up by cells overexpressing HSP90α, the fluorescence was recovered allowing their location to be determined with high specificity through both fluorescence imaging and MRI.[160] Finally, RBC membrane-containing upconversion nanoparticles have shown promise for *in vivo* tumor imaging through active targeting and reduced protein corona formation.[176] These functions have only been

performed by inorganic-organic nanosystems, suggesting that hybridization will continue to be relevant to biomedical imaging.

Detection and monitoring

Hybrid nanosystems have been developed for several detection and monitoring applications, including glucose monitoring,[395] cancer diagnosis,[31], and detection of viral infections.[396] Gold-based hybridizations are prevalent, as the biocompatibility, optical properties, and ability of gold to adsorb nucleic acids lends it widespread value. AuNPs and AuNCs have been incorporated into liposomes to create nanoscale detection kits: Tang *et al.* designed a liposome-based system for glucose detection through selective dequenching of an AuNP-associated fluorophore,[395] whereas Tao *et al.* used the peroxidase activity of AuNCs in a colorimetric assay to detect HER2-positive breast cancer.[31] By replacing AuNPs with IONPs, NIR- and magnetic field-responsive liposome hybrids have demonstrated capabilities to monitor cellular functions to identify targets for cancer therapies.[397]

Monitoring biomolecules such as glucose has been advanced by hybrid nanosystems. Nanoparticle building blocks act as supports for the immobilization of enzymes or perform as mediators or as signal amplifiers. Carbon-based nanomaterials offer chemical inertness and low background current for glucose monitoring. Paper-based technologies enabled low-cost sensors using human sweat and blood to characterize the amount of blood glucose.[398] In a recent study, a photolithographic screen-printing was used to introduce an aldehyde functionalized along with a reference electrode layer to immobilize glucose oxidase (GOx). A GO-tetraethylene pentamine (rGO-TEPA/PB)-based electrode was used as the electrochemically sensitive electrode for H_2O_2 detection (the enzyme-catalyzed product).[399] The proposed sensor responded linearly between 0.1 mM and 25 mM with a 25 μM detection threshold. Metallic nanoparticles can also immobilize enzymes in glucose detection biosensors. A non-invasive wireless glucose biosensor was proposed by Kim *et al.* where a hyaluronate-gold nanoparticle/glucose oxidase (HA-AuNP/GOx) complex was prepared by conjugating thiolated HA to AuNPs. The prepared conjugate was capable of physical binding of GOx and characterized with slow water evaporation as well as fast response (5 s) and high sensitivity of 2.37 $\mu A \cdot dL/mg \cdot cm^2$. Hybrid nanosystems for glucose monitoring are not limited to carbon or metal nanoparticles. Metal oxides[400] and SiO_2[401] are among other candidates for biosensor development. Layered fabrication methods to integrate nanoparticles with polymer matrices are critical in the development of next-generation biosensors.

Inorganic nanoparticle-carbon hybrids have also been used to detect small molecule drugs through accelerated electron transfer and photoluminescence. AuNPs coupled with GQDs or GO have formed systems capable of detecting the antibiotic kanamycin,[402, 403] and AuNPs have also been combined with L-cysteine- and penicillinase-functionalized Pt nanowires to detect penicillin and tetracycline as residual antibiotics in food animals.[404] In other carbon hybrids, GO and silver co-deposited on silver-copper alloy fibers have been utilized to detect sulfadiazine and sulfamethoxazole,[405] while copper oxide nanospheres coated with multiwalled CNTs are sensitive to flunitrazepam, a hypnotic drug utilized in anesthesia.[406]

Virus detection is a third area where nanohybridization excels, with nanohybrids having been developed to detect viruses ranging from human papillomavirus (HPV) and influenza to bursal disease. Jimenez *et al.* reported a hybrid nanosystem containing magnetic glass nanoparticles functionalized with a DNA probe coupled to CdTe/ZnSe core/shell quantum dots for the detection of HPV; interestingly, the system was capable of distinguishing between patients with HPV infections that did and did not develop cancer as a result of infection.[407] AuNPs have been linked to peptide nucleic acids for influenza detection, with AuNP aggregation allowing spectrophotometric detection.[32] Alternatively, functionalized AuNP/IONPs conjugated to CNTs demonstrate the ability to detect influenza DNA *via* conductivity changes.[109] Finally, fluorescence resonance energy transfer (FRET) can be utilized to detect the presence of biomolecules, as FRET properties can be altered through substrate binding;[408] FRET was employed in an AuNP-quantum dot-rhodamine hybrid to detect bursal disease virus.[396] As such, hybrid nanosystems are well-situated for applications in detection and imaging.

In detection and imaging, carbon and gold building blocks are especially suited for their combination of conductive and optical properties. Whereas non-hybridized nanosystems may be limited in their capacities to alter their properties when in contact with a target molecule, hybrid systems allow detection through changes in conductivity, absorption, fluorescence, T_1 relaxation time, and FRET. This range of methods techniques available allows hybrid nanosystems to display flexibility and sensitivity in regions that were previously constrained. Table 2 provides an overview of hybrid nanosystems in non-cancer applications.

Theranostics

To this point, biomedical hybrid nanosystems have been shown effective for targeted delivery, phototherapy, tissue engineering, improved vaccines and antibiotics, and detection of biomolecules; however, we have not yet discussed imaging in concert with therapy. Theranostics is a rapidly growing field in which therapeutic and diagnostic tools are combined for simultaneous imaging and treatment. As expected, hybrid nanosystems are well-situated for theranostic use and have been increasingly employed for such in recent years.

Drug/gene delivery theranostics

Hybrid drug- and gene-based theranostic systems have been designed in a variety of architectures. Inorganic NP-liposome systems are effective theranostics when constructed from several different building blocks. AuNPs and GQDs have been incorporated into DOX-loaded liposomes that display photosensitive drug release and *in vivo* tumor diagnosis through enhanced contrast and emissivity on X-ray computed tomography (CT).[427] AuNRs and ammonium bicarbonate encapsulated in liposomes have formed thermoresponsive nanosystems that generate bubbles for enhanced ultrasound imaging,[428] and gold nanoshells have been incorporated into bubble-generating, dual ligand-functionalized liposomes displaying increased uptake in MCF-7 cells.[429] Theranostic magnetoliposomes are also employed to improve MRI visualization through T_1 reduction and magnetic targeting.[430]

Several magnetoliposomes have been developed to deliver chemotherapeutics to cancer cells, using targeting ligands and functional moieties to improve delivery to the tumor environment and confer stimulus sensitivity.[110, 431–434] Theranostic magnetoliposomes can also display fluorescent properties and generate bubbles for observation *via* fluorescence and ultrasound imaging in addition to MRI.[433, 435] Similarly, IONPs and siRNA encapsulated within stem cell membranes have formed hybrid nanosystems capable of combination gene therapy and PTT in addition to MRI.[179]

Inorganic NPs conjugated with polymers and dendrimers are also useful theranostic vessels. Au nanostar-PAMAM hybrids have delivered siRNA to tumors in combination with PTT and CT imaging,[436] whereas gold-silver alloy nanoclusters conjugated with PEI show improved fluorescent signal and transfection efficiency over each constituent building block.[437] In another hybridization, AuNR-hydrogels were loaded with therapeutics to create bubble-free theranostic devices for ultrasound imaging.[438] In an especially intriguing combination, a nanohybrid made up of AuNRs, MSNs, quantum dots, and poly(glycidyl methacrylate) delivered nucleic acids and chemotherapeutics along with AuNR-mediated PTT and CT/photoacoustic imaging.[439] MSNs have also been hybridized with thermosensitive polymers to produce nanosystems displaying photoacoustic and fluorescence amplification, NIR-triggered release of SN38, and utility in positron emission tomography (PET) when functionalized with 64Cu.[440] Additionally, theranostic IONP-polymer nanosystems have been employed in cancer immunotherapy, with one such architecture inducing immune responses against melanoma cells while allowing the vaccine to be tracked *in vivo via* MRI.[441] Finally, a Bi_2S_3-PLGA nanocapsule was constructed as an ultrasound contrast and therapeutic for high-intensity focused ultrasound therapy. The system also offered dual functionality by inducing radiosensitivity in prostate cancer cells under X-ray radiation.[442]

Several atypical geometries for hybrid drug/gene theranostics exist. AuNPs have been combined with bovine serum albumin (BSA) and MSNs to co-deliver gemcitabine and doxorubicin while allowing *in vivo* fluorescence imaging.[443] Gold nanocages have also been capped with BSA to enable optoacoustic tomography imaging along with chemotherapy and PTT.[444] In another study, CPNP cores were hybridized with rare earth nanoparticles and targeting DNA to create pH-responsive drug delivery systems with lanthanide luminescence-based imaging and magnetic resonance.[445] Furthermore, core-shell hybrids consisting of carbon-coated IONPs decorated with AgNPs showed efficient DOX release under NIR radiation as well as fluorescence and functionality as an MRI probe.[49] Finally, ZIF-8 has been hybridized around palladium nanosheets, loaded with DOX, and conjugated with PDA to produce a dual-responsive pH- and NIR-triggered drug release in conjunction with photoacoustic imaging.[84] As such, these systems display effectivity in theranostic applications despite not falling in the more common hybrid architecture categories.

Phototheranostics

Hybrids combining PDT/PTT and imaging have largely exploited carbon-based building blocks such as GQDs, C60, GO, and carbon nitride (CN). CN is a photocatalyst for water decomposition and can generate sustainable levels of oxygen to relieve

tumor hypoxia and facilitate PDT in conjunction with ultrasound and fluorescence imaging.[446] Correspondingly, GQDs exhibit fluorescent properties and have been adapted as photosensitizers.[108] When utilized in conjunction with mesoporous silica, hybrid CN/GQDs displayed ultrasound and fluorescence imaging combined with PDT uninhibited by hypoxic tumor conditions.[446] CN nanosheets also show photodynamic and fluorescent properties that promote effective therapy and imaging when functionalized with DNA hairpin probes.[113] Fullerene is also useful in this application. IONP-C60s display magnetic targeting capabilities in conjunction with MRI contrast, while AuNP-C60s have been used as probes in X-ray cancer diagnosis.[447, 448] Finally, gadolinium nanoparticles on GO have displayed MRI-guided photothermal properties along with DOX loading for combination chemo-phototheranostics.[107]

The nanosystems about to be described draw from all aspects of biomedical hybridization and are among the most impressive developments in the field in recent years. When hybridized with poly(allylamine)-modified black phosphorus quantum dots, AuNPs displayed enhanced PDT/PTT mediated by plasmon-induced resonant energy transfer in conjunction with photoacoustic imaging and MRI.[449] AuNRs incorporated into a functional DNA-origami nanostructure have shown enhanced *in vivo* diagnostic and therapeutic properties through optoacoustic imaging and PTT.[450] Similarly, Song *et al.* utilized ultrasmall AuNRs within PLGA to create vesicles capable of EPR-mediated tumor accumulation, photoacoustic imaging, and rapid excretion upon nanosystem dissociation.[451] Likewise, Huang *et al.* coated AuNRs in mesoporous silica functionalized with upconversion nanoparticles and photosensitizers to create a nanobubble capable of plasmonically-enhanced PTT and PDT in addition to fluorescent imaging and ultrasound.[452] Furthermore, rattle-type MSN-PDA nanoparticles have been loaded with GOx to create nanohybrid theranostics capable of photoacoustic imaging and low-temperature PTT through GOx suppression of heat shock proteins HSP70 and HSP90.[81] IONPs have been encased into cancer cell membranes alone or with Ce6 to produce nanosystems for combination MRI, fluorescence imaging, and PDT/PTT.[177, 180, 453] Finally, mesoporous copper sulfide nanoparticles have been coupled with an amphiphilic copolymer to create a pH/redox responsive DDS/PTT hybrid capable of fluorescence and photoacoustic imaging.[454] Accordingly, theranostic hybrid nanosystems are among the most impressively engineered nanostructures today.

Theranostic application is where biomedical hybridization surpasses all competition. As with delivery applications and combination therapies, AuNPs and IONPs are widely utilized within liposomes and polymers, and these systems provide numerous expected benefits including real-time observation of therapeutic delivery. However, several atypical hybrid architectures have also been proposed, which not only expand the practical functions of hybrids but also introduce paradigms through which we may view theranostic challenges. For example, protein-conjugated nanoparticles appear promising in drug delivery theranostics, while carbon-based building blocks are useful for phototheranostics. Finally, theranostics is where we see the most creative designs for hybrid nanosystems, with each offering one or more methods of detecting, imaging, and treating maladies *in vivo*. We expect that theranostic hybrids will be one of the major areas of nanosystem

development over the next half-decade. Table 3 displays several notable hybrid nanosystems in theranostics, and Figure 8 displays selected hybrid nanosystems discussed thus far.

Clinical trials

Despite the thoroughly-published efficacy of hybrid nanosystems in pre-clinical evaluations, few have yet entered into clinical trials. Several current clinical trials are investigating AGuIX, a gadolinium-polysiloxane hybrid, for use as an imaging agent in diagnosis, imaging, and treatment of brain metastases and gynecological cancer. Another hybrid of silica, hydrophilic polymers, and targeting peptides is being studied for use in real-time imaging of head and neck melanoma, breast cancer, and colorectal cancer. Finally, in a Phase 1 study targeting Type 1 diabetes, peptide-functionalized AuNPs are being tested to determine their safety and effect in mitigating the body's destruction of insulin-producing cells. Current human trials of hybrid nanosystems are limited, especially when noting that there are over 350,000 ongoing clinical trials worldwide (as per ClinicalTrials.gov). Nevertheless, the recent growth of publications pertaining to hybrid nanosystems suggests that clinical trials incorporating them will expand in the coming years. Table 4 summarizes the active clinical trials involving hybrid nanosystems.

Concluding remarks and future perspectives

Nanotechnology has made notable contributions to the biomedical field within the past two decades. Nanosystems have vastly improved our ability to selectively deliver therapeutics, noninvasively visualize and diagnose maladies, detect biomolecules of interest, and harness light for therapeutic purposes. Despite this progress, further obstacles remain and researchers are turning increasingly to hybridization as a solution. Hybrid nanosystems have improved the efficacy of monotherapies while simultaneously welcoming combination therapies. Single-component inorganic or organic nanosystems represent an "all-or-nothing" approach in which the utility of the system is intrinsically tied to a single function. Hybrid nanosystems, on the other hand, bring flexibility and versatility to the biomedical research table, with many performing several functions within a single design. In these cases, a system's utility can be based on several tasks rather than just one. This could be advantageous in the coming years, as regulatory agencies are more apt to fast-track therapeutic compounds that have been previously approved for other applications. Additionally, several groups have shown that a broad approach to the treatment of human disease offered through hybridization provides previously unattainable treatment opportunities, an exciting development for medical science.

We anticipate that hybrid nanosystem development will continue to increase in the coming years especially in combination therapy, imaging, and theranostics. Moreover, we expect that clinical trials involving hybrid nanosystems will expand greatly in the next decade just as publications of preclinical investigations have since 2010. For this to occur, however, the incongruence of complexity and translational compatibility must be reconciled. Despite the promise of increasingly complex nanosystems, increased intricacy can also introduce challenges in reproducibility, scale-up/out, and quality control. As a result, translation from the benchtop to the clinic can present a notable hurdle, and

successful developers must keep this in mind throughout the design process. In addition to complexity, therapy cost is a notable concern for hybrid nanosystems. The rising cost of healthcare is a pressing challenge, especially in the United States; as such, the increased material resources and extended synthesis procedures that hybrid nanosystems require over non-hybridized alternatives must be justified in therapeutic efficacy. Moreover, translatable hybrid nanosystems must produce clinically-significant improvements to justify the increase in treatment cost. These realities may be reflected in the relative dearth of ongoing clinical trials featuring hybrid nanosystems in comparison to both the number of systems in development and number of ongoing trials. We expect that the number of hybrid nanosystems in clinical trials will increase as the challenges of complexity, mass production, and cost are addressed.

Hybrid nanosystems possess enormous potential for both bench and bedside applications. It may be used as discovery tools to unravel mysteries of many physiological and pathological conditions such as wound healing, cancer, diabetes, cardiovascular, neurodegenerative diseases to name a few. Understanding biological effects of these nanoparticles, particularly long-term effects and toxicity is essential in order to translate their applications from bench to bedside. On the other hand, understanding how these hybrid nanosystems interacts with biological systems such as cells, tissues, biological fluids and their mechanism of interaction may provide opportunities to design hybrid nanosystems for personalized medicine. Nevertheless, based on the progress summarized in this review we expect that hybrid nanosystems will continue to grow in prevalence and importance in the biomedical field in upcoming years.

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Vocabulary

- Hybrid nanosystem
  - A nano-scale device, complex, or assembly containing both inorganic and organic components.
- Inorganic/organic building blocks
  - The fundamental materials that make up a hybrid nanosystem. Hybrid nanosystems are formed through combination of one or more inorganic building blocks with one or more organic building blocks.
- Hybrid architecture
  - The structural and material organization of a hybrid nanosystem; directly associated with the function of a hybrid nanosystem.
- Combination therapy
  - Application of two or more distinct types of treatment (*i.e.* chemotherapy, gene therapy, phototherapy, *etc.*) *via* a single hybrid nanosystem.
- Theranostics
  - The integration of therapeutic properties with diagnostic or imaging properties in a single nanosystem.

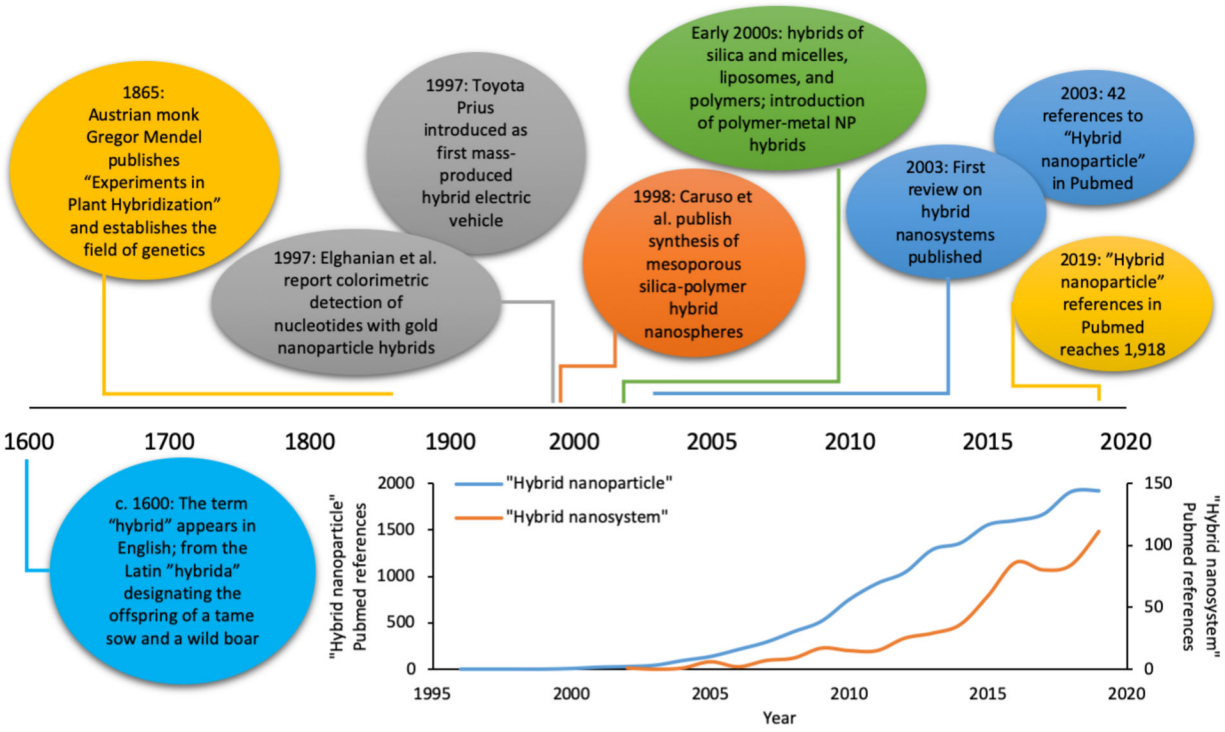

Figure 1:
Timeline of biomedical hybridization milestones[3, 4]

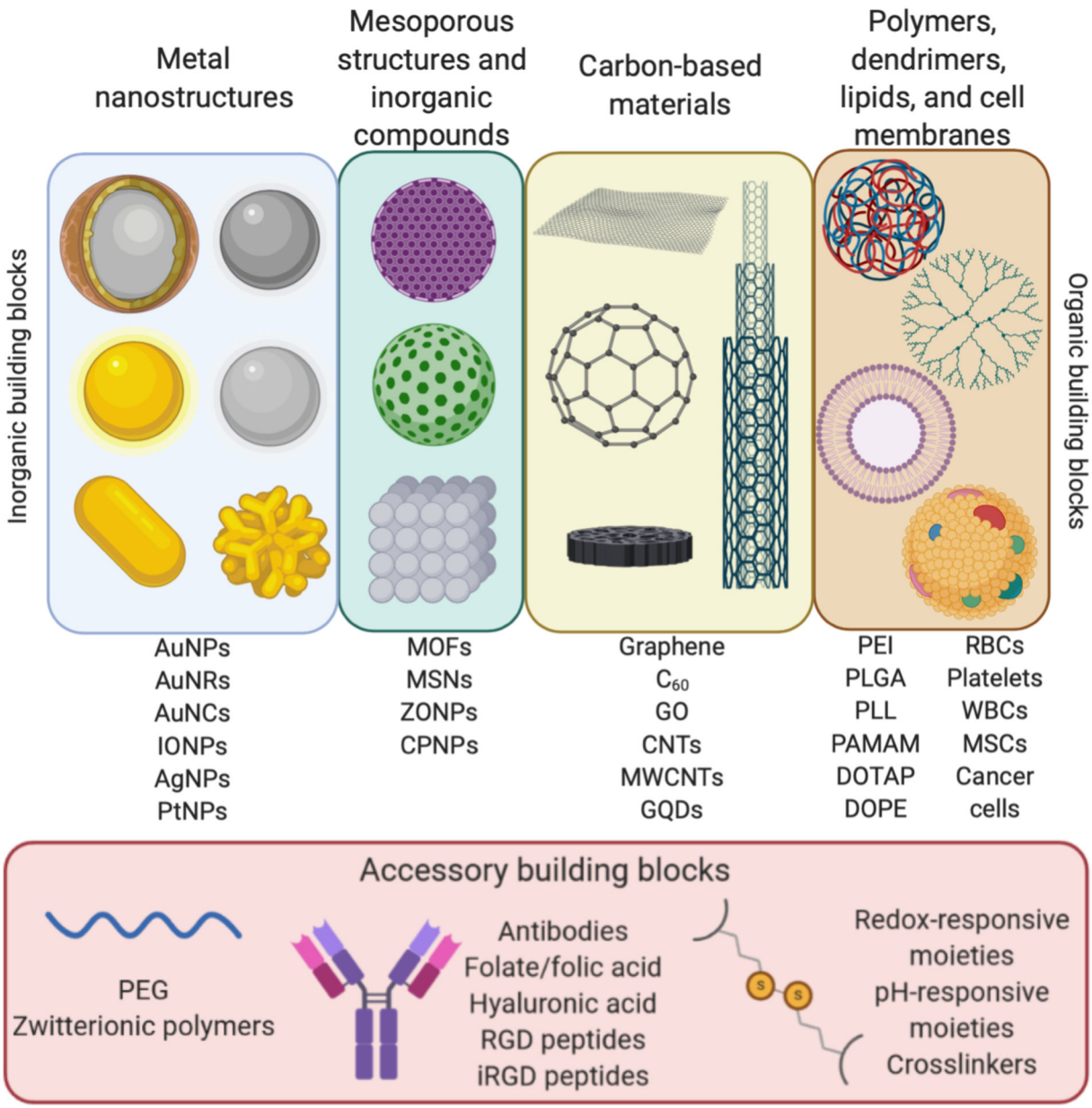

Figure 2:
Building blocks for hybrid nanosystems. Created with BioRender.com.

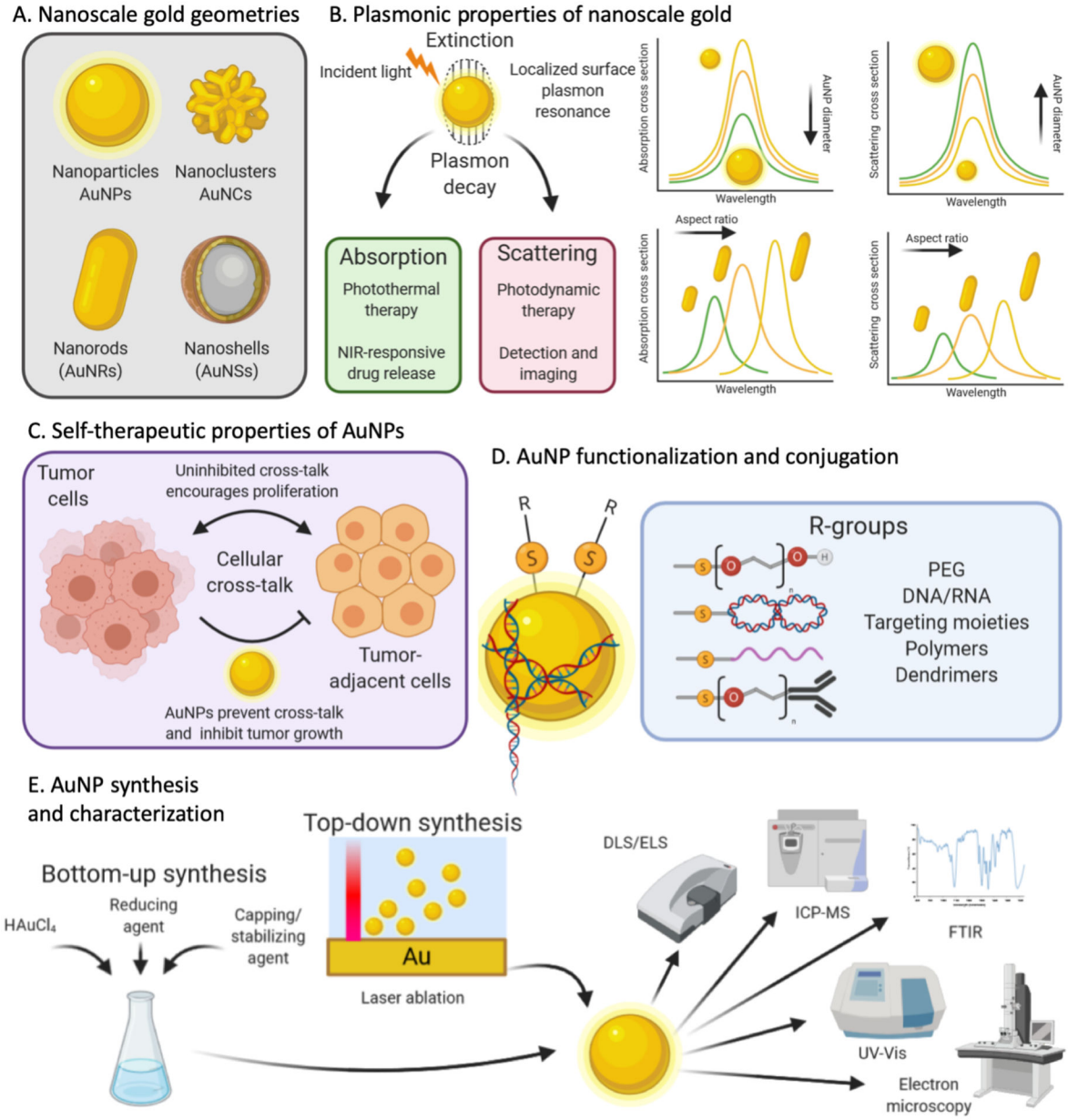

Figure 3:

Nanoscale gold for biomedical applications. A) Geometries for nanoscale gold. B) Plasmonic properties of nanoscale gold. C) Self-therapeutic properties of AuNPs. D) AuNP functionalization and conjugation. E) AuNP synthesis and characterization.[11, 27, 43, 46] Created with BioRender.com.

Figure 4:

Characterization and properties of various inorganic components of hybrid nanosystems. Created with BioRender.com.

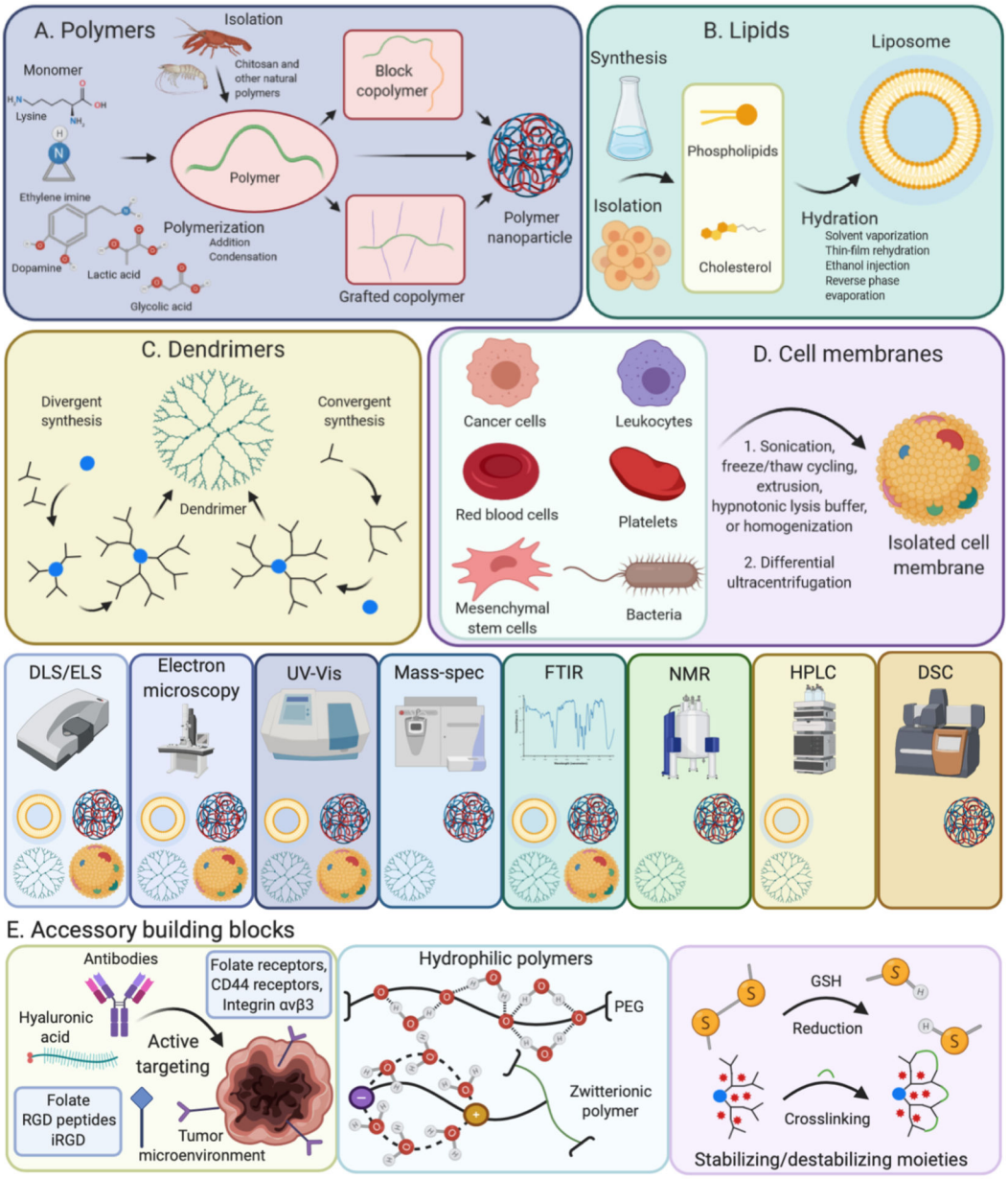

Figure 5:
Organic and accessory building blocks for hybrid nanosystems. Created with BioRender.com.

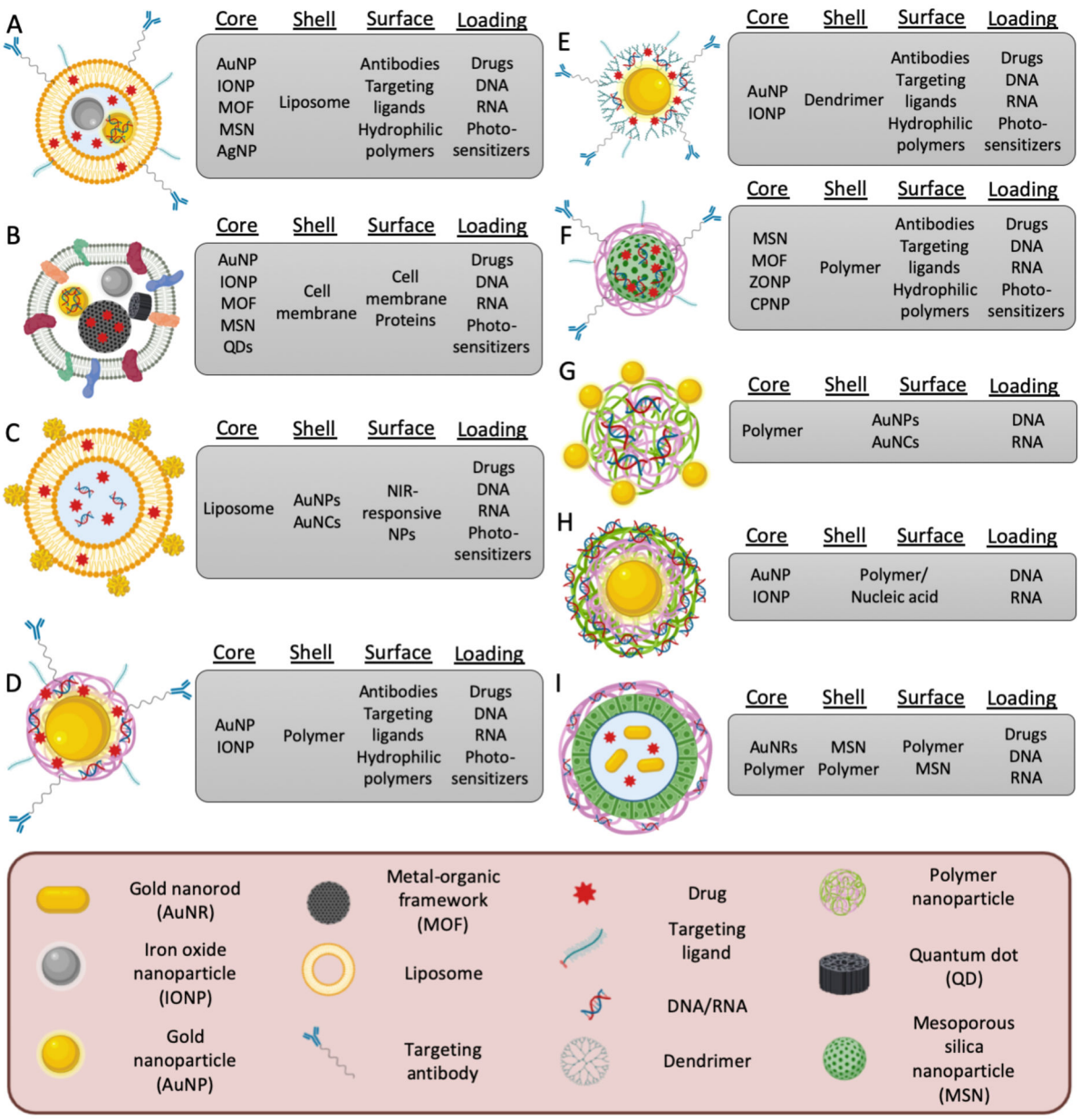

Figure 6:

Architectures for hybrid nanosystems. A) Inorganic-liposome hybrid with nanoparticles incorporated within the liposome.[125, 193–195, 202] B) Cell membrane-coated nanoparticles.[173, 179, 203, 204] C) Liposome with surface-associated nanoscale metals.[28] D) Functionalized polymer-coated metal nanoparticle.[197] E) Dendrimer-conjugated metallic nanoparticles.[165] F) Mesoporous nanostructure with a polymer coating.[205, 206] G) Polymer-nucleic acid complex with metallic nanoparticles on the surface.[198] H) Metallic nanoparticle core coated in sequential layers of polymer and nucleic acid.[199] I) Rattle-type nanostructure of metal nanoparticles within a polymer-coated mesoporous shell.[200] Created with BioRender.com.

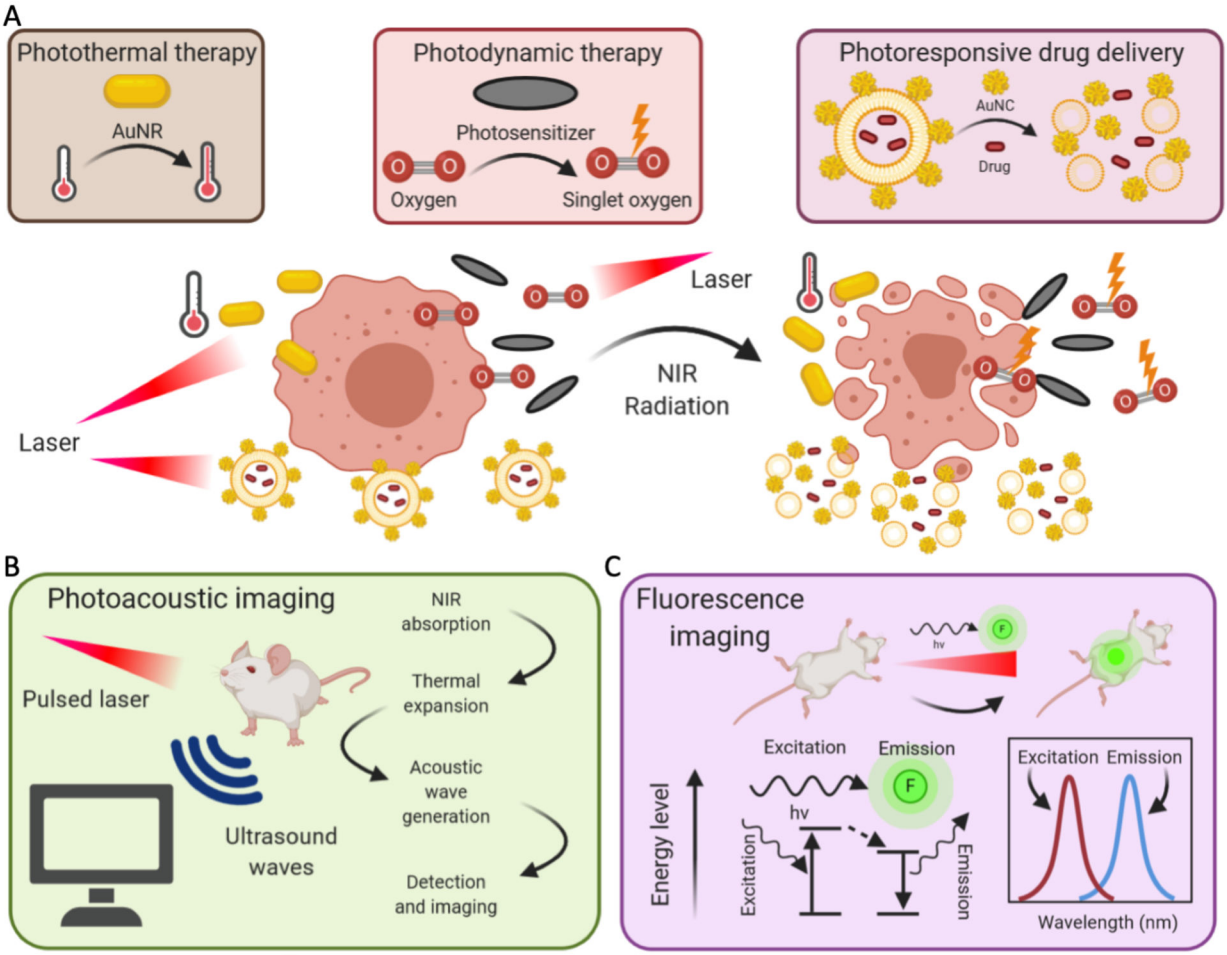

Figure 7:

A) Phototherapy, photoresponsive drug delivery, and photoimaging. B) Photoacoustic imaging. C) Fluorescence imaging. Created with BioRender.com.

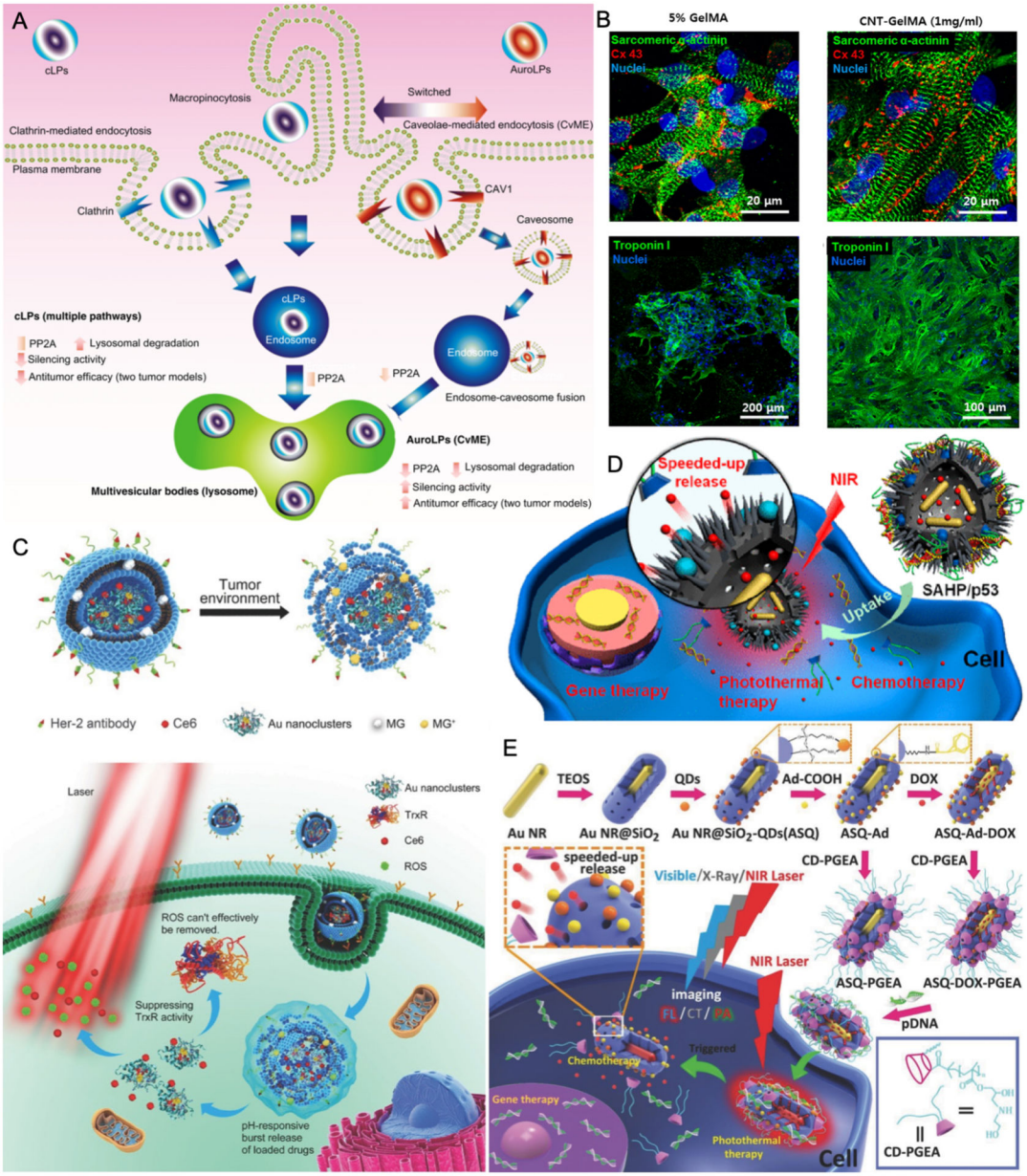

Figure 8:

Select hybrid nanosystems of various applications. A) Auroliposomes shift the gene delivery uptake pathway. From Hossen, M. N. *et al.* Switching the intracellular pathway and enhancing the therapeutic efficacy of small interfering RNA by auroliposome. Science Advances 6, eaba5379, doi:10.1126/sciadv.aba5379 (2020). Reprinted with permission from AAAS.[22] B) CNT-embedded hydrogels create multifunctional cardiac scaffolds. Reprinted with permission from Shin, S. R.; Jung, S. M.; Zalabany, M.; Kim, K.; Zorlutuna, P.; Kim, S. b.; Nikkhah, M.; Khabiry, M.; Azize, M.; Kong, J., Carbon-nanotube-embedded hydrogel sheets for engineering cardiac constructs and bioactuators. ACS Nano 2013, 7 (3), 2369–2380. Copyright 2013 American Chemical Society.[351] C) Dual-loaded liposomal nanocomposite enhances phototherapy by inhibiting thioredoxin reductase. Reprinted by

permission from John Wiley and Sons: Advanced Healthcare Materials. Au Nanoclusters and Photosensitizer Dual Loaded Spatiotemporal Controllable Liposomal Nanocomposites Enhance Tumor Photodynamic Therapy Effect by Inhibiting Thioredoxin Reductase, Gao, F. *et al.* (2017)[16] D) Rattle-structured nanocapsules for gene/chemo/phototherapy. Reprinted by permission from Chen, X. *et al.* Rattle-Structured Rough Nanocapsules with *in-Situ*-Formed Gold Nanorod Cores for Complementary Gene/Chemo/Photothermal Therapy. ACS Nano 12, 5646–5656, doi:10.1021/acsnano.8b01440 (2018). Copyright 2018 American Chemical Society.[200] E) NIR-responsive nanoparticles for imaging-guided triple-combination therapy. Reprinted by permission from Wiley-VHC: Small. NIR-Responsive Polycationic Gatekeeper-Cloaked Hetero-Nanoparticles for Multimodal Imaging-Guided Triple-Combination Therapy of Cancer, Duan, S. *et al.* (2017)[439]

Table 1:

Recent hybrid nanosystems for cancer therapy.

Therapy	Inorganic component	Organic component	Therapeutic compound	Targeting ligand	Stimulus sensitivity	Reference
Cancer immunotherapy	MSN	Dextran, membrane (cancer cell)	Antigen	N/A	N/A	174
Cancer immunotherapy	MSN	Polymer	Antigen	N/A	N/A	302
Cancer immunotherapy	Inorganic compound (zinc phosphate)	Lipid	Antigen	N/A	N/A	303
Cancer immunotherapy	Inorganic compound (zinc oxide)	Polymer	Antigen	N/A	N/A	304
Chemotherapy	Metal (gold)	Lipid	DOX	N/A	NIR	28
Chemotherapy	Metal (gold)	Lipid	DOX	N/A	NIR, temperature	125
Chemotherapy	Metal (gold)	Lipid	DOX	Mucin-1 aptamer	NIR, temperature	17
Chemotherapy	Metal (gold)	Lipid	DOX	Hyaluronic acid	NIR	14
Chemotherapy	Metal (gold)	Lipid	Temozolomide	N/A	N/A	12
Chemotherapy	Metal (gold)	Lipid	DOX	N/A	pH	232
Chemotherapy	Metal (gold)	Lipid	Morin	AS1411 DNA aptamer	pH	193
Chemotherapy	Metal (gold)	Lipid	DOX	N/A	N/A	230
Chemotherapy	Metal (gold)	Lipid	PTX	N/A	N/A	231
Chemotherapy	Metal (gold, iron oxide)	Lipid	Cisplatin	N/A	pH, magnetic field	305
Chemotherapy	Metal (iron oxide)	Lipid	Misonidazole	N/A	pH, magnetic field	306
Chemotherapy	Metal (iron oxide)	Lipid	Curcumin	N/A	magnetic field	236
Chemotherapy	Metal (iron oxide)	Lipid	Cisplatin	N/A	magnetic field	126
Chemotherapy	Metal (iron oxide)	Lipid	DOX	Apolipoprotein E, anti-rat CD71 IgG2a monoclonal antibody	magnetic field	235
Chemotherapy	Metal (iron oxide)	Surfactant	DOX	N/A	magnetic field	234
Chemotherapy	Metal (iron oxide)	Lipid	DOX	N/A	magnetic field	233
Chemotherapy	Metal (iron oxide)	Lipid	Curcumin	N/A	magnetic field	238
Chemotherapy	Metal (iron oxide)	Lipid	Gemcitabine/ oxaliplatin	N/A	magnetic field	202
Chemotherapy	Metal (iron oxide)	Lipid	7-Allylamio-17-desmethoxygelda namycin (17-AAG)	Folic acid	magnetic field, temperature	240

Therapy	Inorganic component	Organic component	Therapeutic compound	Targeting ligand	Stimulus sensitivity	Reference
Chemotherapy	Metal (iron oxide)	Lipid	DTX	Hyaluronic acid	NIR	241
Chemotherapy	Metal (silver)	Lipid	Curcumin	N/A	N/A	245
Chemotherapy	MOF	Lipid	Irinotecan, floxuridine	N/A	N/A	195
Chemotherapy	MSN	Lipid	DOX	N/A	Temperature	243
Chemotherapy	Metal (gold)	Polymer	Curcumin	N/A	N/A	307
Chemotherapy	Metal (gold)	Polymer	Sunitib malate	c(RGDfK) peptide	N/A	21
Chemotherapy	Metal (gold)	Polymer	DOX	N/A	N/A	246
Chemotherapy	Metal (gold, platinum)	Polymer	5-FU	N/A	pH	247
Chemotherapy	Metal (gold)	Dendrimer	PTX	N/A	N/A	159
Chemotherapy	Metal (iron oxide)	Polymer	Cisplatin	N/A	Magnetic field	308
Chemotherapy	Metal (silver)	Polymer	Imatinib mesylate	N/A	pH, enzyme	249
Chemotherapy	MSN	Polymer	DOX	CD133 RNA aptamer	pH	206
Chemotherapy	Inorganic compound (zinc oxide)	Polymer	DOX	N/A	pH	248
Chemotherapy	MOF	Polymer	DOX	N/A	pH	85
Chemotherapy	Metal (platinum)	Polymer	Gemcitabine	N/A	pH/redox	57
Chemotherapy	Inorganic compound (CaP)	Polymer	verapamil, novatrone	RGD peptide	pH	66
Chemotherapy	Inorganic compound (zinc oxide)	Nucleic acid	DOX	N/A	pH, enzyme	67
Chemotherapy	MSN	Carbon	Curcumin	N/A	pH	255
Chemotherapy	Metal (iron oxide)	Lipid	Cuphen	N/A	pH, magnetic field	237
Chemotherapy	Metal (iron oxide)	Lipid	Fe ions	N/A	pH, redox	242
Chemotherapy	Metal (iron oxide)	Dendrimer	DOX	T7 peptide	pH	250
Chemotherapy	Metal (gold)	Polymer	Curcumin	Folic acid	pH	197
Drug+phototherapy	Metal (gold)	Lipid	Au nanoshell, betulinic acid	N/A	NIR	289
Drug+phototherapy	Metal (gold)	Lipid	Au nanoshell, oleanoic acid	N/A	pH, NIR	290
Drug+phototherapy	Metal (gold)	Lipid	Au nanoshell, thienopyridine	N/A	NIR, magnetic field	291
Drug+phototherapy	Metal (gold)	Nucleic acid	AuNRs, DOX	Folic acid	NIR	296
Drug+phototherapy	Metal (gold)	Polymer	AuNP, PTX	N/A	NIR, temperature	294

Therapy	Inorganic component	Organic component	Therapeutic compound	Targeting ligand	Stimulus sensitivity	Reference
Drug+phototherapy	Metal (gold)	Lipid	AuNPs, DOX	N/A	NIR, temperature	292
Drug+phototherapy	Metal (gold)	Lipid	AuNPs, DOX	N/A	NIR	293
Drug+phototherapy	Metal (gold)	Nucleic acid	AuNR, DOX	MUC-1 DNA aptamer	NIR	295
Drug+phototherapy	Metal (gold)	Membrane (cancer cell)	Au nanocage, DOX	N/A	NIR	175
Gene therapy	Metal (gold)	Lipid	DNA	monosialodihex osylganglioside	N/A	208
Gene therapy	Metal (gold)	Lipid	DNA	Folic acid	pH	209
Gene therapy	Metal (gold)	Lipid	RNA	Apolipoprotein E, RVG peptide	N/A	210
Gene therapy	Metal (gold)	Lipid	DNA, protein	N/A	NIR, temperature	212
Gene therapy	Metal (gold)	Lipid	RNA, protein	TAT peptide	N/A	211
Gene therapy	Metal (gold)	Nucleic acid	RNA	N/A	N/A	309 215, 219 39
Gene therapy	Metal (gold)	Nucleic acid	DNA	N/A	NIR	310
Gene therapy	Metal (gold)	Polymer	DNA	TAT peptide	N/A	216
Gene therapy	Metal (gold)	Polymer	RNA	Folic acid	N/A	24
Gene therapy	Metal (gold)	Polymer	DNA	Histidine, arginine	N/A	136
Gene therapy	Metal (gold)	Polymer	DNA	Folic acid	N/A	137
Gene therapy	Metal (gold)	Polymer	RNA	N/A	N/A	Above
Gene therapy	Metal (gold)	Polymer	DNA	TAT peptide, hyaluronic acid	Redox	223
Gene therapy	Metal (gold)	Polymer	RNA	N/A	N/A	Above
Gene therapy	Metal (gold)	Polymer	RNA	N/A	N/A	Above
Gene therapy	Metal (gold)	Polymer	RNA	RGD peptide	N/A	217
Gene therapy	Metal (gold)	Polymer	DNA	Folic acid	N/A	218
Gene therapy	Metal (gold)	Polymer	DNA	N/A	NIR	38
Gene therapy	Metal (gold)	Polymer	RNA	2-deoxyglucose	pH	40
Gene therapy	Metal (gold)	Polymer	RNA	Anisamide	N/A	213
Gene therapy	Metal (gold)	Polymer	RNA	N/A	N/A	214
Gene therapy	Metal (gold)	Polymer	DNA	NLS peptide	NIR, redox	198
Gene therapy	Metal (gold)	Polymer	RNA	N/A	N/A	196
Gene therapy	Metal (gold)	Polymer	RNA	Glucose	N/A	220
Gene therapy	Metal (gold)	Polymer	RNA	N/A	Electrical potential	222
Gene therapy	Metal (gold)	Polymer	DNA	N/A	N/A	199
Gene therapy	Metal (gold)	Dendrimer	DNA	N/A	N/A	164
Gene therapy	Metal (gold)	Dendrimer	RNA	Folic acid	N/A	158
Gene therapy	Metal (gold)	Dendrimer	RNA	N/A	N/A	190

Therapy	Inorganic component	Organic component	Therapeutic compound	Targeting ligand	Stimulus sensitivity	Reference
Gene therapy	Metal (gold)	Dendrimer	RNA	RGD peptide	N/A	161
Gene therapy	Metal (gold)	Dendrimer	DNA	Hyaluronic acid	N/A	165
Gene therapy	Metal (iron oxide)	Polymer	RNA	gh625 peptide	magnetic field	225
Gene therapy	Metal (iron oxide)	Polymer	DNA	N/A	magnetic field	224
Gene therapy	Inorganic compound (CaP)	Polymer	DNA	Stearic acid	N/A	228
Gene therapy	MOF	Polymer	RNA	N/A	N/A	228
Gene therapy	MOF	Membrane (platelet)	RNA	N/A	pH	173
Gene+chemo+phototherapy	Metal (gold)	Lipid	Verteporfin, calcein, RNA	N/A	X-ray	301
Gene+chemo+phototherapy	Metal (gold), MSN	Polymer	AuNRs, DNA, sorafenib	N/A	NIR	200
Gene+chemotherapy	Metal (gold)	Lipid	RNA, PTX	N/A	NIR, temperature	277
Gene+chemotherapy	Metal (gold)	Polymer	AuNR, RNA	RGD peptide	Redox	279
Gene+chemotherapy	Metal (gold)	Polymer	RNA, cisplatin	N/A	N/A	280
Gene+chemotherapy	Metal (gold)	Protein	RNA, DOX	N/A	N/A	281
Gene+chemotherapy	Metal (gold)	DNA	DNA, DOX	AS1411 DNA aptamer	pH	282
Gene+chemotherapy	Metal (gold)	Dendrimer	RNA, gemcitabine	N/A	Ultrasound	283
Gene+chemotherapy	MOF, MSN	Polymer	DNA, DOX, proteins	N/A	pH	205
Gene+chemotherapy	Metal (gold)	Lipid	DNA, DOX	N/A	Magnetic field	276
Gene+phototherapy	Metal (gold)	Nucleic acid	Au nanoshell, RNA	N/A	NIR	284
Gene+phototherapy	Metal (gold)	Nucleic acid	Au nanoflower, siRNA	N/A	NIR	287
Gene+phototherapy	Metal (gold)	Polymer	AuNP, DNA	N/A	NIR	286
Gene+phototherapy	Metal (gold)	Polymer	Au nanoprism, RNA	N/A	NIR	285
Gene+phototherapy	Inorganic compound (CaP)	Polymer	Polydopamine, RNA	N/A	NIR, pH	288
Photodynamic therapy	Metal (gold)	Lipid	Chlorin e6	N/A	pH, NIR	16
Photodynamic therapy	Metal (iron oxide)	Lipid	Photoporphyrin IX	N/A	NIR	266
Photodynamic therapy	MOF	DNA	MOF	N/A	NIR	267
Photodynamic therapy	Metal (titanium oxide), MSN	Polymer	Chlorin e6	N/A	NIR	271
Photodynamic therapy	Inorganic compound (W18O49)	Membrane (platelet)	Metformin, W18O49	N/A	NIR	268

Therapy	Inorganic component	Organic component	Therapeutic compound	Targeting ligand	Stimulus sensitivity	Reference
Photothermal therapy	Metal (gold)	Lipid	AuNPs	N/A	NIR	[261]
Photothermal therapy	Metal (gold)	Lipid	AuNPs	Cy5 marked molecular beacon	NIR	[262]
Photothermal therapy	Metal (gold)	Lipid	AuNPs	N/A	NIR	[263]
Photothermal therapy	Metal (lanthanides)	Polymer	Polyaniline	N/A	NIR	[265]
Photothermal therapy	Metal (gold)	Polymer	AuNRs, polyaniline	N/A	NIR	[13]
Photothermal therapy	Metal (gold)	Membrane (leukocyte)	Janus AuNP	N/A	NIR	[264]
Photothermal therapy	Inorganic compound (phosphorus)	Membrane (RBC)	Black phosphorus nanoparticle	N/A	NIR	[178]

Table 2:

Hybrid nanosystems for non-cancer applications.

Category	Application	Inorganic component	Organic component	Active compound	Reference
Antimicrobial	Antibacterial	Metal (AgNPs)	Carbon	AgNPs	409
Antimicrobial	Antibiotic	Metal (AgNPs)	Carbon	Tobramycin	366
Antimicrobial	Antibacterial	Metal (AgNPs)	Carbon	AgNPs	410
Antimicrobial	Antibiotic deactivation	Inorganic compound (TiO_2)	Carbon	TiO_2	411
Antimicrobial	Antibacterial	Metal (AgNPs), MOF	Carbon	AgNPs	58
Antimicrobial	Antifungal	Metal (IONPs)	Carbon	Benzamide	254
Antimicrobial	Antimicrobial, wound healing	Metal (AgNPs)	Polymer	Chlorhexidine	412
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	AgNPs	306
Antimicrobial	Antibacterial	Metal (AgNPs), inorganic compound (ZnO)	Polymer	AgNPs, ZnO	362
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	AgNPs	413
Antimicrobial	Antibiotic	Metal (AgNPs), silica	Polymer	Ciprofloxacin	367
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	Antibacterial peptides	369
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	AgNPs	414
Antimicrobial	Antibacterial	Metal (CuNPs)	Polymer	CuNPs	375
Antimicrobial	Antibacterial	Inorganic compound (cerium oxide)	Polymer	Cerium oxide	377
Antimicrobial	Antibacterial	Metal (AuNCs)	Polymer	Antibacterial peptides, daptomycin	374
Antimicrobial	Antibacterial	Metal (AgNPs, ZnO)	Polymer	AgNPs	415
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	AgNPs	416
Antimicrobial	Antibacterial	Metal (AgNPs, CuNPs)	Polymer	Polydopamine, AgNPs	59
Antimicrobial	Antibacterial, larvicidal	Metal (ZnO, CuO)	Polymer	ZnO, CuO	376
Antimicrobial	Antibiotic	Metal (AuNPs)	Polymer	Gentamicin	370
Antimicrobial	Antibacterial	Metal (AgNPs)	Polymer	AgNPs	417
Antimicrobial	Antibacterial	Metal, inorganic compound (AgNPs, MnO_2)	Polymer	AgNPs, MnO_2	418
Antimicrobial	Antibacterial	Metal (AgNPs), inorganic compound (hydroxyapatite)	Polymer	AgNPs	419
Antimicrobial	Antibacterial	Silica, inorganic compound (ZnO)	Polymer	ZnO	378
Antimicrobial	Antibacterial, antifungal	Metal (CuNPs, FeNPs)	Polymer	CuNPs	420
Antimicrobial	antibacterial	Silica	Polymer	Chlorhexidine	421
Antimicrobial	Antibacterial	Metal (AgNPs)	Protein	AgNPs	368
Antimicrobial	Antibiotic	Metal (AuNCs)	Protein	Ampicillin	373

Category	Application	Inorganic component	Organic component	Active compound	Reference
Antimicrobial	Antibacterial	Metal (AuNPs)	Protein	Rose bengal	371
Antimicrobial	Antibacterial, antitoxin	Metal (Au nanowire)	Membrane (RBC)	Membrane	372
Detection and Imaging	Antibiotic detection	Metal (AgNPs)	Carbon	AgNPs, Cu	405
Detection and Imaging	Antibiotic detection	Metal (AuNPs, CuS)	Carbon	CuS	403
Detection and Imaging	Antibiotic detection	Metal (CuNPs)	Carbon	Cu, MWCNTs	406
Detection and Imaging	MRI contrast, RNA detection	Metal (IONPs)	Dendrimer, polymer	Alexa Fluor 488	160
Detection and Imaging	Cancer detection	Metal (AuNPs), silica	DNA	AuNPs, DNA	422
Detection and Imaging	Bursal disease virus detection	Metal (AuNPs), quantum dots	DNA	Rhodamine	396
Detection and Imaging	HPV detection	Inorganic compound (glass NPs), quantum dots	DNA	Glass NPs, quantum dots, DNA	407
Detection and Imaging	Influenza A detection	Metal (AuNPs)	DNA	AuNPs	32
Detection and Imaging	Photoacoustic tomography	Metal (AuNRs)	Lipid	Indocyanine green	393
Detection and Imaging	Biological autoluminescence enhancement	Metal (AuNPs)	Lipid	AuNPs	394
Detection and Imaging	Glucose monitoring	Metal (AuNPs)	Lipid	Fluorophore	395
Detection and Imaging	Cancer detection	Metal (AuNCs)	Lipid	AuNCs	31
Detection and Imaging	Analysis of cellular functions	Metal (IONPs)	Lipid	IONPs	397
Detection and Imaging	MRI contrast	Metal (gadolinium)	Polymer	Gadolinium	389
Detection and Imaging	Biosensor	Silica	Polymer	Spiropyran	408
Detection and Imaging	MRI contrast	Metal (IONPs)	Polymer	IONPs	390
Detection and Imaging	Antibiotic detection	Metal (AuNPs), quantum dots	Polymer	AuNPs, graphene quantum dots	402
Detection and Imaging	MRI contrast	Metal (IONPs), inorganic compound (manganese oxide)	Surfactant	IONPs, manganese oxide	391
Detection and Imaging	Cancer imaging	Inorganic compound (upconversion nanoparticle)	Membrane (RBC)	Upconversion NP	176
Drug Delivery	Radical scavenging	Metal (IONPs)	Lipid	Curcumin	236
Drug Delivery	Enzyme delivery	MOF	Membrane (RBC, mesenchymal stem cell)	Uricase	252
Gene Delivery	Osseointegration of dental implants	Metal (AuNPs)	Polymer	pDNA	221
Vaccine	General vaccine	MOF	DNA	Ovalbumin	423

Category	Application	Inorganic component	Organic component	Active compound	Reference
Vaccine	General vaccine	MOF	DNA	Ovalbumin	387
Vaccine	General vaccine	Metal (IONPs)	Lipid	Ovalbumin	424
Vaccine	Japanese encephalitis	Silica	Polymer	Japanese encephalitis antigen	385
Vaccine	General vaccine	Silica	Polymer	Bovine serum albumin	386
Vaccine	Burkholderia mallei	Metal (AuNPs)	Polymer	Burkholderia mallei protein	383
Vaccine	General vaccine	Metal (IONPs)	Polymer	pDNA	384
Vaccine	General vaccine	Inorganic compound (Copper sulfate)	Protein	Ovalbumin	425
Vaccine	Dengue virus	Inorganic compound (CaP)	Protein	Dengue virus protein	426
Vaccine	Dengue virus	Metal (AuNPs)	Protein	Dengue virus protein	382

Table 3:

Theranostic hybrid nanosystems

Application	Inorganic material	Organic material	Gene therapy	Drug therapy	Phototherapy	Imaging	Targeting	Stimulus responsivity	Source
αvβ3 integrin-expressing cancers	Aunanostars	PAMAM	siRNA	N/A	PTT	CT imaging	RGD peptides	NIR	436
Adenocarcinoma	IONPs	Liposome	N/A	PTX	N/A	MRI	$H_7K(R_2)_2$, Magnetic targeting	pH, magnetic field	434
Adenocarcinoma	C60@Au	PEG	N/A	DOX	PDT, RTT	X-ray imaging	N/A	pH, radio waves	447
Breast cancer	AuNRs	DNA origami	N/A	N/A	PTT	Optoacoustic imaging	N/A	N/A	450
Breast cancer	GQDs	Polydopamine	N/A	CpG oligonuc leotides	PDT/PTT	MRI, fluorescence imaging	N/A	Magnetic field, NIR	108
Breast cancer	IONPs	C60, PEG	N/A	N/A	PDT, RTT	MRI	Folic acid, magnetic field	Radio waves, NIR, magnetic field	448
Breast cancer	MSNs, CN, GQDs	CN, PEG	N/A	N/A	PDT/PTT	Ultrasound, fluorescence imaging, infrared thermal imaging	RGD peptides	Ultrasound, NIR	446
Breast cancer	Gadolinium NPs, GO	GO, PEG	N/A	DOX	PTT	MRI	Folic acid	Magnetic field, NIR	107
Breast cancer	IONPs, C60	DPPC (phospholipid)	N/A	DTX	PTT	MRI	Folate, magnetic field	Radio waves, magnetic field, temperature	110
Breast cancer	Hollow mesoporous copper sulfide	fPEDC copolymer	N/A	Maytansinoid	PTT	Photoacoustic, fluorescence imaging	RGD peptides	NIR	454
Breast cancer	Pd@ZIF-8	Polydopamine	N/A	DOX	PTT	Photoacoustic imaging	N/A	pH, NIR	84
Breast cancer	AuNS	Liposome	N/A	DTX	PTT	Ultrasound imaging	N/A	NIR, temperature	429
Breast cancer	IONPs	Membrane (RBC)	N/A	N/A	PTT	MRI	N/A	NIR, magnetic field	180
Breast cancer	IONPs	Membrane (RBC)	N/A	N/A	PTT	MRI	Magnetic targeting	Magnetic field	177
Cervical cancer	Au@Cu2O, QDs	Polyallylam ine	N/A	N/A	PDT/PTT	MRI, photoacoustic imaging	N/A	NIR	449
EGFR-expressing tumors	AuNRs, IONPs	Liposome	N/A	DOX	PDT/PTT	MRI	Cetuximab (Anti-EGFR antibody), magnetic targeting	NIR, magnetic field	431

Application	Inorganic material	Organic material	Gene therapy	Drug therapy	Phototherapy	Imaging	Targeting	Stimulus responsivity	Source
EGFR-expressing tumors	AuNCs	BSA	N/A	Erlotinib	PTT	Optoacoustic, fluorescence imaging	N/A	pH, NIR	444
Folate receptor-expressing cancers	AuNPs, GQDs	Liposome	N/A	DOX	PDT/PTT	Contrast and fluorescent imaging	Folic acid	NIR	427
Folate receptor-expressing cancers	AuNRs	Liposome	N/A	DOX	PDT	Ultrasound, CT imaging	Folic acid	NIR, ultrasound	428
Glioblastoma	AuNRs	PLGA	N/A	N/A	PTT	Photoacoustic imaging	N/A	NIR	451
Glioma	IONPs, QDs	Liposome	N/A	Cilengitide	N/A	MRI, fluorescence imaging	Magnetic targeting	Magnetic field, NIR	433
Glioma	AuNRs, mesoporous silica, QDs	PGMA	pDNA	DOX	PTT	Photoacoustic, X-ray CT, fluorescence imaging	N/A	NIR, X-ray	439
Glioma	MSNs	PEG-perylene diimide	N/A	SN38	PTT	Photoacoustic, fluorescence imaging, PET imaging	N/A	NIR	440
Hepatocellular carcinoma	IONPs	Liposome	N/A	anetholedithiolethione	N/A	MRI, ultrasound imaging	Magnetic targeting	Magnetic field	435
Lymphoma	IONPs	Liposome	N/A	Rituximab	N/A	MRI	Rituximab (Anti-CD20 antibodies), magnetic targeting	Magnetic field	432
Melanoma, cervical cancer	Ag/AuNPs	PEI	pDNA	N/A	N/A	Fluorescence imaging	N/A	NIR	437
Pancreatic carcinoma	AuNPs, mesoporous silica	BSA	N/A	Gemcitabine, DOX	N/A	Fluorescence imaging	N/A	Photo	443
Prostate cancer	Bi2S3	PLGA	N/A	N/A	RTT	Ultrasound, X-ray imaging	N/A	Ultrasound, X-ray	442
Prostate cancer	IONPs	Membrane (MSC)	siRNA	N/A	PTT	MRI	Magnetic targeting	Magnetic field, NIR	179

Table 4:

Active clinical trials involving hybrid nanosystems (from ClinicalTrials.gov, accessed Aug. 2020).

Title	Phase	Status	Conditions	Interventions	Inorganic material	Organic material	Locations
Evaluating AGuIX¬Æ Nanoparticles in Combination With Stereotactic Radiation for Brain Metastases	Phase 2	Recruiting	Brain Metastases	Drug: AGuIX	Gadolinium	Polysiloxane	Centre Léon Bérard, Lyon, France; Centre Antoine Lacassagne, Nice, France
AGuIX Gadolinium-based Nanoparticles in Combination With Chemoradiation and Brachytherapy	Phase 1	Recruiting	Gynecologic Cancer	Drug: Polysiloxane Gd-Chelates based nanoparticles (AGuIX)| Radiation: External beam radiotherapy (EBRT)| Radiation: Uterovaginal brachytherapy| Drug: Chemotherapy (cisplatin)	Gadolinium	Polysiloxane	Gustave Roussy, Villejuif, Val De Marne, France
Enhanced Epidermal Antigen Specific Immunotherapy Trial −1	Phase 1	Active, not recruiting	Type 1 Diabetes	Drug: C19-A3 GNP	AuNP	Peptide	Cardiff and Vale University Health Board, Cardiff, United Kingdom
Radiosensitization of Multiple Brain Metastases Using AGuIX Gadolinium Based Nanoparticles	Phase 1	Completed	Brain Metastases	Drug: AGuIX| Radiation: whole brain radiation therapy	Gadolinium	Polysiloxane	University Hospital Grenoble, Grenoble, France
Targeted Silica Nanoparticles for Real-Time Image-Guided Intraoperative Mapping of Nodal Metastases	Phase 1, Phase 2	Recruiting	Head and Neck Melanoma| Breast Cancer| Colorectal Cancer	Drug: fluorescent cRGDY-PEG-Cy5.5-C dots	MSN	Peptide	Memorial Sloan Kettering Cancer Center, New York, New York, United States|Weill Cornell Medical Center, New York, New York, United States
Radiotherapy of Multiple Brain Metastases Using AGuIX®	Phase 2	Recruiting	Brain Metastases, Adult Radiotherapy	Drug: AGuIX® Radiation: Whole Brain Radiation Therapy	Gadolinium	Polysiloxane	Centre hospitalier universitaire Grenoble-Alpes