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SELF-ASSEMBLING NANOCARRIERS FOR PRECISION DRUG DELIVERY: FROM MOLECULAR DESIGN TO THERAPEUTIC APPLICATION

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ABSTRACT

The development of precision drug delivery systems has become an important area of pharmaceutical research, aiming to improve drug delivery to diseased tissues while limiting exposure to healthy cells. Self-assembling nanocarriers offer a promising approach by transforming molecular building blocks into organized structures with potential therapeutic benefits. Most drugs spread through the whole body, so only a small share of the dose reaches the diseased tissue and healthy cells are exposed along the way. Self-assembling nanocarriers try to fix this by building the delivery vehicle from small units that organise themselves through non-covalent forces. This review draws on twenty-eight published papers, mostly reviews, and follows the idea from molecular design to clinical use. We first describe the interactions that hold an assembly together and show how the choice of building block (peptide, protein, small-molecule drug, prodrug or nucleic acid) shapes the structure that forms. The main carrier classes are then compared, followed by the pH, enzyme and redox triggers that start drug release and the passive and active routes carriers use to find their target. Pharmacokinetic questions and the obstacles to clinical translation come next, together with applications in cancer therapy, gene delivery, protein and peptide delivery and imaging. Many of the sources warn that clinical success has been limited, and most of the evidence reviewed here is preclinical. The most promising way forward seems to be a closer union of molecular design, stimulus response and targeting, with the aim of carriers that can be tailored to individual patients.

KEYWORDS: Self-assembly; nanocarriers; precision drug delivery; stimuli-responsive release; peptide nanostructures; prodrugs; nucleic acid nanostructures; cancer therapy.

1. INTRODUCTION

For thousands of years, people have used medicinal mixtures to prolong and enhance their quality of life. The use of molecular therapeutic agents has grown dramatically in recent decades, particularly in the detection and treatment of cancer. Dropping the carrier has clear appeal, since carrier-related side effects disappear and the formulation, and with it quality control, can be simpler.[1] Low targeting accuracy, systemic toxicity, and subpar bioavailability are some of the major drawbacks of conventional administration methods, such as intravenous and oral formulations.[2] The domains of nanoscience and nanotechnology in particular have drawn a lot of attention throughout the past ten years. Applied sciences from basic sciences on the nanoscale can currently be used in a wide range of industrial activities and research sectors.[4] Self-assembly is a process where components interact with each other and form ordered structures or patterns without external guidance. In this review, the term “self-assembly” is also used to identify structures resulting from self-assembling processes.

Chen and colleagues point to two features that matter for delivery: self-assemblies can adopt complex structures that are hard to obtain by chemical synthesis, and they can fall apart in response to an outside stimulus, which gives a built-in way of letting go of the payload. Natural examples such as proteins and viral capsids, and engineered ones such as vesicles, micelles, proteins, hydrogels and inclusion complexes, have all been explored as delivery vehicles.[5] Nanoparticles, liposomes, dendrimers and nanostructured lipid carriers have all been tested for site-specific delivery, and combining them with targeting groups and local administration is said to cut side effects further.[6] Nanocarriers were introduced to close this gap. A drug placed inside or on a nanoscale particle is protected while it travels in the blood, its pharmacokinetics can be adjusted, and the particle can be steered towards chosen tissues and cells, with less of the drug collecting in the kidney, liver and spleen. The same particle can also carry an imaging agent, so delivery can be followed in real time. Even so, these established platforms bring problems of their own, such as stability, toxicity and difficult manufacturing.[7] Researchers from all over the world have recently become interested in using supramolecular self-assembly to create nanostructures and nanomaterials with distinctive chemical and physical characteristics. These nanoassemblies' molecular arrangement has enabled the creation of novel gadgets that can communicate with living cells and elicit a reaction.[8] Although nanotechnology is an essential tool in many different but related fields, such as engineering, chemistry, physics, and biotechnology, it is the "shining star" of the health sciences and has caused a paradigm shift in how the scientific community approaches unmet medical needs.[9]

The next step is to let the drug itself join the assembly. Prodrugs, amphiphilic drugs, drug–drug conjugates and related molecules can form nanostructures with no separate carrier material.[1,3,14] The idea has a long history in pharmaceutics. Short peptides were shown to organise into tubes, fibres, tapes and vesicles when their sequence was changed, and self-assembling materials had already been reviewed as vehicles for therapeutic delivery in 2009 [19,20]. More recently, Tang and colleagues described self-assembled nanoparticles as forming through weak interactions between drugs and functional molecules, with no need for complicated carrier synthesis.[16]

What links self-assembly to precision delivery is control at the molecular level. In this review, precision drug delivery means the design aim of getting better spatial and temporal control over drug distribution, cellular uptake and release; it does not claim complete tissue specificity or a proven personalised treatment. Because the structure of a nanocarrier follows from its building blocks, a change at the molecular scale can alter size, shape, targeting and release. One review shows that particle shape, which comes directly from how the building blocks assemble, changes circulation time, cell

uptake and drug loading. Another describes stimulus-responsive carriers that bring targeting, imaging and therapy together and a third presents supramolecular self-assembled nanomaterials as stimulus-responsive platforms aimed at better control over where, when and how much drug is released.[12,13,18] Taken in order, these levels (molecular design, self-assembly, morphology, biological behaviour, drug loading and release, therapeutic outcome and translational barrier) form the backbone of the paper.

It starts with the forces that drive assembly (Section 2) and the design of building blocks (Section 3), then covers the main carrier types (Section 4), stimulus-responsive release (Section 5), targeting (Section 6), applications (Section 7), the role of self-assembly in precision delivery (Section 8), pharmacokinetic considerations (Section 9), clinical translation (Section 10) and future directions (Section 11).

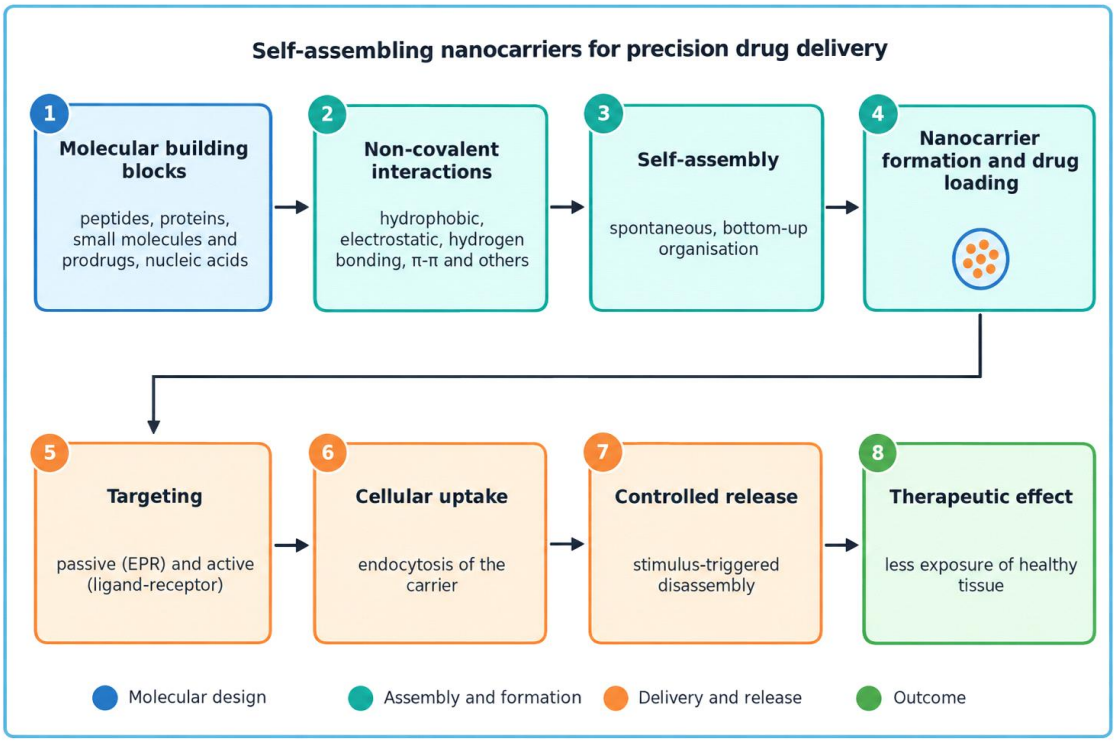

Figure 1: Overview of self-assembling nanocarriers for precision drug delivery.

Overview of self-assembling nanocarriers for precision drug delivery: Molecular building blocks form drug-loaded nanocarriers through non-covalent interactions, enabling targeted delivery, cellular uptake, stimulus-responsive drug release, and therapeutic effects with reduced exposure of healthy tissues. based on references.[1,2,5,7,8,13]

2. Fundamentals of Molecular Self-Assembly

2.1 Definition and routes of assembly

For drug carriers, the preparation methods named in the literature include assembly in solution, template-assisted assembly, assembly at interfaces and assisted assembly. Self-assembly is the association of individual units of a material into highly ordered structures through non-covalent interactions. Two broad routes are described. In the top-down approach, a bulk material is cut or shaped into small structures, while in the bottom-up approach the molecules build the structure themselves. Assemblies can also be classed by how they form (thermodynamic or kinetic) and by the nature and size of the building units (atomic, molecular or colloidal). Tang and colleagues list a related set of practical

routes for self-assembled nanoparticles: antisolvent precipitation, template-assisted preparation, microfluidics, emulsification and assembly triggered inside the body. The same weak interactions that make assembly possible also make it sensitive to temperature, pH and ionic strength.[4,8,16] The choice matters, because it affects particle size, drug loading and reproducibility. Work on short peptides showed that sequences can be designed to organize into defined nanostructures such as tubes, fibers and vesicles, and later reviews extended the idea to therapeutic delivery.[19,20]

2.2 Interactions that drive assembly

No single force explains how a nanocarrier forms. Several weak interactions work together, and the balance among them decides which structure is stable. The main ones are summarized in Table 1 and Figure 2.

Hydrophobic interactions: In water, the non-polar parts of amphiphilic molecules cluster together, away from the solvent, and leave the polar parts exposed. The outcome is a micelle or vesicle with a hydrophobic interior that can hold poorly soluble drugs. Numerous observations in the literature indicate that π-π stacking and hydrophobic interactions cause aromatic moieties like Fmoc and pyrene-protected peptides to form nanofibrillar hydrogel networks. Polymeric micelles made of poly (ethylene glycol) and polycaprolactone blocks and loaded with paclitaxel are one example discussed in the literature.[2,8,16]

Electrostatic interactions: Components with opposite charges attract each other. This underlies polyelectrolyte complexes, where charged polymers or biomolecules pair up into particles. Charge can also keep a drug inside a carrier; peptide-based nanocarriers for epirubicin are reported to depend on electrostatic and π–π contacts with the drug. Electrostatic forces can also act together with π–π stacking and hydrogen bonding to set the structure, size and shape of an assembly.[2,7,16]

Hydrogen bonding: Hydrogen bonds are directional and matter especially in peptides, where bonding between the backbones of neighbouring strands gives β-sheet arrangements that grow into fibres and tubes. They weaken when pH or temperature changes, so they can also serve as a trigger for disassembly.[2,7,16]

Table 1: Molecular interactions that drive the self-assembly of nanocarriers.

Interaction	Basic principle	Role in self-assembly	Possible influence on nanocarrier properties	Ref.
Hydrophobic	Non-polar regions cluster together in water	Forms the core of micelles and vesicles	Sets the space available for poorly soluble drugs	[2,8]
Electrostatic	Attraction between opposite charges	Pairs charged polymers and biomolecules; holds charged drugs	Sensitive to pH and ionic strength	[2,7]
Hydrogen bonding	Directional bonds between donor and acceptor groups	Links peptide strands into β-sheets, fibres and tubes	May weaken with pH or temperature change, which aids release	[2,7]
π–π	Stacking of aromatic rings	Drives assembly of aromatic peptides and drugs	Affects packing and stability	[2,7]
Van der Waals	Weak, short-range attraction	Supports close packing	Adds to overall cohesion	[2]
Host–guest	A guest fits into a host cavity	Forms inclusion complexes	Can hold hydrophobic guests in water	[2,5]
Metal coordination	Metal ion binds to side chains	Stabilises some peptide assemblies	Adds to the stability of the structure	[7]

π–π interactions. Aromatic groups stack on top of one another. Peptides rich in aromatic residues, and aromatic drugs such as the anthracyclines, use this stacking to assemble. Because stacking is directional, the relative orientation of the molecules affects the result.[2,7,16]

Van der Waals forces: These forces are weak and act over short distances, but they add up when molecules pack closely and so contribute to the cohesion of the assembly.[2,16]

Host–guest interactions: A small guest molecule sits in the cavity of a larger host, as in cyclodextrin inclusion complexes. Chen and colleagues count inclusion complexes among the five engineered self-assembly classes they review.[2,5]

Metal coordination: Metal ions can bind to side chains and lock the structure in place. In one peptide design discussed by Kumar and colleagues, Zn (II) coordination to histidine stabilized the assembly and helped carry the drug epirubicin.[7]

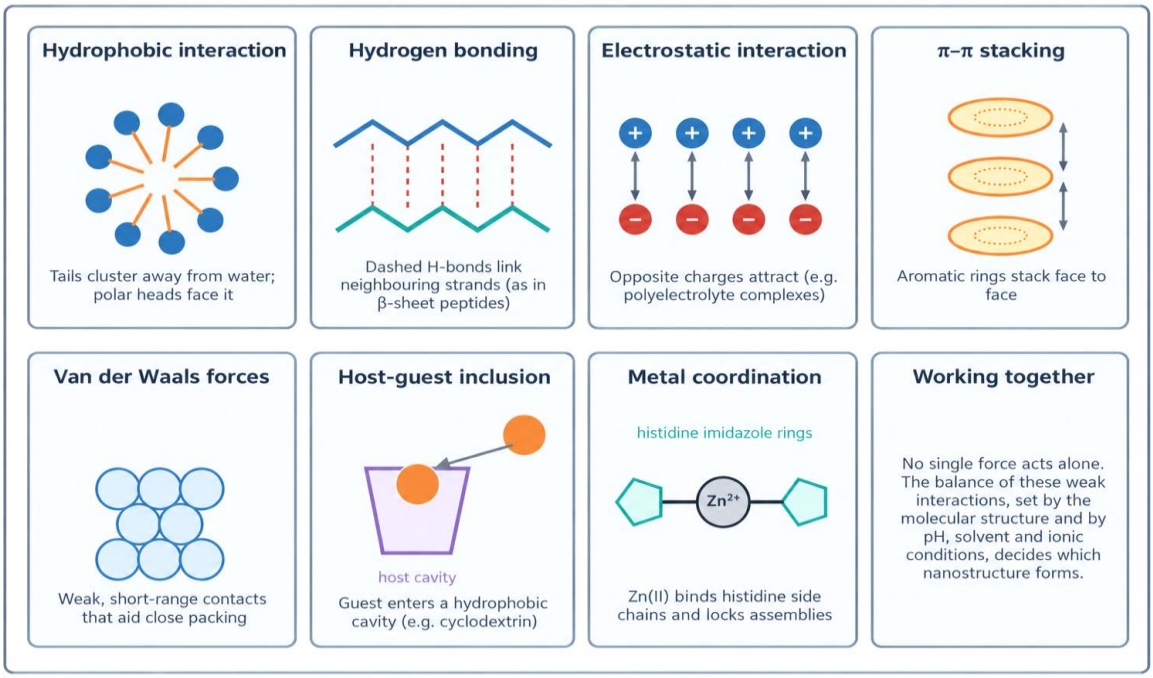

Figure 2: Non-covalent interactions that drive molecular self-assembly.

Non-covalent interactions driving molecular self-assembly, Schematic illustrating hydrophobic effects, hydrogen bonding, electrostatic attraction, π–π stacking, van der Waals forces, host–guest inclusion, and metal coordination, which often act together in nanocarrier formation. based on references.[2,5,7,8,16]

2.3 From molecular structure to nanocarrier

For polymer-based systems the relevant parameters are the balance between hydrophilic and hydrophobic parts, the packing of the chains and the conditions of the medium. For prodrugs, the choice of the hydrophilic pro-moiety is important for promoting assembly, and the linker and the stability of the resulting morphology must be considered too.[2,3] Small changes in a building block can produce large changes in the final structure. In peptides, length, sequence and side chains are intrinsic factors, whereas pH, temperature, solvent and pressure act from outside. Kumar and

colleagues point out, for example, that diphenylalanine tends to form nanotubes while diphenyl glycine forms spheres, although the two molecules differ only slightly.[7] The length of a lipid tail matters as well: in a C16-capped dodecapeptide, breaking hydrogen bonds near the hydrophobic core shifted the structures from fibrous to globular, and longer alkyl chains on an octapeptide favoured assembly and a more stable secondary structure. External conditions act on the same interactions. Tang and colleagues note that rising temperature generally weakens hydrogen bonds and electrostatic forces, that solvent polarity shifts the balance between hydrogen bonding and hydrophobic contacts, and that pH and ionic strength change the charge state of ionizable groups.[16,17] For ionisable peptides, pH is therefore a deliberate design variable, and pH-responsive self-assembling peptide biomaterials have been reviewed as a class of their own.[21] The palmitoylated peptide C16-KTTKS gives a good example from the peptide literature: its tapes change into twisted fibrils at pH 4 and the peptide becomes spherical micelles at pH 2.[19]

3. Molecular Design of Self-Assembling Nanocarriers

3.1 Design principles

Two ways of making a nanocarrier from a drug and a building block are described. In one, the drug is simply encapsulated or adsorbed. In the other, it is linked covalently to a component that drives assembly. In either case the designer has to balance several demands: an assembly strong enough to survive in blood, enough responsiveness to release the drug at the target, and a size and surface that suit the biological route taken. Abdelhamid and colleagues, reviewing protein nanocarriers for cancer, name loading capacity inside the protein cage as a major challenge and describe ways of raising it; loading doxorubicin in one step at pH 9, for instance, increased loading about threefold compared with the usual disassembly and reassembly route.[2,10] Kumar and colleagues add that peptide nanocarrier design can be guided by intuition, by structure-based methods or by computation, and that the best design may depend on the drug, the carrier and the cell type.[7] Liu and colleagues make a related point for supramolecular nanocarriers, saying that stimulus responsiveness has to be designed together with stability if release is to be controlled.[18] Self-assembled systems face a further constraint: the dynamic bonds that allow responsiveness can also let the assembly dissociate after dilution in the blood, a problem studied in detail for polymeric micelles.[22]

3.2 Amphiphilic molecules

Amphiphiles, which have both water-loving and water-avoiding parts, assemble into micelles, vesicles and hydrogels because of the physical interactions between them and the solvent. Polymer-based systems use block copolymers in which a hydrophilic block such as poly (ethylene glycol) forms the outer layer and a hydrophobic block forms the core. Lipids give vesicles that can carry both hydrophobic and hydrophilic drugs. Drugs themselves can be amphiphilic, and amphiphilic drugs are one of the classes of drug-based self-assembled nanostructures reviewed by Nsairat and colleagues.[1,2,8] Micelles show the stability issue clearly. Lu and colleagues explain that micelles break up when diluted below their critical micelle concentration, which is roughly 10^{-6} to 10^{-7} M for polymeric micelles and 10^{-3} to 10^{-4} M for small-molecule ones, and that serum proteins can also disrupt them and trigger early drug release; they then review ways of making micelles more stable, mainly cross-linking and extra non-covalent interactions. Zhou and colleagues report that three block-copolymer micelle products, Genexol-PM, Nanoxel-M and Paclical, are already on the market,[22,23] which shows that this class has come closer to patients than most of the systems discussed here.

3.3 Peptides

Peptides are attractive because their sequence can be edited one residue at a time. Kumar and colleagues organise peptide design around metal coordination, structural stabilisation by cyclisation, and minimalism. Cyclisation can raise stability against proteases and help control the diameter of the assembled structure, although cyclic peptides are harder to synthesise. Minimalism means using very short building blocks, dipeptides included, to make nanocarriers. A cyclic peptide containing histidine and Zn(II) has been reported to encapsulate epirubicin with a drug loading of about 15.7% and to release it in an acidic environment.[7] A 2024 review of peptide-mediated carriers adds that peptides can form nanofibers, nanosheets, nanotubes, vesicles and micelles, that cyclic peptides build nanotubes through hydrogen bonding along the axis of the ring, and that cyclic RGD resists degradation better than linear RGD because the rigid ring blocks reactions of the aspartic acid side chain.[17] Ionizable residues make pH a convenient trigger, and pH-responsive self-assembling peptide biomaterials and their designs have been reviewed separately.[21] The wider principle, that peptide sequences can be engineered to assemble into defined nanostructures, is well illustrated by Mandal and colleagues, who describe diphenylalanine nanotubes, cyclic peptide rings that stack into tubes whose inner diameter depends on the number of residues, and vesicles that begin to form at pH 5.0.[19]

3.4 Proteins

Chen and colleagues also count proteins, natural and engineered, among the main self-assembling classes for delivery.[5] Proteins offer something peptides cannot always match: a complete folded domain whose function can be built into the carrier. Abdelhamid and colleagues review protein nanocarriers made from natural cages and engineered polypeptides. Human ferritin is a 24-subunit cage with an outer diameter of about 12 nm and an inner diameter of about 8 nm; it comes apart in strong acid and reassembles at physiological pH, which traps drug inside. Vault particles are much larger, at roughly 67 × 40 × 40 nm, and the Thermotoga maritima encapsuling is built from 60 identical subunits and measures about 24 nm across. Elastin-like polypeptides are another group: block copolymers made by genetically joining hydrophilic and hydrophobic blocks can form particles, and coiled-coil dimers are used as modular units for building cages. Because these building blocks are genetically encoded, function can be designed in a modular way, with near-complete control over the particle.[10] In biological systems, peptides and proteins frequently self-assemble to produce fibrillar structures. Important instances of proteins self-assembling into nanofibrillar structures are amyloid fibrils. and materials for therapeutic delivery.[19,20] were being reviewed years earlier. Compared with short peptides, engineered proteins offer larger functional domains.

3.5 Small molecules and prodrugs

Nsairat and colleagues add drug–drug conjugates, squalene conjugates and amphiphilic drugs to the list.[1] Wang and colleagues describe the prodrug approach as a way of combining the delivery construct and the therapeutic agent in a single molecule, with the pro-moiety promoting assembly, the linker controlling release kinetics, and polymeric prodrugs, small-molecule prodrugs and peptide–drug conjugates as the main groups.[3] Small-molecule self-assembled nanodrugs go a step further by using the drug itself as the building block. Zhang and colleagues, writing about carrier-free nanodrugs for cancer, sort their assembly mechanisms into three groups: non-covalent interactions, covalent bonds combined with non-covalent ones, and metal-ion coordination.[14] Tang and colleagues describe a doxorubicin prodrug whose hydrophobic fatty acid chain was tuned to give a nano assembly that stayed stable in blood in the study they cite and released drug in response to high glutathione.[16] In such designs the drug is not just carried; it is part of the structure. Chen and colleagues combined anticancer drugs into a pure-drug cocktail that assembled quantitatively into

injectable nanoparticles for synergistic delivery. Jiang and colleagues assembled paclitaxel with indocyanine green so that the structure, held together mostly by van der Waals forces, fell apart under laser irradiation and released the drug in situ.[25,26] These examples show the chemistry-based control available in this class, but they come from individual preclinical studies.

3.6 Nucleic-acid-based systems

Nucleic acids can be assembled bottom-up into defined shapes. Safarkhani and colleagues review DNA nanostructures that carry aptamers: DNA origami, in which a long scaffold strand (often M13mp18) is folded with short staple strands into triangles, tubes, pyramids, discs and other shapes; the DNA tetrahedron, built from four single strands and often about 10 nm in size; and ribbons and nanoflowers made by rolling-circle or hybridisation-chain amplification. These carriers have been loaded with small drugs (doxorubicin is the most common), with nucleic acids such as siRNA, antisense oligonucleotides and Cas9/sgRNA, with photosensitisers and gold nanomaterials, and with proteins including thrombin and insulin. Nucleic-acid carriers combine structural programmability with the option of adding targeting ligands; the AS1411 aptamer, which binds nucleolin, and a MUC1 aptamer that recognises MCF-7 breast cancer cells are both used in this role. Stability against nucleases is a real concern for DNA carriers. Safarkhani and colleagues report that coating a DNA octahedron with a PEGylated lipid bilayer raised the intact fraction from 30% to 85% after a day in DNase I, and that DNA origami was reported to last only about 2 to 8 hours in fetal bovine serum.[11] Examples summarized by Emadi and colleagues include DNA-based structures carrying doxorubicin together with an aptamer for tumour recognition.[2] In the gene-targeting nanocarrier of Li and colleagues, the AS1411 aptamer directs a mesoporous silica particle towards tumour cells while an antisense anti-miR-155 oligonucleotide acts as the gene-regulating cargo, so nucleic acids serve more than one purpose in the same construct.[15] Tang and colleagues also list gene therapy among the therapeutic modes in which self-assembled nanoparticles have been combined with other treatments.[16]

3.7 Control of size, morphology and stability

Three properties come up again and again as targets for design. Size matters, but the sources give different working ranges: roughly 50 to 200 nm in connection with accumulation in tumours. Stability involves a trade-off. Emadi and colleagues point out that adding many pH- or redox-sensitive links can improve release but may make the carrier less stable, and that some temperature-responsive polymers may be harder to store.[2] whereas protein cages are much smaller, with ferritin at about 12 nm and encapsulin at about 24 nm across.[10] These ranges depend on the carrier, the route of administration and the tissue, and no single range should be taken as optimal for all systems. Shape matters because elongated assemblies behave differently from spheres. In the work reviewed by Lagarrigue and colleagues, long filamentous micelles circulated about ten times longer than spherical ones and stayed in rodent blood for about a week; the effect grew with length up to roughly 8 μm, and structures longer than 10 μm tended to break into shorter pieces under flow.[12] Since assembly depends on weak interactions, Tang and colleagues note that batch-to-batch variation is a real risk when conditions are not reproduced exactly, and that microfluidic mixing gives more uniform size but at higher cost and complexity.[16] Stability in physiological fluids is a different property from stability on the shelf, and work on micelles shows that dilution can destabilise assemblies that are stable at higher concentrations.[22]

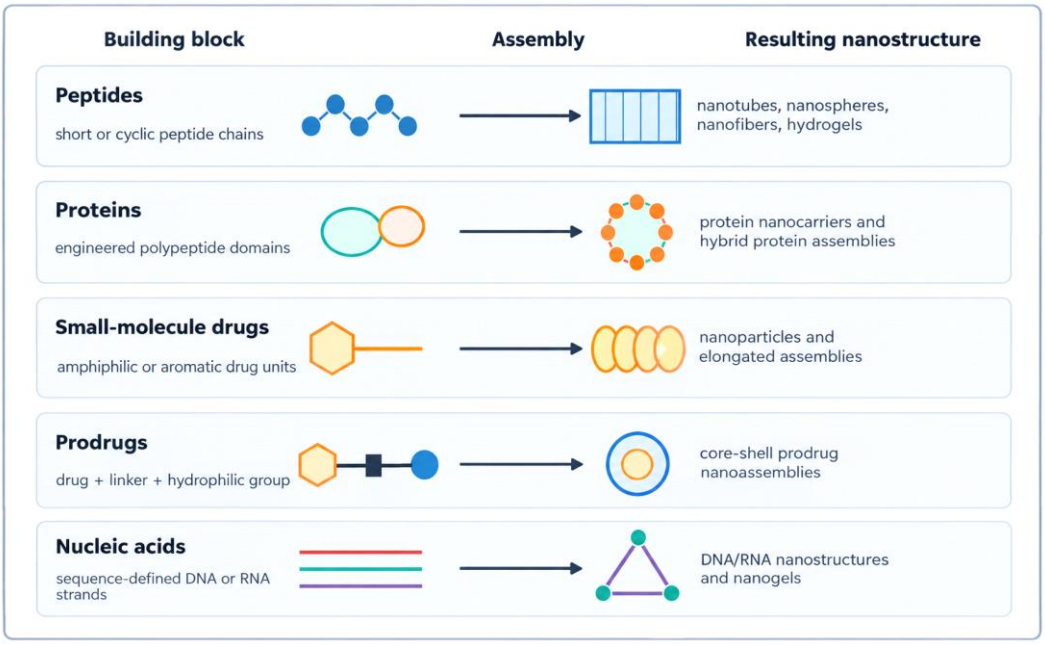

Figure 3: Molecular design strategies for self-assembling nanocarriers.

Molecular design strategies for self-assembling nanocarriers, Peptides, proteins, small-molecule drugs, prodrugs, and nucleic acids form diverse nanostructures, including spheres, fibres, tubes, gels, core–shell assemblies, and DNA/RNA nanostructures. Schematic illustrations are not to molecular scale; concepts based on references.[1,3,5,7,10,11,12,14,25]

4. Types of Self-Assembling Nanocarriers

The sources group self-assembling nanocarriers in more than one way, either by building block or by morphology. This section follows the building block, since it is most closely tied to molecular design. Table 2 gives a side-by-side comparison.

Peptide nanocarriers: Self-assembling peptides are described as an emerging class of nanomaterials that can help release drugs, improve their stability and reduce side effects. They have been shaped into nanotubes, nanosheets, nanorods, nanogels, nanofibers and nanospheres. The 2024 review adds vesicles and micelles. Their strengths are the control available through sequence and the chance to build in targeting or responsiveness; the same review describes enzyme-triggered designs, such as a micelle-like particle with a paclitaxel core and an MMP-cleavable peptide shell that turns into micron-sized assemblies after cleavage.[7,17]

Protein nanocarriers: Protein nanocarriers include natural cages such as ferritin, vaults and encapsulins, small heat-shock proteins and engineered elastin-like polypeptide particles. Their genetic encoding allows modular design, drug encapsulation and targetability; in one example, ferritin carrying paclitaxel gave a median survival of 30 days in a glioma model, against 13 days for saline and 14 days for free paclitaxel. Compared with peptides, proteins carry more structural information in each building block, though loading into the cage remains a challenge.[10]

Small-molecule nanodrugs and prodrug assemblies: Their appeal is simplicity: with no separate carrier, carrier-related side effects are avoided and quality control may be easier.[1] show that two agents can be co-assembled into a single particle. The cost is that the molecule has to be designed so that it works as a drug and also assembles, with the

linker and pro-moiety setting the balance.[3] When creating carrier-free nanodrugs, noncovalent forces are crucial. Active agents' unique functional groups cause them to interact noncovalently with other molecules or with molecules of water.[14] Carrier-free does not mean free of formulation problems: Tang and colleagues describe sensitivity to temperature, pH and ionic strength, and batch-to-batch variation, as obstacles to the scale-up of self-assembled nanoparticles.[16] Here, we demonstrate that DAS helps water-insoluble, hydrophobic CTX self-assemble into colloidally stable nanoassemblies without the use of exogenous excipients by taking use of its amphiphile function. Interestingly, nanoassemblies incorporating pure drug mixtures were created by a one-pot self-assembly technique,and combinations of clinically approved drugs.[25,26]

Nucleic-acid nanocarriers: DNA assemblies such as origami, tetrahedra, ribbons and nanoflowers can carry small drugs, nucleic acids, photosensitizers and proteins, accept aptamers and other ligands for targeting, and release their cargo in response to several triggers, as reviewed by Safarkhani and colleagues.[11]

Elongated nanocarriers: Filamentous or worm-like micelles, assembled from block copolymers, are longer than they are wide and behave differently from spheres. Lagarrigue and colleagues report that they can circulate far longer, that high aspect ratios (above about 20) lower uptake by macrophages, and that in some systems they carry more drug; for doxorubicin in one polymer, loading was 10.6% for filomicelles, 7.4% for nanorods and 5.2% for spheres. They also note that few non-spherical particles have reached clinical trials.[12]

Table 2: Comparison of the major self-assembling nanocarrier types.

Nanocarrier type	Building block	Major assembly mechanism	Therapeutic cargo	Main advantage	Major limitation	Ref.
Peptide	Short, cyclic or modified peptides	Hydrophobic, π–π, electrostatic, hydrogen-bond and metal-coordination interactions	Anticancer medications like epirubicin and doxorubicin	Control of structure and function at the sequence level	Cyclic peptides are harder to synthesise	[7,17]
Protein	Ferritin and other cages, vaults, encapsulins, small heat-shock proteins, elastin-like polypeptides, coiled coils	Self-association of protein subunits; assembly of elastin-like block copolymers	Cisplatin, paclitaxel, doxorubicin, and other anticancer medications	Genetically encoded, so targeting and encapsulation can be built in modularly	Loading into cages is low unless optimised (3–4% by disassembly and reassembly)	[10]
Small-molecule nanodrug	Drug molecules, amphiphilic drugs	Non-covalent assembly of the drug itself	The drug itself	No separate carrier needed	Sensitivity to temperature, pH and ionic strength; batch-to-batch variation	[1,14,16]
Prodrug assembly	Drug–linker–pro-moiety conjugate	Assembly promoted by the pro-moiety	The conjugated drug	Delivery construct and drug in one molecule; the linker sets release	Linker design and stability of the morphology must be tuned	[3]
Nucleic-acid nanocarrier	DNA strands (origami,	Bottom-up assembly of	Small drugs, siRNA and	Programmable shape; aptamers	Vulnerable to nucleases unless	[11]

	tetrahedra, ribbons, nanoflowers); RNA and composites	strands, often with aptamer ligands	other nucleic acids, photosensitisers, proteins	and several release triggers available	protected	
Elongated assembly	Block-copolymer filomicelles and worm-like micelles	Growth of cylindrical micelles from amphiphilic polymers	Hydrophobic drugs such as doxorubicin and paclitaxel	Longer circulation and, in some systems, higher loading than spheres	Shape is hard to separate from size and rigidity; few in clinical trials	[12]
Polymer, lipid and inorganic composites	Block copolymers, lipids, silica and others	Mixed interactions	Hydrophobic and hydrophilic drugs	Wide choice of materials	Scale-up, stability, storage, Biocompatibility and regulation	[2]

Polymer, lipid and inorganic assemblies: Emadi and colleagues cover polymer-, lipid- and inorganic based self-assembling nanocomposites, along with hydrogels, polyelectrolyte complexes and nanocapsules. based self-assembling nanocomposites, along with hydrogels, polyelectrolyte complexes and nanocapsules.[2] Paliwal and colleagues list polymeric nanoparticles, dendrimers, liposomes, inorganic nanocarriers, solid lipid nanoparticles, polymersomes, micelles and niosomes as self-assembled carriers, and report that some are in clinical trials or approved. Paliwal and colleagues list polymeric nanoparticles, dendrimers, liposomes, inorganic nanocarriers, solid lipid nanoparticles, polymersomes, micelles and niosomes as self-assembled carriers, and report that some are in clinical trials or approved.[4]

Polymeric micelles: Polymeric micelles are the best-established self-assembled carriers in the sources used here. Zhou and colleagues list Genexol-PM, Nanoxel-M and Paclical as marketed block-copolymer micelles and name NK012 and NK105 among those in clinical trials, while Lu and colleagues explain why dilution below the critical micelle concentration and contact with serum proteins limit micelle stability, and how it can be improved.[22,23] Micelles are therefore a useful reference point: they show that an assembled carrier can reach patients, and that stability, not assembly alone, decides whether it does. Two broad patterns emerge from the comparison. Peptide, protein and nucleic-acid carriers get their precision from sequence, so a change in the sequence changes the structure. Small-molecule and prodrug carriers get theirs from chemistry, through the choice of linker and pro-moiety, and have the advantage of delivering the drug without a carrier.

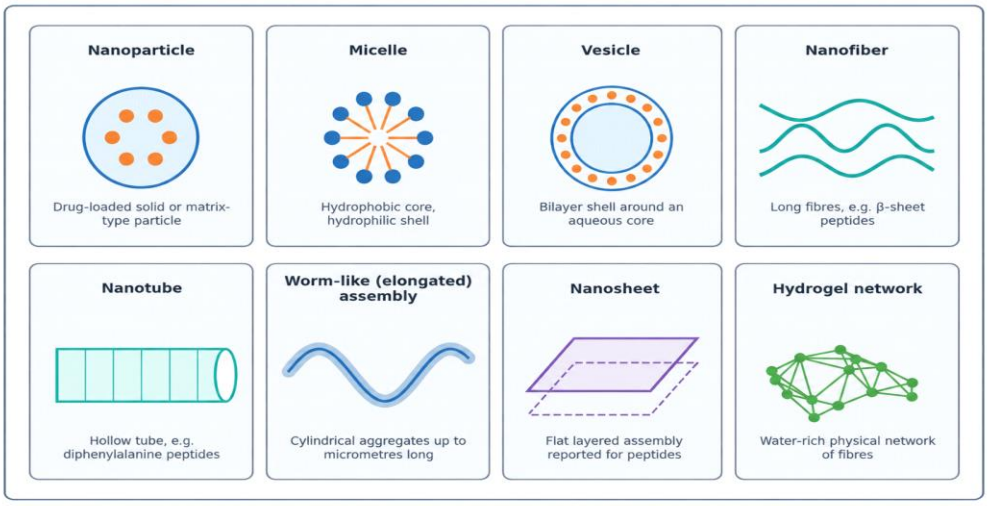

Figure 4: Morphologies of self-assembled nanocarriers.

Morphologies of self-assembled nanocarriers Self-assembled nanocarriers exhibit diverse structures, including nanoparticles, micelles, vesicles, nanofibres, nanotubes, worm-like assemblies, nanosheets, and hydrogels, depending on the building blocks and assembly conditions. Morphologies based on references.[2,7,8,12]

5. Stimuli-Responsive and Smart Self-Assembling Nanocarriers

The practical aim of stimulus-responsive design is a carrier that stays stable enough under physiological conditions and changes structure when it meets the intended stimulus. Self-assembly suits this aim because assemblies held by weak interactions can dissociate when conditions change.[5] Liu and colleagues review supramolecular self-assembled nanomaterials built as stimulus-responsive platforms for cancer therapy,[18] and Mi reviews stimulus-responsive nanocarriers more broadly, covering their use in drug delivery, tumour imaging, therapy and theranostics. Mi also gives one reason for turning to stimuli: HER2 is expressed in fewer than 25% of breast cancer patients, which argues for stimulus-responsive designs and not receptor targeting alone.[13] In DNA carriers, release can be set off by pH, light, glutathione, hydrogen peroxide or strand displacement.[11]

5.1 pH-responsive systems

Healthy blood has a pH of about 7.4, tumour tissue is more acidic, and the endosomes and lysosomes inside cells are more acidic still. Emadi and colleagues give the extracellular pH of tumours as about 6.5 to 7.0 and that of endosomes as about 4.5 to 5.5.[2] Mi reports a tumour range of 6.5 to 6.8 and a range of pH 6 to 4 for endosomes and lysosomes.[13] and Kumar and colleagues describe a somewhat wider tumour range, 6.2 to 7.4, so the exact figure depends on the tumour and on how it was measured. The behaviour is design-specific and not universal. The histidine-containing peptide system described above released epirubicin in acid whereas a different peptide hydrogel was reported to release 5-fluorouracil at basic pH. Carriers use this gradient through groups that pickup protons, such as histidine, or through acid-labile bonds, so the structure swells or breaks apart.[2,7] Among peptides, the H6 sequence forms fibres at pH 7.5 and nanoparticles at lower pH, and H6 fibres reached about 60% encapsulation of camptothecin, roughly seven times more than control micelles. In an acid-responsive amphiphilic peptide carrier described by Tang and colleagues, the change from spheres to long nanofibres in the acidic tumour environment was linked to longer drug retention in the study they cite.[16,17] Peptides with ionisable side chains are a natural fit for pH control, and pH-responsive self-assembling peptide biomaterials have been reviewed in terms of both design and application.[21]

5.2 Enzyme-responsive systems

Some enzymes are present at higher levels in diseased tissue, and linkers that these enzymes cut can hold a carrier together until it arrives at such a site. Emadi and colleagues describe cleavable peptide and polysaccharide linkers sensitive to enzymes such as matrix metalloproteinases and hyaluronidase.[2] Enzymes can also work the other way round, triggering assembly instead of disassembly, as in peptide systems that are converted into self-assembling forms at the site of enzyme activity.[7] Mi notes that MMP-2 can shrink particles of about 100 nm to about 10 nm, which helps them move through tumour tissue.[13] Tang and colleagues describe enzyme-controlled cascade assembly, in which a stable precursor is cleaved by a tumour-associated or disease-associated enzyme so that its morphology changes or larger aggregates form at the target; one cited example uses matrix metalloproteinases to convert small micelles into larger aggregates in infarcted heart tissue.[16] Guo and colleagues group such in situ transformable assemblies with programmable delivery and immune-reprogramming nanomaterials as multistage self-assembled systems meant to cope with the series of biological barriers a nanomedicine meets.[27]

5.3 Redox-responsive systems

The concentration of glutathione inside cells is far higher than outside them. Emadi and colleagues use this gradient in carriers whose disulfide links stay intact in the oxidising extracellular space but are reduced inside cells, releasing the cargo there.[2] Peptide-capped mesoporous silica systems that open in a reducing environment are described by Kumar and colleagues.[7] Mi puts the intracellular level at 2–10 mM, against 2–10 µM in normal regions. Among carrier-free systems, an IND-S-S-PTX nanoparticle with a disulfide link was reported to have an IC50 about one third that of paclitaxel.[13,14] As with pH, a redox trigger is useful only if there is a real gradient between the circulation and the target compartment, which the sources describe for tumour cells. Peptide systems give a concrete example: Tang and colleagues cite a cystine-cored diphenylalanine peptide that assembled into carriers for doxorubicin, responded to glutathione and fluoresced in a way that let release be followed. Tang and colleagues cite a doxorubicin prodrug designed to remain assembled in blood and to release drug in response to the high glutathione level in tumour cells.[2,16]

5.4 Other stimuli and combined responses

Multi-stimulus designs allow tighter control but also make the carrier harder to make and to keep stable, a concern the authors raise directly.[2] DNA carriers can respond to pH, near-infrared light, glutathione, hydrogen peroxide and microRNA-triggered strand displacement.[11] Mi describes thermal-sensitive carriers designed to stay stable up to 37 °C and to respond above 40 °C, for example a liposome loaded with ammonium bicarbonate that generates carbon dioxide at 42 °C and swells to release its drug.[13] Tang and colleagues also describe ultrasound as a way of assembling nanodrugs, citing the acoustic assembly of doxycycline into nanoparticles with selective toxicity towards cancer cells in the study they report.[16] Temperature and light are also used as triggers, and some designs respond to more than one stimulus at once. Light offers an external trigger that does not depend on the tissue environment. In paclitaxel–indocyanine green nanoparticles held together mainly by van der Waals forces, laser irradiation broke up the assembly and released paclitaxel in situ, while the freed dye acted as a photothermal agent. Yazdani and colleagues address AI-assisted design and optimization of stimulus-responsive nanocarriers,[26,28] an approach that may help when several parameters must be balanced at once, although it is still a developing area.

5.5 Controlled release and personalised delivery

In all these systems the structure works as the switch: a carrier that is stable enough in circulation changes form on meeting a stimulus and lets go of the drug.[5,13] Release of this kind can concentrate the drug where it is needed, but a switch helps only if the trigger is stronger at the target than elsewhere, and a trigger that is also present in healthy tissue gives only partial selectivity. Whether stimulus-responsive release can also support personalised therapy depends on matching the stimulus to an individual patient's disease. Emadi and colleagues present smart self-assembling nanocomposites as a route to personalised, stimulus-responsive therapeutics.[2] Yazdani and colleagues see AI-assisted design as a way of tailoring such carriers.[28] Both are best read as aims, since the sources report little direct evidence of patient-specific design in practice. Liu and colleagues describe the broader goal as control over the timing and dose of release as well as its location.[18]

Table 3: Stimulus-responsive self-assembling systems.

Stimulus	Response mechanism	Expected outcome	Application	Ref.
Lower pH	Protonation of groups such as histidine; cleavage of acid-labile bonds	Swelling or disassembly; faster release	Tumour tissue and endosomal compartments	[2,7,13]
Enzymes	Cleavage of enzyme-sensitive	Release where the	Tumour and inflamed	[2,7,13]

	peptide or polysaccharide linkers; enzyme-triggered assembly	enzyme is abundant	tissue	
Redox (glutathione)	Reduction of disulfide bonds in the cell interior	Disassembly inside cells	Intracellular delivery of anticancer drugs	[2,7,13]
Temperature and light	Change in polymer behaviour or light-driven triggering	Triggered release; stability and storage need attention	Externally controlled release	[2,13]
Combined stimuli	Two or more triggers in one carrier	Tighter control of release	Complex disease environments	[2,11]

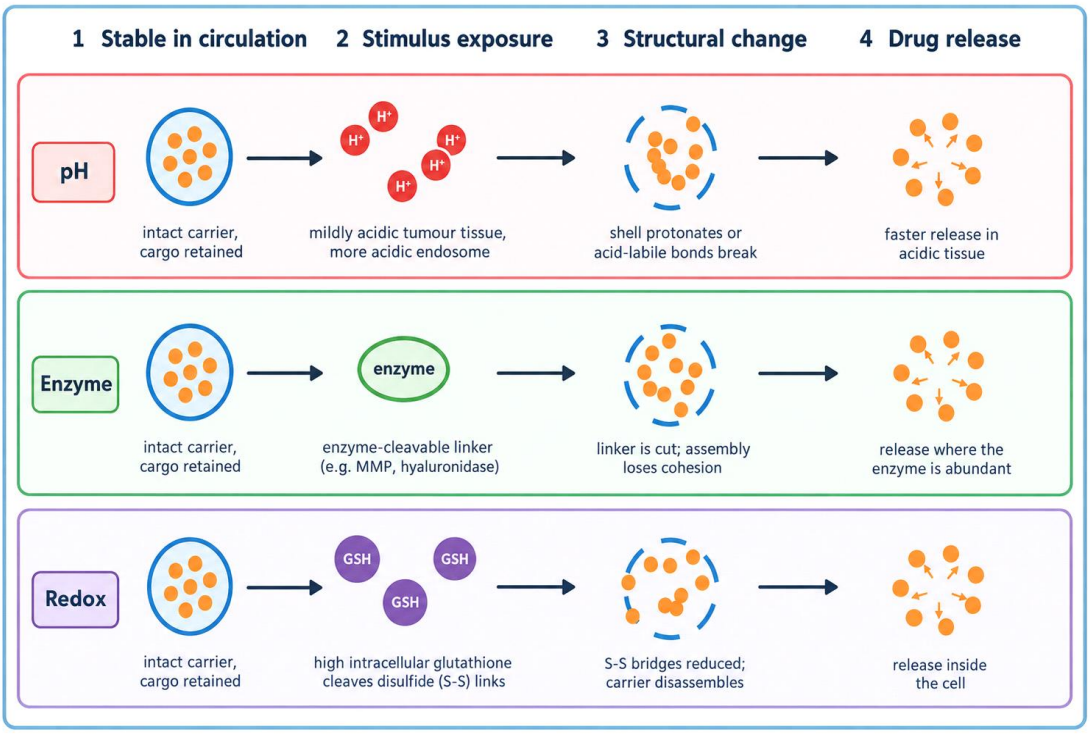

Figure 5: Stimulus-responsive drug release from self-assembled nanocarriers.

Stimulus-responsive drug release from self-assembled nanocarriers, Nanocarriers remain stable under physiological conditions but release their cargo in response to low pH, enzyme activity, or intracellular glutathione, enabling targeted drug delivery. Schematic illustration of the mechanism, not release kinetics; based on references.[2,5,7,13,16,18]

6. Targeted Drug Delivery

6.1 Passive targeting

Passive targeting relies on the enhanced permeability and retention (EPR) effect: leaky tumour vessels may let nanoparticles of suitable size enter the tumour and stay there. EPR-mediated accumulation may occur in some tumour models, but its size and clinical relevance vary a great deal between tumour types and between patients. The EPR effect is widely used as a design rationale, yet Kumar and colleagues remind readers that the design criteria for nanomedicines are still debated, that most cancer nanomedicines have failed to improve clinical efficacy, and that a universal platform seems unlikely: the best design is probably specific to the drug, the carrier and the cell type.[2,7] Mi gives 10–200 nm as the size range more likely to accumulate in solid tumours by passive extravasation.[13] Tang and colleagues contrast accumulation alone with systems that respond to signals such as acidic pH, overexpressed enzymes or glutathione, moving from passive accumulation towards controlled release at the target.[16] Guo and colleagues

describe the biological barriers a nanomedicine meets after injection as a sequence, so crossing the vessel wall is only one of several hurdles.[27]

6.2 Active targeting and receptor-mediated uptake

Active targeting adds a ligand that recognises a molecule on the target cell. Antibodies and antibody fragments against cancer cells have been used for this. Emadi and colleagues add receptor-mediated endocytosis and multi-targeting designs to the list.[2,6] Peptides such as RGD, which bind integrins, have been attached to peptide carriers, and nucleic-acid aptamers can act as targeting units. One example is the AS1411 aptamer, which binds nucleolin, a protein found in large amounts on tumour cell surfaces. In the mesoporous silica carrier of Li and colleagues the aptamer is attached to a polydopamine coating, and tumour fluorescence at 24 hours was strongest with the aptamer-modified particles, which the authors credit to a combination of passive EPR targeting and active aptamer targeting.[7,15] Safarkhani and colleagues show that AS1411 and a MUC1 aptamer are used on DNA origami, tetrahedra and ribbons, along with other ligands such as sgc8, Gint4.T and folic acid.[11] Mi describes a poly(lactic-co-glycolic acid) system in which RGD targeting and magnetic targeting each raised tumour accumulation about eightfold over passive targeting in a mouse model.[13] Multistage designs go a step further by combining targeting with structural changes at the target site.[27] Ligands add function, but each one is another component whose behaviour in the body has to be shown, and the examples above are preclinical.

6.3 Site-specific delivery and cellular uptake

Site-specific delivery can also come from the route of administration. Majumder and colleagues state that targeting combined with local administration can further improve efficacy and limit side effects. After arriving at the target tissue, the carrier must enter the cell and release its drug. In one peptide system, studied in cultured HeLa cells, the assembly bound to the membrane, entered the cell, released epirubicin in the acidic environment, and the drug then built up in the nucleus.[6,7] Emadi and colleagues describe a related idea in which nuclear localisation signals on micelles help carry nucleic-acid cargo towards the nucleus.[2] Intracellular trafficking is itself one of the barriers that shape clinical performance,[7,27] so uptake by a cell does not guarantee that the drug reaches its site of action show in (fig 6). Designs that change structure after arrival are meant to deal with part of this problem, and in one acid-responsive peptide carrier the change was linked to longer drug retention.[16]

6.4 Reducing off-target effects

The intended benefit of targeting is that less drug reaches healthy tissue. Peptide nanocarriers are said to limit drug accumulation in organs such as the kidney, liver and spleen, and targeted nanocarriers in general are reported to improve efficacy while limiting side effects.[6,7] Particle size plays a part: Đorđević and colleagues cite work in which a smaller diameter lowered liver and spleen accumulation and improved accumulation in the tumour.[9] Tang and colleagues state that self-assembly can reduce drug distribution in normal tissue and so lessen damage to normal cells.[16] These statements describe goals and laboratory observations. None of the sources shows that targeted self-assembled carriers have removed off-target effects, and the word 'precision' in this review should be read as a design aim, as defined in Section 1. Judging how far a carrier has met that aim needs biodistribution and safety data, which the sources report mainly for animal models. The balance between safety and efficacy also depends on how much drug is released outside the target, which ties targeting to stability: a carrier that dissociates early in blood may lose much of its targeting advantage.[22]

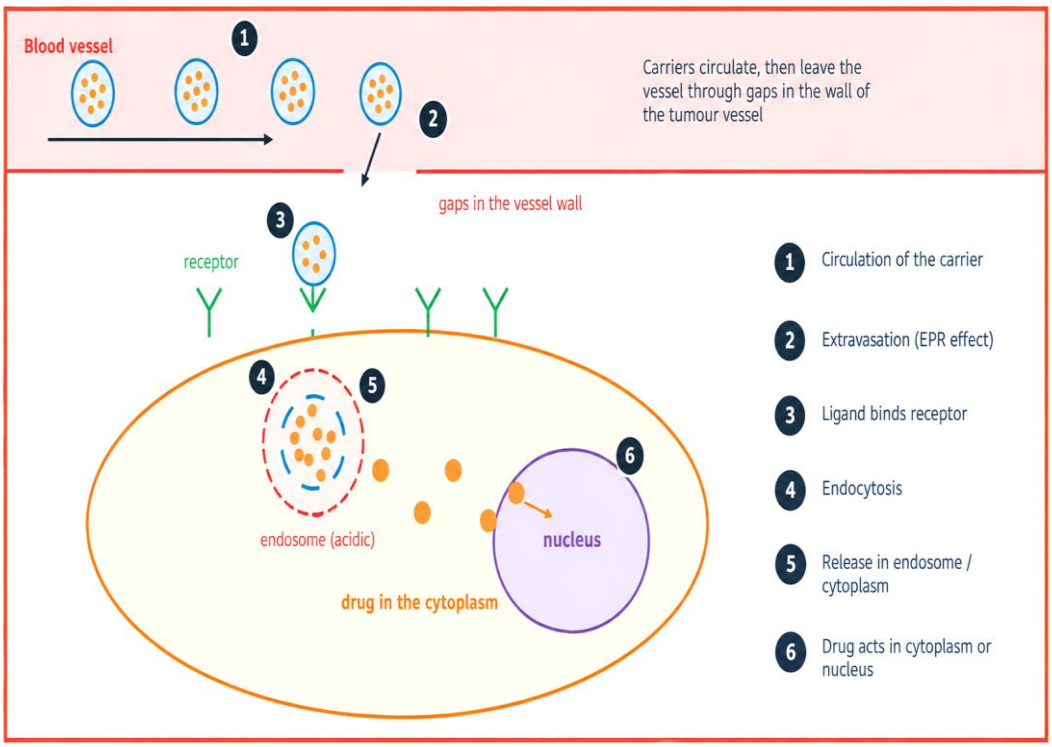

Figure 6: Targeted precision drug delivery by a self-assembling nanocarrier.

Targeted precision drug delivery by self-assembling nanocarriers Nanocarriers circulate in blood, accumulate in tumour tissue through passive targeting, bind to specific receptors via ligands, enter cells, release drugs intracellularly, and produce therapeutic effects. Schematic combining different delivery pathways; Based on references.[2,6,7,11,13,27]

7. Therapeutic Applications

7.1 Cancer therapy

Cancer is the most studied application. Peptide nanocarriers have been designed for anthracyclines such as doxorubicin and epirubicin and for 5-fluorouracil. One example in the review by Kumar and colleagues is a cyclic peptide carrying an RGD motif and epirubicin for oesophageal cancer, followed by near-infrared fluorescence.[7] Other peptide examples from a 2024 review include the amphiphilic peptide KLAK, which induces apoptosis by disrupting mitochondrial membranes, and a RADA16 hydrogel delivering tamoxifen that inhibited MCF-7 breast cancer cells.[17] Zhang and colleagues, who focus on carrier-free nanodrugs for cancer, describe DiR-DOX-PEG nanoparticles that combine chemotherapy and photothermal therapy, and a three-component nanodrug that joins a photosensitiser, an ASCT2 inhibitor and a PD-1/PD-L1 blocker. Li and colleagues built a mesoporous silica carrier coated with polydopamine and the AS1411 aptamer to deliver anti-miR-155 to colorectal cancer; the full construct inhibited the growth of subcutaneous SW480 tumours in mice, whereas free anti-miR-155 and the carrier without the drug did not. Tang and colleagues review self-assembled nanoparticles across chemotherapy, photodynamic and photothermal therapy, immunotherapy and gene therapy, and describe them as platforms for multimodal treatment.[14,15,16] Carrier-free examples include an injectable pure-drug cocktail with synergistic anticancer effects, and a paclitaxel–indocyanine green nanomedicine that combined chemotherapy with photothermal therapy in vitro and in vivo.[25,26]

Cancer immunotherapy is a separate application. Guo and colleagues review multistage self-assembled nanomaterials for cancer immunotherapy, organised around the biological barriers nanomedicines face, programmable delivery, in situ

transformable assemblies and immune-reprogramming nanomaterials. likewise list immunotherapy among the therapeutic modes in which self-assembled nanoparticles have been combined with other treatments. These reports describe mainly preclinical work, and the sources present immunotherapy applications as promising rather than established.[16,27]

7.2 Gene and nucleic-acid delivery

Nucleic acids are fragile and need protection. Safarkhani and colleagues review DNA nanostructures as vehicles for siRNA, antisense oligonucleotides, microRNA and Cas9/sgRNA, with release controlled by triggers such as microRNA-driven strand displacement, and describe peptide micelles with nuclear localisation signals and DNA-based structures for gene delivery.[2,11] The gene-targeting system of Li and colleagues delivers an anti-miR-155 oligonucleotide with an aptamer for tumour recognition. Tang and colleagues describe self-assembly in gene therapy as a way to protect fragile nucleic acids, prolong circulation and improve tumour targeting. Most reported examples, including the anti-miR-155 system above, are laboratory or animal studies, and the sources give no clinical evidence for self-assembled gene carriers. Tang and colleagues cite examples that include siRNA co-assembled with a zinc-containing framework to combine gene therapy with photothermal therapy, a CRISPR-Cas9 plasmid assembled with a modified polylysine for bladder cancer cells, and peptide–siRNA nanoparticles aimed at glioblastoma, all as preclinical reports.[11,15,16]

7.3 Protein and peptide delivery

Abdelhamid and colleagues review protein carriers built from natural cages and engineered proteins as vehicles for drug encapsulation and targeting. Ferritin loaded with cisplatin and attached to an antibody, for example, worked about 25 times better in melanoma cells than the unconjugated particle, and an anti-TNF fusion with an elastin-like polypeptide raised serum half-life 24-fold.[10] Emadi and colleagues discuss protein-based assemblies that protect therapeutic proteins, including insulin, from degradation. and DNA nanostructures have also been used to carry proteins such as thrombin and insulin. These reviews mostly treat peptides and proteins as building blocks of carriers. Delivery of therapeutic proteins and peptides as cargo is covered more thinly in the sources used here, apart from the insulin examples mentioned above.[2,11] The wider literature on peptide materials has been covered by Mandal and colleagues, and earlier by Branco and Schneider.[19,20]

7.4 Imaging and theranostics

Self-assembled carriers can carry imaging agents together with the drug. Kumar and colleagues describe fluorescent peptide systems in which drug release and accumulation can be followed in real time, and Zhang and colleagues describe GA-Ce6-FA nanoparticles, made from gambogic acid, chlorin e6 and folic acid, which allowed fluorescence imaging alongside chemotherapy and photodynamic therapy.[7,14] Chen and colleagues note that self-assembled systems have been developed for therapeutic and imaging agents together.[5] Indocyanine green illustrates the dual role: in the paclitaxel nanomedicine of Jiang and colleagues the dye was part of the assembly and, once released, acted as a photothermal agent for combined chemotherapy and photothermal therapy.[26] Tang and colleagues also describe a peptide nanocarrier with fluorescence properties that allowed the release of doxorubicin to be monitored.[16]

7.5 Other applications and the state of the evidence

A carrier-free system that contains celecoxib is described for anti-inflammatory use. Paliwal and colleagues mention self-assembled systems aimed at inflammatory cells Taken together, though most examples in the reviews are

laboratory or animal studies. Paliwal and colleagues state that some self-assembled products are in clinical trials or approved.[4,14] Tang and colleagues add that self-assembled nanoparticles have shown effects in tumour, antibacterial and anti-infective applications. Polymeric micelles are the class with the most clinical experience in the sources used here, with Genexol-PM, Nanoxel-M and Paclical on the market and others in trials.[16,23] Mi also lists stimulus-responsive carriers that have reached trials, including ThermoDox (liposomal doxorubicin, phase III in hepatocellular carcinoma), NC6300 (pH-responsive epirubicin micelles, phase I/II) and LiPlaCis (cisplatin liposomes sensitive to sPLA2, phase I/II).[13] Lagarrigue and colleagues point out that few non-spherical nanoparticles have reached clinical trials and that shape is hard to separate from size, surface chemistry and rigidity,[12] which suggests that translation of newer classes may also be slow.

Table 4: Therapeutic applications of self-assembling nanocarriers, as reported in the reviewed sources.

Application	Nanocarrier type	Therapeutic cargo	Targeting or release strategy	Reported outcome	Ref.
Oesophageal cancer (model)	Cyclic peptide–Zn(II) nanoparticle with RGD	Epirubicin	Integrin-binding RGD; EPR; fluorescence tracking	Tumour-directed delivery and imaging reported in preclinical work	[7]
Cancer cells in culture (HeLa)	Cyclic histidine peptide–Zn (II) assembly	Epirubicin	Self-encapsulation; release in acid	Nuclear accumulation of drug; loading about 15.7%	[7]
Colorectal cancer, gene therapy (mouse xenograft)	Mesoporous silica nanocarrier with polydopamine and AS1411 aptamer	Anti-miR-155	AS1411 binds nucleolin; EPR	Tumour growth inhibited in SW480 xenografts	[15]
Gene delivery	DNA nanostructures; peptide micelles	siRNA, antisense oligonucleotides, Cas9/sgRNA, DNA	Aptamers, nuclear localisation signals; strand-displacement release	Preclinical gene silencing reported	[2,11]
Protein delivery	Protein cages and fusion proteins	Therapeutic proteins such as insulin; chemotherapeutics in cages	Protection from degradation; disassembly and reassembly of cages	Reported in preclinical studies	[2,10]
Imaging and theranostics	Fluorescent peptide systems and carrier-free nanodrugs	Drug plus imaging agent	Real-time monitoring of release	Delivery tracked in model systems	[7,14]
Anti-inflammatory and anti-infective use	Carrier-free nanodrugs and self-assembled nanoparticles	Celecoxib; antibacterial agents	Not specified in detail	Listed as application areas	[14,16]

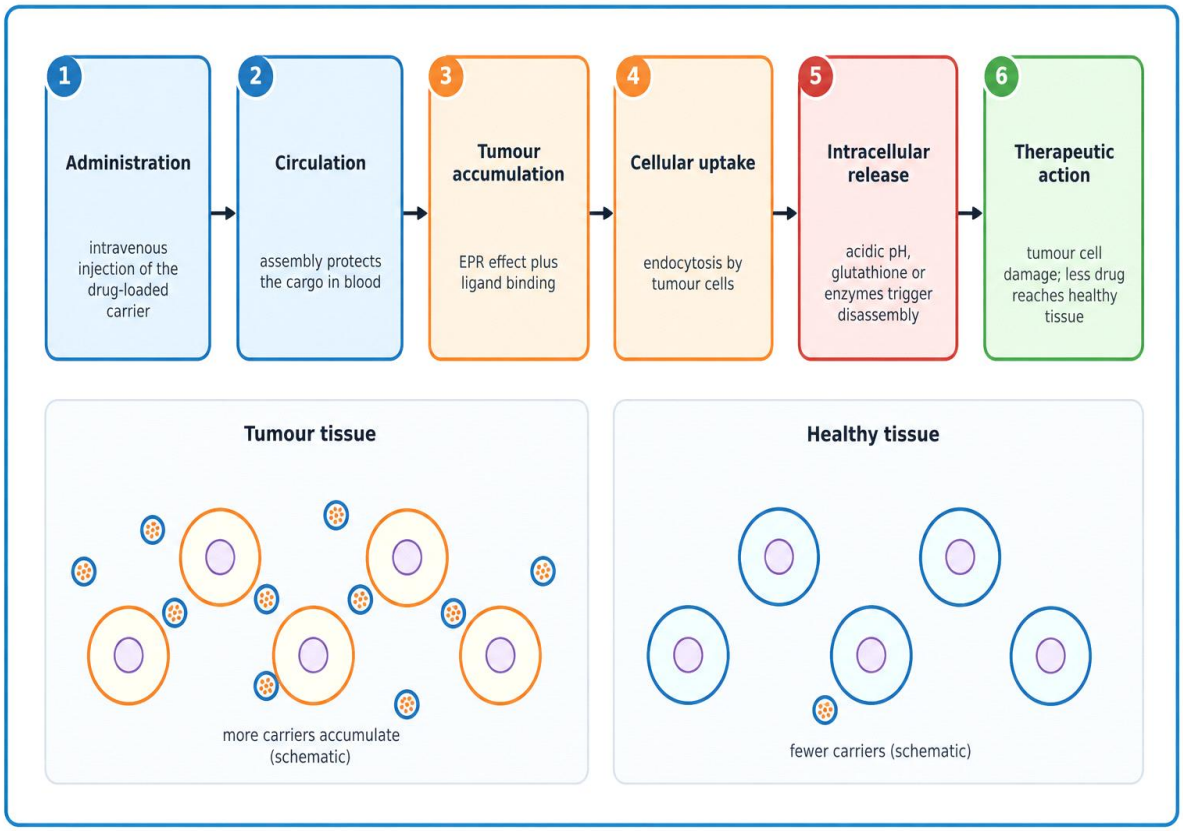

Figure 7: Self-assembling nanocarriers in cancer therapy.

Self-assembling nanocarriers in cancer therapy Nanocarriers travel from intravenous administration to tumour accumulation, cellular uptake, intracellular drug release, and therapeutic action, aiming to reduce exposure of healthy tissues. Qualitative schematic based on references.[2,6,7,13,14,16]

8. Role of Self-Assembly in Precision Drug Delivery

Molecular-level control: As defined in Section 1, precision in this review is a design objective and not a demonstrated clinical property. Within that limit, the strongest argument for self-assembly is that function can be written into the molecules. One amino acid change can switch a peptide from tubes to spheres. The caveat is that molecular structure does not fix biological behaviour by itself: the environment, the dose and the route of administration also matter, a pro-moiety can decide whether a prodrug assembles, a protein sequence can carry targeting and encapsulation functions,[3,7,10] and nucleic-acid strands can be fitted with targeting aptamers.[11] Tang and colleagues describe this as a relationship between structure, self-assembly and function, in which the behaviour of the assembly follows from the molecular structure. and even the protein corona that forms on a particle in vivo is hard to predict.[9,16]

Target specificity and controlled release: Targeting ligands and stimulus-sensitive links can be built into the assembly as part of its design.[11,13] Where the structure is itself the release switch, as in Section 5, targeting and release are linked: the carrier is built to open where it should. Multistage designs extend the idea by letting a carrier change form more than once, for example after reaching the tumour and again after entering cells, so that each barrier is met by a different property.[27] The carrier of Li and colleagues shows a combined approach in one construct: EPR-mediated

accumulation together with aptamer-mediated recognition.[15] The price of such sophistication is complexity, and complexity can make reproducible manufacture harder.[2,16]

Improved performance and fewer off-target effects: Carrier-free systems avoid carrier-related side effects,[1] and targeting aims to reduce accumulation in healthy organs.[6,7] Tang and colleagues report that self-assembled nanoparticles can combine high drug loading, stimulus responsiveness and a simple preparation without complicated carrier synthesis.[16] Better performance is still a potential and not a result established across the field. Most of the supporting evidence comes from cell and animal studies, and a fair assessment would also compare these systems with nanomedicines already in clinical use, including the polymeric micelle products.[23]

Personalised strategies: Emadi and colleagues point towards personalised design, and Kumar and colleagues suggest that the best nanocarrier depends on the drug and the cell type.[2,7] AI-assisted design is one proposed way of tailoring stimulus-responsive nanocarriers to specific needs.[28] Together, these views suggest that molecular tunability is the property that makes personalisation conceivable. It has not been shown clinically in the sources used here, and a personalised carrier would also have to be manufactured reproducibly, which the sources identify as a general difficulty for self-assembled systems.[2,9,16]

A comparison across building blocks: The classes differ in what they offer. Peptides give fine control through sequence, at the cost of more demanding synthesis for cyclic forms.[7] Proteins give modular function in a larger unit.[10] Small-molecule and prodrug systems give high simplicity but make the drug molecule do two jobs.[1,3,14] Nucleic acids give programmable assembly and many ligand and release options.[11]

9. Pharmacokinetic and Therapeutic Considerations

Drug loading: Carrier-free systems are interesting because the drug makes up most of the particle, and Nsairat and colleagues present this as a way to avoid the drawbacks of added carrier materials.[1] A review of carrier-free nanodrugs frames the idea as assembling active ingredients with little or no inert carrier.[14] Tang and colleagues likewise describe high drug loading and a simple preparation without complicated carrier synthesis as advantages of self-assembled nanoparticles, and the pure-drug cocktail of Chen and colleagues was assembled in a quantitative process.[16,25] Where a carrier is used, loading depends on the design; the cyclic peptide–Zn (II) system loaded about 15.7% epirubicin, while protein cages loaded by disassembly and reassembly reached only 3–4%.[7,10] High loading is useful only if the assembly stays stable and releases the drug in the right place, so loading should be read together with the release and stability data below.

Drug release: Release can be tied to a stimulus (Section 5) or controlled by the properties of the assembly. Wang and colleagues emphasise that the linker in a prodrug sets release kinetics.[3] In carrier-free nanodrugs the choice of bond matters: imine bonds are stable at pH 7.4 but hydrolyse quickly in acid, disulfide bonds are cleaved by glutathione, and some peptide linkers are cut by cathepsin B or MMP-2.[14] In DNA carriers, release is again controlled mainly through the trigger,[11] and in micelles it is tied to how long the assembly survives after dilution.[22] Tang and colleagues describe examples in which release was set off by acidic pH, enzymes, glutathione or light,[16] and Jiang and colleagues showed laser-triggered release from a paclitaxel–indocyanine green assembly.[26] Most release data come from in vitro measurements or animal models, and the sources report little release data from patients.

Stability and circulation: A carrier must stay intact long enough to reach its target. Circulation data from protein systems show what is possible: an elastin-like polypeptide fused to an anti-CD99 fragment formed worm-like particles that circulated for 16 hours, and an anti-TNF fusion raised serum half-life 24-fold.[10] Cyclisation can protect peptides from enzymatic breakdown,[7] and a PEG outer layer is described as a way to extend circulation in polymer systems.[2] For newer self-assembled systems built on weak interactions, in vivo stability is still described as an area that needs improvement.[16] For micelles, Lu and colleagues discuss what decides whether the assembly persists after injection and how it can be stabilised, for instance by cross-linking, where a diselenide-cross-linked micelle delivered 1.69-fold more drug to tumours than the non-cross-linked version, the polymeric micelle products on the market show that adequate stability can be reached in practice.[22,23]

Biodistribution and cellular uptake: Nanocarriers can be designed to reduce accumulation in the kidney, liver and spleen.[7] Đorđević and colleagues note that the structure of the protein corona is still controversial, because it varies in vitro and exchanges quickly in vivo, so what a particle meets in the body is not easy to predict.[9] Guo and colleagues describe the sequence of barriers a nanomedicine meets after systemic administration and present multistage self-assembled designs as a way of dealing with each in turn.[27] Cellular uptake is therefore only one step in a longer chain, and biodistribution measured in a mouse does not by itself predict distribution in patients.

Toxicity: Self-assembled carriers made without extra carrier material avoid carrier-related toxicity.[1] Systems with metal ions or inorganic components raise their own safety questions that need to be studied case by case.[2,15] Tang and colleagues describe low toxicity as an expected advantage of self-assembled nanoparticles, while noting that clinical data remain limited.[16] Biocompatibility is listed among the open challenges of self-assembling nanocomposites. Machine-learning and QSAR models for predicting nanotoxicity have been mentioned as a possible aid. Tang and colleagues cite an example in which a self-assembled nanoparticle was reported to be metabolised and cleared quickly, lowering the risk of long-term toxicity,[2,9,16] but such reports are specific to individual formulations and do not establish the safety of the whole class.

Advantages and limitations: The advantages named in the sources are structural tunability, the possibility of carrier-free formulation, built-in stimulus sensitivity and the ability to combine targeting with release.[1,5,13] The limitations are scalability, stability, storage, biocompatibility and regulatory approval,[2] together with the uncertainty about EPR-based targeting.[7] Tang and colleagues contrast traditional nanomedicines, which have mature processes and defined quality control but are limited by carrier toxicity and drug loading, with self-assembled nanoparticles, which offer higher loading and responsiveness but face difficulties in large-scale production, in vivo stability and early-stage clinical translation. Herdiana discusses how advanced formulation strategies bear on the clinical translation of nanoparticle systems.[16,24]

10. Clinical Translation and Challenges

The distance between laboratory promise and clinical use is the most consistent theme across the sources. Emadi and colleagues list scalability, stability, storage, biocompatibility and regulatory approval as the main hurdles for self-assembling nanocomposites.[2] Đorđević and colleagues look at the problem from the translational side. About 100 nanomedicines are approved worldwide, yet the road from bench to clinic is long: the RNAi lipoplex Onpattro received orphan designation in 2011 and was approved only in 2018. The review goes through manufacturing and scale-up, quality by design, safety and regulation, and notes that the success rate falls at each successive clinical phase in

oncology. Kumar and colleagues state that most cancer nanomedicines have not improved clinical efficacy and that few nanomaterial-based systems are in clinical trials. Tang and colleagues state that clinical translation of self-assembled nanoparticles is at an early stage, with few large confirmatory trials and limited public clinical data.[7,9,16] Herdiana reviews formulation strategies as a way of bridging the gap between nanoparticle design and clinical use.[24] Preclinical findings should therefore be kept apart from clinical evidence throughout this field.

Stability, reproducibility and manufacturing: Because self-assembly is spontaneous, the final structure can depend on small changes in conditions, so reproducible production and quality control are real concerns. Moving from laboratory batches to industrial volumes is described as a major challenge, whether the route is top-down (milling, high-pressure homogenisation) or bottom-up (liposome manufacturing, microfluidics).[2,9] Tang and colleagues note that antisolvent precipitation is simple but hard to reproduce, that microfluidic methods give more uniform size but are costly, and that simplified systems such as carrier-free prodrugs may be less sensitive to process variation. Carrier-free systems may also simplify composition and so quality control.[1,16]

Toxicity and safety: Inorganic components, metal ions and new materials need dedicated safety evaluation. Even where biosafety is discussed, as with the mesoporous silica carrier of Li and colleagues, the evidence comes from laboratory and animal studies.[2,15]

Biological barriers: Carriers have to cross extracellular and intracellular barriers before the drug can act. These include immune clearance, tissue penetration, endosomal trapping and trafficking.[7,27] Đorđević and colleagues add that the protein corona, whose exact structure remains controversial, shapes how a carrier behaves once injected.[9] Guo and colleagues describe these barriers as a sequence and argue that multistage self-assembled nanomaterials are more likely than conventional nanocarriers to cope with the complex tumour environment.[27] That argument rests on preclinical work and still has to be tested in patients.

Regulatory aspects: Regulatory requirements differ between regions, and designs that combine many functions may face more complex evaluation. Đorđević and colleagues describe how the 2011 European Commission recommendation gave the first EU definition of a nanomaterial but is not legally binding, how the FDA issued non-binding draft guidance for drug products containing nanomaterials in 2017, how the UK regulator assesses nanomedicines case by case, and how Japan published guidelines for liposome-based products in 2016; they also note that the ICH's International Pharmaceutical Regulators Programme is working towards harmonised frameworks.[2,9] This indicates that a carrier developed for one market may meet different requirements in another. The sources provide no specific regulatory pathway for self-assembled carriers, so the route for these carriers is still to be defined.

From laboratory to clinic: Paliwal and colleagues report that some self-assembled nanoproducts are in clinical trials or approved, and polymeric micelles are the clearest example of a self-assembled class that has reached the market, with Genexol-PM, Nanoxel-M and Paclical approved and NK012 and NK105 in trials. Stimulus-responsive carriers have also reached trials, such as ThermoDox in phase III for hepatocellular carcinoma.[4,13,23]

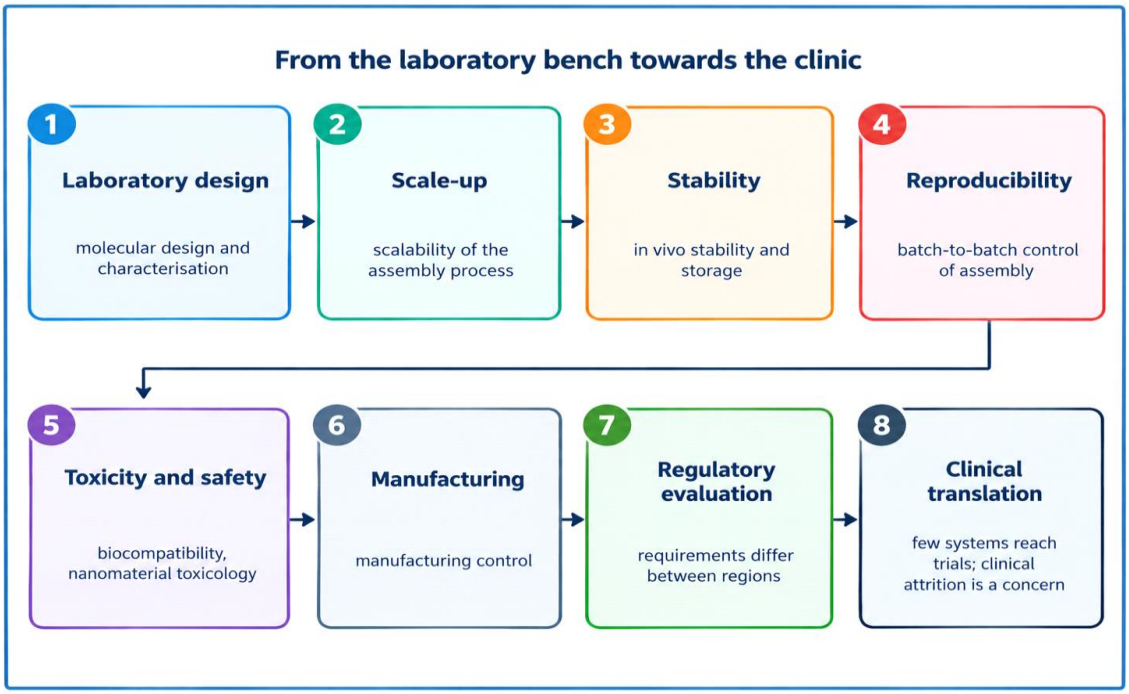

Figure 9: Challenges in clinical translation of self-assembling nanocarriers.

Challenges in clinical translation of self-assembling nanocarriers: Key barriers include scalability, stability, reproducibility, toxicity, manufacturing control, regulatory compliance, and clinical attrition. Based on references.[2,7,9,16,24]

11. Future Perspectives

Rational design supported by computation: Carriers on the order of micro and nanoscale, loaded with medications capable of targeting tumor areas, have a great deal of potential to address the difficulties in treating aggressive or resistant tumors. Higher tolerated dosages and reduced systemic toxicity can come from more favorable medication biodistribution, which can be achieved by effective targeting. Emadi and colleagues discuss AI guided design as a way to speed up development.[2,7] Yazdani and colleagues address AI-assisted design and optimisation of stimulus-responsive nanocarriers,[28] Đorđević and colleagues mention machine-learning and QSAR models for predicting nanotoxicity.[9]

Smart and multifunctional carriers: Mi describes stimulus-responsive nanocarriers that bring together delivery, imaging and therapy, and shows that targeting groups and stimuli can be combined, as with RGD and magnetic targeting.[13] Guo and colleagues describe multistage self-assembled nanomaterials that combine stimulus responsiveness, programmable delivery and immune modulation.[27] Emadi and colleagues likewise look at systems that combine several responses and functions, while warning that complexity must not cost stability.[2] Tang and colleagues stress that simplifying the assembly, for example with carrier-free prodrugs, may reduce sensitivity to process variation.[16]

12. CONCLUSION

Self-assembly turns the problem of drug delivery into a problem of molecular design. The forces holding a nanocarrier together are weak, and this is both the source of the approach's flexibility and its main difficulty: structures that respond

to a stimulus can also be sensitive to storage, dilution and the variability of the body. The reviewed literature shows a wide range of building blocks, with peptides and nucleic acids offering control at the sequence level, proteins offering modular function, and small molecules and prodrugs offering carrier-free simplicity. Evidence for better targeting and release is mostly preclinical. The critical voices in the sources, especially on the EPR effect and on clinical attrition, are a useful corrective to optimistic language. The most credible next step is not yet another carrier class but better integration of design, responsiveness and targeting, tested in models that resemble patients and made by processes that can be reproduced. Keeping molecular design, self-assembly, morphology, biological behaviour, therapeutic outcome and clinical translation apart as separate levels of evidence is what allows the strengths of the field, and its gaps, to be judged fairly.

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