Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal of Controlled Release 329 (2021) 552–569

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Biomedical nanoparticle design: What we can learn from viruses

Sara Maslanka Figueroa [1], Daniel Fleischmann [1], Achim Goepferich [*]

Department of Pharmaceutical Technology, University of Regensburg, Universitaetsstrasse 31, 93053 Regensburg, Germany

ARTICLE INFO

Keywords:
Nanoparticles
Virus-mimetic
Targeting

ABSTRACT

Viruses are nanomaterials with a number of properties that surpass those of many synthetic nanoparticles (NPs) for biomedical applications. They possess a rigorously ordered structure, come in a variety of shapes, and present unique surface elements, such as spikes. These attributes facilitate propitious biodistribution, the crossing of complex biological barriers and a minutely coordinated interaction with cells. Due to the orchestrated sequence of interactions of their stringently arranged particle corona with cellular surface receptors they effectively identify and infect their host cells with utmost specificity, while evading the immune system at the same time. Furthermore, their efficacy is enhanced by their response to stimuli and the ability to spread from cell to cell. Over the years, great efforts have been made to mimic distinct viral traits to improve biomedical nanomaterial performance. However, a closer look at the literature reveals that no comprehensive evaluation of the benefit of virus-mimetic material design on the targeting efficiency of nanomaterials exists. In this review we, therefore, elucidate the impact that viral properties had on fundamental advances in outfitting nanomaterials with the ability to interact specifically with their target cells. We give a comprehensive overview of the diverse design strategies and identify critical steps on the way to reducing them to practice. More so, we discuss the advantages and future perspectives of a virus-mimetic nanomaterial design and try to elucidate if viral mimicry holds the key for better NP targeting.

1. Introduction

Biomedical nanomaterials for therapeutic or diagnostic applications face myriads of obstacles upon administration. As soon as particles are exposed to biological media, they are subjected to protein adsorption on their surfaces. The resulting protein corona [1] affects not only their stability [2] but also their toxicity [3], targeting capabilities [4] and clearance [5], and thus, may become a handicap for their efficacy. Additionally, depending on their intended application and route of administration, they have to overcome complex biological barriers [6]. Examples are the blood-brain barrier (BBB) in cerebral disease or the mucus and epithelial barrier following oral or pulmonary administration. Additionally, nanomaterials are required to specifically identify their targets among a plethora of off-target cells to fulfil their therapeutic objective and avoid deleterious side effects. Furthermore, the cellular membrane is an additional impediment that hinders nanoparticles (NPs) from freely entering the intracellular compartment. Even once this obstacle is overcome, particles are required to escape from endocytic vesicles to release their cargo or further disseminate to distinct organelles. Viruses in contrast, are nanosized particles that are exceptional at overcoming these impediments. To perpetuate their life cycle they are able to cross even complex biological barriers, evade immune-mediated clearance and specifically recognize and invade their host cells [7]. Subsequently they are able to replicate and eventually be disseminated from one cell to another. Especially due to the latter two characteristics, most viruses would not necessarily depend on a maximum infectivity or a quantitative target accumulation. However, natural evolution has shaped many virus-types to develop remarkable strategies to overcome above mentioned obstacles that they are facing during various stages of their host infection (Fig. 1).

Several distinct viral traits have been identified as the source of these abilities, such as their morphology, surface characteristics, like roughness, glycosylation or charge, their stimuli responsiveness, and their interactions with cellular receptors. Virus-based delivery systems that inherit these properties to some extent, such as viral vectors or virus-like particles, also hold great biomedical potential but are frequently associated with considerable safety concerns [8,9]. Therefore, over the years, research has deeply focused on implementing favorable viral

* Corresponding author.
E-mail address: achim.goepferich@ur.de (A. Goepferich).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jconrel.2020.09.045
Received 29 June 2020; Received in revised form 24 September 2020; Accepted 25 September 2020
Available online 30 September 2020
0168-3659/© 2020 Elsevier B.V. All rights reserved.

properties into nanomaterials to improve their performance. Thereby, synthetic NPs appear as a safer and more versatile option. They additionally facilitate the incorporation of multiple different cargos for a broad spectrum of applications and have clear advantages regarding production, storage and reproducibility [10].

In this review we give an overview of the viral traits adopted in targeted nanomaterial design to improve NPs' efficiency. Starting with simple structural characteristics and ligand display, and ending with more complex attributes, such as the sequential interaction with surface receptors, stimuli responsiveness or cell-to-cell spreading. We critically examine the advances that viral mimicry has enabled for targeted nanotherapy and outline pivotal design parameters that must be considered for a rational NP optimization. Finally, we discuss the latest trends and outline future perspectives for the virus-like nanomaterial design.

2. Structural characteristics

2.1. Morphology

Viruses are nanosized entities of about 20–200 nm (with the 400 nm Mimivirus being the largest one described to date) [11]. There is little research on the effects that size has on the viral life cycle. However, it is known that it is related to the length of the genome the virus is enclosing [12]. This can be also related to nanomaterials, as there are spatial constrictions that determine their cargo loading [13]. However, a nanomaterial's size is a fundamental parameter determining its suitability for concrete applications. For example, for the extravasation to specific tissues, the NP size must be under a (patho)physiologically determined cutoff [14,15]. More so, a particle's size determines its blood residence, clearance [16–18], and interaction with the immune system [19–21].

Viruses come in various shapes and forms, such as polyhedral, rod-like, or filamentous, which bestow them with distinct biodistribution and targeting properties [22]. For example, it has been shown that the filamentous form of the Influenza virus has a higher specific infectivity than their spherical virion counterparts [23]. Mimicking this morphology with synthetic filamentous NPs could be a viable option for an efficient drug delivery *via* inhalation. [24] Due to their rod-shaped form, filamentous NPs would thereby prevent phagocytic internalization and - *via* paracellular translocation through the air-blood barrier - enter blood circulation, where they have been shown to possess a prolonged circulation time as well [25]. A rod shape is also associated with higher virus diffusion rates in tumor tissue [26], and can be mimicked with synthetic NPs by techniques such as the *co*-assembly of polyanions and artificial virus capsid proteins [27], the condensation of DNA and block copolymers [28], or the seeded growth synthesis of gold NPs [29,30]. A polyhedral virus shape has been linked to a high targeting specificity [31], a very sought after property for targeted NPs. However, despite the influence that a NP's geometry has on its blood residence, biodistribution and cellular uptake [32], most therapeutic NPs still are designed in a spherical shape, as their straight forward preparation is of advantage [15]. Nevertheless, the new accessible methodologies that are being developed to achieve a higher variety of shapes, such as the use of self-folding polymers to produce polyhedral particles [33], provide new platforms that may ease future particle shape optimization.

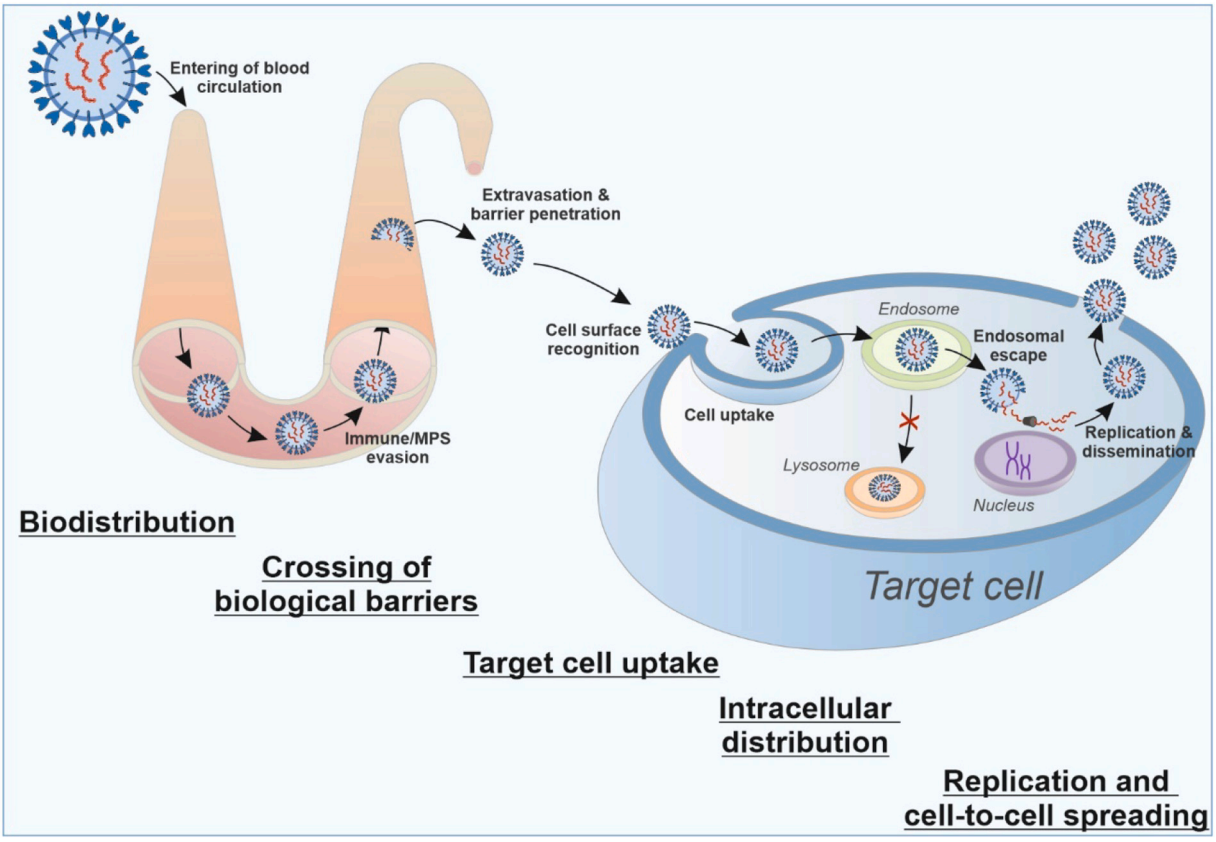

Fig. 1. Viral strategies to overcome obstacles in biological media. During the viral host infiltration, virus particles initially have to enter blood circulation and/or their respective site of interest, whereas an excessive immune recognition has to be evaded and further physiological barriers such as the BBB need to be overcome. After a subsequent target cell attachment *via* cell-selective recognition sequences, viral endocytosis or membrane fusion is initiated. Having entered the target cell, viruses can prevent lysosomal degradation *via* a stimuli-responsive escape from early endosomes, followed by a release of the viral genome, its replication and translation into novel virus particles and their final dissemination from the host cell.

2.2. Surface properties

The surface of viruses [34] is crucial for the infection process, as it determines their interaction with the surrounding medium and distribution to specific compartments, such as the central nervous system [35]. The mimicking of viral surface properties can enhance the cellular interaction of synthetic NPs. Especially the characteristic surface roughness of spiked enveloped viruses is usually associated with a higher infectivity and enhanced cellular internalization [36].

Interestingly the same effects of increased targeting and cell penetrability were seen when spikes were introduced on the surface of NPs. This has been demonstrated with inorganic materials, such as silica- [37] or Au@Ag- [38] NPs but also with fluorinated peptide dendrimer-based polymer vectors [39] and carrier-free polyethyleneimine (PEI)/DNA nanosystems [40]. In all cases a higher cellular endocytosis and enhanced cargo delivery was observed, indicating that surface roughness is a highly important design parameter leading to the success of nanomaterials.

Furthermore, it was recently linked to a quicker NP-cell interaction [41]. Mesoporous silica nanospheres surrounded by spike-forming mesoporous nanotubes were able to strongly interact with their target cells after only 5 min incubation, in contrast to non-functionalized spherical particles, which required extensive cell contact [41]. Furthermore, the spikes changed the particle internalization route from a clathrin-mediated endocytosis for non-functionalized particles, to a combination of caveole-mediated endocytosis and macropinocytosis.

Synthetic spikes can also be constituted by targeting ligands themselves, as it was shown by the formulations developed by Liu et al. [42] and Xu et al. [43]. The former developed lentivirus mimicking NPs displaying Zn-dipicolylamine analogue-spikes, a zinc coordinative ligand with high affinity to phosphate moieties on cell membranes [42]. The latter, imitated coated viruses, such as influenza or herpesvirus (HV), by displaying transferrin (TF) spikes on the surface of their liposome-DNA complexes [43]. In both cases the spikes were able to bind the cell membrane and mediate internalization. Additionally, spikes conferred endosomal escape abilities through membrane destabilization [42] or a higher *in vivo* stability and gene transfer [43], respectively, compared to non-functionalized particles.

A typical viral characteristic is surface glycosylation [44]. In some cases, such as for the influenza virus, glycosylation is essential to enhance cellular internalization [45] and in others, such as for the human immunodeficiency virus (HIV), it is crucial for the evasion of excessive immune recognition by preventing the attachment of neutralizing antibodies [46]. For synthetic NPs there seems to be contradictory evidence regarding the influence of glycosylation on immune activation, and it is often viewed as an obstacle for the generation of an adequate immune response. However, Tokatlian *et. al* [47] recently highlighted that adjusting the NP immunogen glycosylation is critical for vaccine design, as they demonstrated that deglycosylation significantly affects antibody response. Mannose presentation on self-assembling ovalbumin carrying NPs was also associated with a higher *in vivo* immune response compared to non-glycosylated NPs [48]. Regarding the efficiency of NP-cell interactions, glycosylation is generally considered an improvement in NP design. Pinnapireddy et al. [49] mimicked enveloped viruses with glycosylated anionic liposomes prepared from lipids found in the envelopes of HIV and herpes simplex virus (HSV). The formulation, intended for gene delivery, achieved an increased particle internalization through lectin receptors [50]. Also, the addition of mannose to cationic albumin NPs allowed for an enhanced brain targeting and *in vivo* glioma treatment [51]. As for viruses, which ideally possess an optimal glycosylation balance that "shields" from the immune system but still allows efficient receptor binding [52], virus-mimetic NP approaches likewise need to be manufactured with respect to these factors. While nanoparticular vaccine approaches would generally benefit from an adequate immune response, drug delivery approaches using virus-mimetic nanomaterials could be severely limited by an excessive recognition *via* the immune system. Especially in the latter case, incorporation of additional surface elements such as glycosylation or also specific targeting sequences to more realistically mimic viral particles always bears the risk of an undesirable immune recognition and should therefore be exactly tailored for each formulation in accordance with its physicochemical characteristics and the intended application.

Once particles enter biological media, they are subjected to protein adsorption and the formation of a protein corona. For viruses, several host factors indispensable for infectivity can attach to their surface, like Apo-E lipoprotein for hepatitis C virus (HCV) [53]. A recent study that evaluated the protein corona formation on respiratory syncytial virus and HSV type-1 when incubated with different bodily fluids showed that the surface properties of the virus were responsible for determining the enrichment with different corona elements [54]. Furthermore, the fluid from which the proteins proceeded, determined the corona composition, which in turn affected the viral infectivity. However, viral and NP corona formation may be quite different, due to the diverging surface materials and compositions. Additionally, the attachment of a protein corona to the particle surface is oftentimes followed by an undesirable NP clearance *via* the mononuclear phagocyte system (MPS), which has been identified as one of the major obstacles for a successful NP targeting [55]. While numerous approaches try to avoid this impediment by manufacturing so-called "stealth" NPs with additional surface coatings such as PEGylation [56], viral particles may be subjected to a generally reduced protein corona formation. In this regard, Pitek et al. [57] discovered that after plasma incubation, virus particles derived from the tobacco mosaic virus bound 6-times less protein than synthetic NPs. The authors associated this with the display of positive and negative charge patches on the viral particles in combination with hydrophobic and hydrophilic domains. Recently, our group also showed that zwitterionic polymeric NPs adsorbed less protein when incubated in serum compared to positive, negative or uncharged particles, as it provides less domains allowing for hydrophobic or electrostatic interactions [2]. This is in accordance with previous studies that demonstrated that the protein binding suppression of such materials is due to their ability to electrostatically bind great amounts of water molecules [58–60]. Therefore, in addition to the typically implemented strategies used to suppress protein corona formation, such as above-mentioned PEG coating, an adjustment of the surface charge of particles, imitating the charged but net-neutral viral surface, must be considered. Furthermore, a virus-like exploitation of the protein corona may enhance the targeting abilities of NPs, as recently reviewed by Maiolo and coworkers [61].

Close mimicking of the viral surface has also been extremely useful to achieve mucus-penetration. Surface characteristics that allow viral particles to overcome the mucus barrier are a charged but net-neutral surface and a hydrophilic nature [62]. It has been demonstrated that particles that hold these features are able to overcome the mucus barrier [63], making them appropriate vehicles for oral [64] and vaginal drug administration [65]. However, the combination of these surface properties with a virus-like active targeting has been shown to further increase the penetrability of nanomaterials, which is especially interesting for the oral insulin delivery. Liu et al. [66] were able to overcome the mucus barrier with polyelectrolyte complexes mimicking the viral envelope, composed of polysaccharides, peptides and lipids, with L-Phenylalanine-functionalized chitosan polymers. The authors found that functionalized polymers yielded a 2-fold higher bioavailability than non-modified particles. Zhu et al. [67] demonstrated that active targeting can be used to surmount not only the mucus- but also the epithelial absorption barrier. They functionalized polymeric insulin carriers with poly(ethylene glycol) (PEG)-shielded poly-arginine which was able to mediate epithelial cell penetration and produce hypoglycemia *in vivo*. They further demonstrated the particle safety [68] and expanded on their mimicry concept implementing the densely charged but net-neutral surface of viruses [69]. In this manner the NPs displayed the distinct viral attributes needed to overcome not one, but two

barriers.

Viruses are meticulously built systems in that every component holds an exact function. This promotes their paramount goal of delivering their genetic content into host cells. The success of this endeavor strictly depends on a perfect interworking of all constituents. Size, shape and surface properties are apparently simple elements of particle design. However, they can have enormous influence on a particle's cellular interaction and biodistribution [70]. Mimicking the viral morphology and surface characteristics can lead to faster and greater NP-cell interactions and even bestow barrier penetration abilities. Therefore, the structural replica of a virus must be considered the first step when trying to achieve viral traits on synthetic NPs (Fig. 2).

3. Ligand display and cell recognition

To promote the infection of the host-cell, viruses usually display surface components that bind to specific cell membrane structures. Usually an initial attachment through the interaction of membrane glycoproteins or viral capsid sites with factors, such as heparan sulphate proteoglycans [7], is followed by the binding of viral ligands to cell surface receptors that are distinct for each virus [71]. This specific interaction leads either to endocytosis, to the activation of signalling pathways promoting internalization, or to the induction of conformational changes on the virus, which promote fusion and cellular penetration [71]. The targeting of specific receptors has been widely implemented on NPs, not only to achieve the crossing of cellular membranes but also to endow particles with a higher specificity towards distinct cell types.

3.1. Multivalent display of ligands

The multivalent ligand display is one of the viral attributes that has had the most impact on the field of targeted nanomaterials. Viruses present numerous copies of the same ligand on their surface, which allows them to interact with multiple receptors on the cellular surface (Fig. 3). It is broadly accepted that mimicking the viral multivalent ligand display improves a NP's target cell-recognition. Generally, the tethering of ligands to the NP surface is associated with an affinity loss of the individual ligands, which is compensated by the binding of several receptors simultaneously [72]. This has led to enhanced targeting through avidities in the nano- [73] or even picomolar range [74].

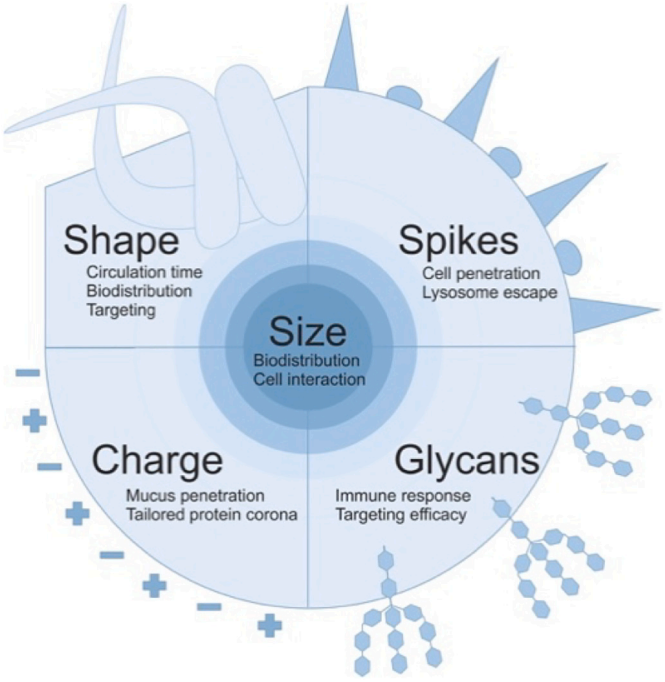

Fig. 2. Structural viral properties and their effects on synthetic NP design.

3.1.1. Multivalent display of virus-derived ligands

A frequently used design approach to mimic the viral targeting principles is the decoration of NPs with natural viral surface "ligands", like attachment factors, cell penetrating peptides, fusion-proteins, and antigen-derived peptides (Table 1). Viral surface antigens tethered to NPs are mainly of interest in the field of vaccine development which will not be addressed here, as they are outside of the scope of this review and have extensively been reviewed elsewhere [75,76]. In this section, we will focus on systems displaying viral surface molecules seeking an increase in target cell recognition for drug delivery, with diagnostic or therapeutic purposes.

During the initial phases of cell entry, viruses make use of attachment factors that anchor them to the host cell membrane. Despite it being a low-affinity binding, it is of importance in the viral cycle, as it aids receptor recruitment [77]. Furthermore, its inhibition can suppress the infection process [78]. Almost three decades ago, Rubas et al. [79] discovered that modifying liposomes with the reovirus M cell attachment protein σ1 increased their cellular uptake *in vitro* by 10-fold compared to non-targeted formulations. Also, the recent identification of a new heparin-binding domain, pre-S1(30–42), of hepatitis B virus (HBV) involved in initial virus attachment enabled the development of virus-mimicking liposomes for the specific identification of human hepatic cells [80]. Interestingly, particles functionalized with the attachment peptide were able to deliver doxorubicin (DOX) to hepatic cells more efficiently than liposomes functionalized with the peptide associated with viral targeting, *i.e.*, pre-S1(2–47) [81], corroborating the immensely important role of attachment in viral infectivity.

Viral surface antigens can also be used for the targeting of specific cell types. Somiya and Kuroda [82] developed a HBV-mimetic nanocapsule using the hepatitis B surface antigen L protein for specific drug delivery to human hepatocytes. To overcome the elicitation of an immune response resulting from the repeated administration of viral antigens on the surface of NPs, they made use of an additional viral trait, which is the ability to mutate [83]. To that end, the Gln-292 and Gly-302 were substituted with Arg, suppressing the immunogenicity of the formulation [84], which is indispensable for repeated administrations.

Additionally, viral surface ligands can be used to overcome barriers which normally present a huge difficulty for nanocarriers, such as the BBB. In this regard, a small peptide derived from the rabies virus (RABV) glycoprotein (RVG), RVG29, that interacts with high specificity with the cell entry-mediating neuronal nicotinic acetylcholine receptor, was used by several authors as targeting entity to enable BBB crossing. It was coupled to polymeric PEG-poly(lactic acid) (PLA) NPs to increase the BBB penetration of deferoxamine, an iron chelator used to protect against oxidative damage [85]. A higher BBB crossing of the drug enabled by this formulation prevented neuron damage and neurobehavioral deficits in mice with no systemic adverse effects. RGV29 was also grafted onto calcified calcium carbonate- and DOX-containing polymeric PLGA NPs to address brain tumors [86]. After ligand-mediated uptake, the calcium carbonate contained in the particles generated carbon dioxide gas upon acidification, increasing DOX release, and achieving tumor size suppression in a mouse model. Lee et al. [29] also used RVG29 to develop a nano formulation for the treatment of brain tumors based on silica-coated gold nanorods.

During infection, viruses present different proteins and peptides that aid cell penetration. Several cell penetrating peptides (CPPs) used in active targeting [87] are derived from viral capsids [88], such as the HIV [89] and the Brome mosaic virus [90]. One of the most commonly used CPPs is the HIV derived trans-activating transcriptor (TAT) peptide [91]. It has been used to decorate the surface of several different nanomaterials, such as silica- [92,93], magnetic- [94,95], Au- [96,97], lipid- [98], and polymeric NPs [99–101], among many others, to accomplish

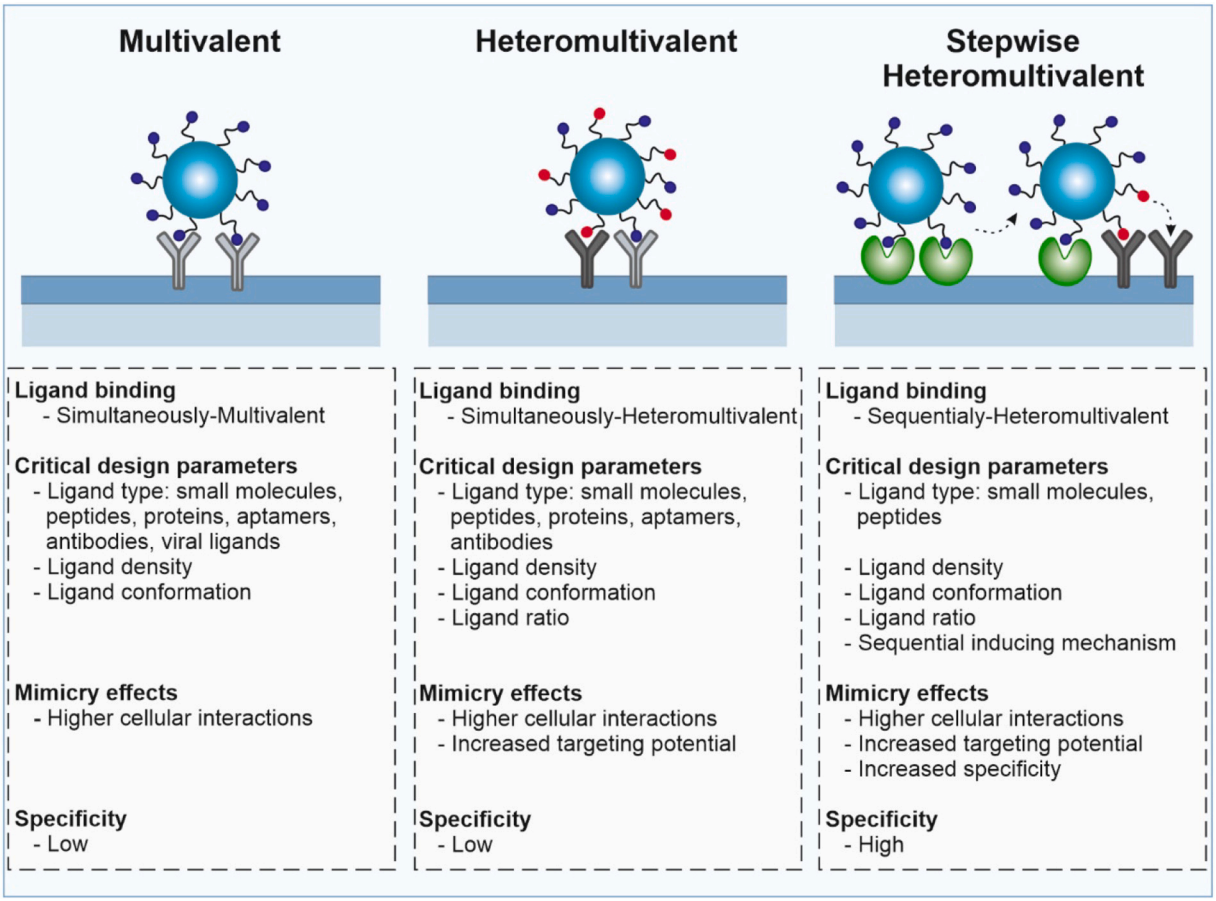

Fig. 3. Comparison of virus-mimetic ligand presentation approaches on synthetic NPs.

Table 1
Examples of viral ligands used for nanomaterial targeting.

Viral ligand	Targeting element	Function	NP	*In vivo*	Therapy/Cargo	Ref.
Attachment factor	Reovirus M cell attachment protein σ1	Higher cell uptake	Liposomes	–	–	[79]
	HBV heparin binding-domain	Hepatic cell targeting	"-"	–	DOX	[80]
	HBV heparin binding-domain	Higher cell uptake	"-"	Mouse	Lipopeptide	[81]
Surface antigens	HBV surface antigen L protein	Hepatic cell targeting	Bionanocapsule	–	–	[82]
	Modified HBV surface antigen L protein	Hepatic cell targeting/reduced immunogenicity	"-"	Mouse	DNA	[84]
	RVG29	BBB crossing	PEG-PLA NPs	Mouse	DFM	[85]
	RVG29	"-"	PLGA NPs	Neuroblastoma (mouse)	DOX	[86]
	RVG29	"-"	Silica-coated gold nanorods	N2a brain/side flank tumor (mouse)	Photothermal therapy	[29]
CPPs	TAT	Nuclear targeting	Mesoporous silica NPs	–	DOX	[92]
	TAT	Bioimaging	Silica NPs	Rat	–	[93]
	TAT	"-"	Superparamagnetic NPs	Mouse	–	[94]
	TAT	Tracking and recovery of progenitor cells	"-"	Mouse	–	[95]
	TAT	Cell membrane binding	Au NPs	–	–	[96]
	TAT	Nuclear targeting	"-"	–	–	[97]
	TAT	BBB crossing	PEG-b-cholesterol NPs	Rat	CPFX	[98]
	TAT	"-"	PLA and PLGA NPs	Mouse	Ritonavir	[101]
	TAT	Cancer treatment	Polymeric micelles	MDA-MB-435/LCC6MDR1 tumor (mouse)	siRNA/DOX	[100]
	TAT	Protein delivery	Supramolecular NPs	–	Transcription factor	[99]
Viral fusion protein	Parainfluenza fusion protein	Cancer targeting	Fusiogenic vesicles	–	–	[102]
	Phage fusion protein pVIII	"-"	Ag@Au nanorods	–	Photothermal therapy	[38]

cell or nucleus penetration and BBB-crossing for diagnostic and therapeutic purposes.

Lastly, ligands inducing viral fusion can also be grafted onto NPs. Gao et al. [102] functionalized parainfluenza virus envelope-mimicking fusiogenic vesicles with hemagglutinin-neuraminidase protein and the viral fusion protein, which bind sialic acid-containing receptors and initiate fusion, respectively. After fusion, the molecular beacons contained in the NP target miRNAs and generate a quantifiable fluorescence signal, which can be applied in exosome mRNA detection and cancer diagnosis. Wang et al. [38], took advantage of a phage fusion protein, pVIII, and prepared phage-mimetic rod-shaped NPs self-assembled from Ag@Au nanorods for specific targeting and photothermal therapy. The fusion proteins allowed for a specific colorectal carcinoma cancer cell targeting and ablation. Interestingly, the assembly of the phage proteins on the NP surface was achieved through electrostatic interactions, a coupling which is usually mediated by covalent bonds. However, this allowed the pVIII protein to maintain its natural conformation and orientate itself outwards, facilitating targeting.

Taken all together these results show that by isolating viral ligands and displaying them on NPs we are not only able to enhance important NP characteristics, such as targeting, penetration, and barrier crossing, but also shed some light on their involvement during viral infection.

3.1.2. *Multivalent display of non-viral ligands*

To direct nanomaterials towards specific cell types, particles can also be decorated with whichever ligand that targets physio- or pathologically surface receptors on the cell of interest (Table 2).

Multivalent NPs have been used to target G protein-coupled receptors (GPCRs) [73,103,104], integrins [105,106] and lectin receptors [107] with ligands such as peptides or proteins, aptamers and small molecules [108]. But, even though the virus-like ligand display seems like an easy enough concept to be reproduced with synthetic materials, it is noteworthy to mention that several distinct parameters have an influence on the success of a multivalent NP. One of the most relevant ones is ligand density, which is frequently neglected in nanomaterial design. In their excellent recent review Alkilany et al. [109] calculated the number of ligands displayed by viruses on their surface. Depending on the virus, they obtained a range between 7 and 659 ligands per virus particle. Interestingly, this number is usually greatly exceeded in synthetic NPs, where sometimes thousands of molecules are tethered to a single NP. More so, results show that the optimal ligand density is a unique characteristic for each formulation. In some cases, a minimum threshold needs to be surpassed to induce targeting effects. For example, for folate-functionalized NPs, a ligand density over 10% was needed in order to exceed the internalization of non-targeted particles [110]. In other cases, an optimum ligand density may exist, its alteration leading to a decrease in targeting. Fakhari et al. [111] demonstrated that a medium (50%) cLABL density on poly(lactic-*co*-glycolic acid) (PLGA) NPs achieved the optimum targeting of ICAM-1 expressing cells. Lower or higher ligand densities resulted in a poor particle uptake. Similarly, Elias et al. [112] found that an intermediate ligand density was optimal for targeting purposes using antibodies against HER2/neu, overexpressed in cancer cells. Generally, decreases in targeting with higher grafting densities are explained by a steric hindrance of the ligands and decreased ligand mobility [113]. This may disrupt interaction with the receptors to a point where their internalization is impeded. Another scenario is presented when a targeting plateau is reached above a certain ligand density. Poon et al. [114] showed that low ligand densities (20% folate density) were ideal for their system and higher functionalization did not enhance targeting. Lastly, there are systems where an increase in ligand number results in a continuous enhancement of NP targeting efficiency, which is frequently detected for RGD-ligands [115,116]. Therefore, it is essential to carefully and individually adjust the number of ligands on the particle corona for each system.

An additional factor to be considered for the multivalent NP design is the ligand conformation. Viruses often display ligands with defined conformations and regular spacings. This is the case of adenovirus, which presents RGD clusters [117] on five penton base proteins with a 5.7 nm spacing [118], indispensable for viral infection [119]. RGD ligands are also one of the most frequently used candidates for targeting purposes, as integrins are expressed in both tumor- and tumor endothelial cells [106]. Using adenovirus physical structure as a guide, Ng et al. [120] studied the influence of the ligand clustering on the targeting efficiency. RGD ligands were tethered to Au NPs to generate clusters, which were subsequently attached to PEI polyplexes. The cluster-presenting particles achieved a 5.4- or 35- fold increase in gene transfer in cells expressing low and high integrin densities, respectively, compared to non-modified polyplexes, showing a higher sensitivity to receptor density. This selectivity towards cells expressing high target receptor levels is fundamental for the design of nanomaterials which base their targeting principle on receptor overexpression by specific cells in a diseased state. The clustering principle has also been applied to folate molecules [114,121] with similar results, demonstrating that it is a promising approach to optimize ligand presentation.

The interactions of ligands with their targets may also be defined by the length of the linkers used to tether them to the particle surface. First, it may increase or decrease the particle size, which highly influences the cellular interaction [14]. Second, it can alter the ligand disposition, which can be spaced out or tightly grouped by using longer or shorter tethers, respectively [116]. Thirdly, it can influence the ligand mobility on the particle surface, which has a tremendous influence on the cellular internalization of a NP [113].

It is generally accepted that the virus-like multivalent ligand display enhances the particles overall avidity and targeting capabilities. Nevertheless, it does not increase the nanomaterials overall specificity, which is indispensable for therapeutic applications of such materials. Despite generally addressing disease-related overexpressed receptors, they are often also prevalent in "healthy" off-target tissues, which leads to poor material bioavailabilities and deleterious side effects. One of the elements that can negatively impact the specificity of multivalent NPs is the elevated number of ligands displayed on their corona, which is usually higher than the one presented by viruses [109]. *In vivo* this may

Table 2
Examples of non-viral ligands used for nanomaterial targeting.

NP	Ligands	Targets	Optimal ligand density/structure	*In vivo*	Therapy/Cargo	Ref.
Quantum dots	Peptide	NPY_1 receptor	–	–	–	[73]
PAMAM dendrimers/Branched PEG	Small molecule	AT1R	–	–	–	[103]
PEG-PLA/PLGA NPs	"-"	"-"	20% (+ high mobility)	–	–	[113]
PEG-PLGA NPs	Folate	Folate receptor	>10%	–	DNA	[110]
Linear dendritic polymer NPs	"-"	"-"	20%	KB/A375 tumors (mouse)	–	[114]
Polystyrene/Ovalbumin NPs	"-"	"-"	clustered	–	–	[121]
PLGA NPs	Peptide	ICAM-1	50%	–	–	[111]
Iron oxide NPs	Antibody	HER2/neu	23 ligands/NP (medium density)	–	–	[112]
PEG-Au NPs	RGD	αvβ3 integrin	high	–	–	[115]
PEG-PLA/PLGA NPs	c(RGDfK)	"-"	"-"	–	–	[116]
DNA/PEI/Au polyplexes	RGD	"-"	clustered	–	–	[120]

additionally cause a particle stealth loss and increased protein corona formation, which also hinders targeting. A very precise control over NP design features besides ligand density, such as linker length and ligand conformation, is crucial to achieve optimal effects. Altogether, a multivalent ligand display seems to be a prerequisite but not sufficient to effectively mimic the viral target cell recognition.

3.2. Heteromultivalent ligand display

The virus-like multivalent display of tethered ligands on NPs highly increases their targeting abilities. However, the cellular interplay of viruses is usually mediated by more than a single ligand. Therefore, as an approach to increase the specificity and targeting capacity of multivalent systems, heteromultivalent NPs, displaying different types of ligands on their surface, were developed (Fig. 3). They more closely mimic viruses, which require several recognition molecules for host-cell identification. For example, the HCV depends on the co-expression of four proteins (SR-B1, CD81, claudin-1, and occludin) to mediate cell entry [71]. This concept's increase in cell specificity is based on the fact that the probability of more than one cell expressing the same receptors decreases with the number of receptors that are addressed. More so, by using an additional set of ligands, the targeting capacity of heteromultivalent particles should be enhanced compared to multivalent NPs. Heteromultivalently binding NPs have been extensively investigated over the past years [122]. They find mostly application in cancer [123], and vascular pathologies [124,125], characterized by a concomitant spatiotemporal upregulation of several surface receptors, such as the TF receptor (TfR) [126], folate receptor (FR) [127], epidermal growth factor receptor (EGFR) [128], integrins [129], and selectins [130]. Like for multivalent systems, antibodies, small molecules, and peptides [131], are mainly used as targeting moieties. An overview of different formulations developed over the past years is depicted in Table 3.

It is essential to note that as for multivalent systems, there are several factors that can determine the cellular outcome of a heteromultivalent system, such as ligand density, ligand ratio and ligand arrangement. However, for most published formulations there is a lack of information

Table 3
Heteromultivalent NP formulations.

NP	Ligands	Targets	LD and/or LR	*In vivo*	Therapy/Cargo	Ref.
Liposome	Ab (1) Ab (2)	CD19 CD20	–	Namalwa B-cell lymphoma (mouse)	DOX/VIN	[154]
Liposome	Antibody NGR peptides	GD_2 AN	–	SH-SY5Y tumor (mouse)	DOX	[155]
Liposome	Ab (1) Ab (2)	CD19 CD20	50% of each ligand	–	DOX	[134]
Liposome	Ab FA	EGFR FR	3 Ab molecules + 200 folate molecules per NP	–	DOX	[156]
Liposome	Ab (1) Ab (2)	ICAM ELAM	1:1 ligand ratio	–	–	[145]
Liposome	Ab (1) Ab (2)	ICAM *E*-selectin	–	–	–	[144]
Liposome	Peptide (1) Peptide (2)	αvβ3 integrin Galectin-1	–	–	–	[151]
Liposome	Ab (1) Ab (2)	VCAM1 E-selectin	1:1 ligand ratio	–	–	[130]
Liposome	Peptide (1) Peptide (2)	αvβ3 integrin Galectin-1	–	B16F10 tumor (mouse)	–	[152]
Liposome	Ab fragment (1) Ab fragment (2)	EGFR CEA	–	–	–	[157]
Liposome	Peptide (1) Peptide (2)	P-selectin αvβ3 integrin	–	MDA-MB-231/4 T1 tumor (mouse)	–	[147]
Liposome	Peptide cRGDfc	EGFR αvβ3 integrin	1:1 ligand ratio	D2.A1 tumor (mouse)	DOX	[146]
PEI polyplex	B6 RGD-motif	TfR Integrin	–	–	–	[10]
Au NPs	Ab (1) Ab (2)	FR EGFR	–	–	–	[127]
Au NPs	FA Glucose	FR GR	–	–	DOX	[158]
Au NPs	Peptide (1) Peptide (2)	EGFR TfR	–	U87-MG tumor (mouse)	Phtalo-cyanine 4	[159]
PEG-PAMAM	TF WGA	TfR Endothelium	–	–	DOX	[133]
Polymer NPs	c(RGDfK) TF	αvβ3 integrin TfR	–	–	PTX	[126]
PEG-PLGA NPs	FA HA	FA Receptor CD44	5:2 ligand ratio	SKOV3 tumor (mouse)	–	[139]
Quantum dots	GE11 c(RGDfK)	EGFR αvβ3 integrin	–	–	siRNA + ON	[128]
Silica NPs	cRGD ATWLPRR peptide	αvβ3 integrin Neuropilin 1	–	U87-MG tumor (mouse)	–	[150]
Nanographene oxide	Folate cRGD	FR αvβ3 integrin	1:1 ligand ratio	KB cell tumor (mouse)	Photothermal therapy	[160]
DNA Nanoclaws	Ab (1) Ab (2) Ab (3)	EpCAM EGFR HER-2	–	–	DNA	[143]
Liposome/Silica NPs	Peptide (1) Peptide (2) Peptide (3) Peptide (4)	P-selectin αvβ3 integrin EGFR Fibronectin	500 ligands of each type	4 T1/D2A1/D2OR tumor (mouse)	–	[148]

regarding these parameters (Table 3). As they have enormous influence on the establishment of receptor interactions [109,132], it should come as no surprise that heteromultivalent NPs frequently achieve only moderate improvements, regarding targeting and specificity, compared to "simple" multivalent systems [126,133]. The addition of a second ligand type increases the complexity of the system and does not equal the rise in number of a single ligand. Furthermore, excessive particle functionalization can propitiate targeting ability loss [134] and off-target interactions [135]. A higher functionalization is usually associated with a higher avidity of the particle system. However, a high avidity attachment to the cell surface is not always positive seen from the viral perspective. It can hinder virus diffusion through the cell membrane and reduce the chances to find the cell entry mediating receptor [136]. Furthermore, the number of interactions between viruses and their receptors are limited. Delguste et al. showed that only 2 or 3 simultaneous interactions occurred between HV and glycosaminoglycans [136]. This is something that should be considered when designing functionalized particles.

Ligand arrangement on the particle surface can also determine the enhancement, or lack thereof, in particle internalization through a heteromultivalent system. For instance, HIV initially binds to the CD4 receptor on the membrane of its target cells *via* the gp120 subunit of its envelope protein (Env). Only then, conformational changes in the Env reveal a variable loop (V3) that subsequently binds a coreceptor and initiates membrane fusion *via* the fusogenic peptide of the second Env subunit gp41 [137].

In that regard, dissipative particle dynamics stimulations also showed that length mismatch or interactions between ligands can impede dual ligand binding [138]. When Liu et al. systematically evaluated the influence of ligand ratio and tether length of hyaluronic acid (HA) and folic acid (FA) presenting NPs [139], they saw that a precise formulation achieved maximum selectivity. A 1:5 HA:FA ratio resulted in maximum binding to double positive cancer cells with minimum binding to cells expressing only one of the targeted receptors. HA had to be tethered to a longer 7k PEG chain, than the 5k PEG chain used to link FA, to achieve selectivity. This sheds light to the complexity of the formulations and the need for a systematic review of every design parameter.

The nature of the ligand coupling can also influence targeting abilities. It has been demonstrated that non-specific ligand attachment during linkage is a fact that frequently occurs. Unfortunately, non-covalently bound ligands can be exchanged in biologic fluids by new peptides and proteins, which hinder targeting [140].

Both for (hetero)multivalent NPs and viral particles, ligand availability also plays an important role for a sufficient targeting efficacy. For instance, it could be shown, that the spike glycoprotein of SARS-CoV as well as SARS-CoV-2 exists in an either inactive ("down") or active ("up") position [141,142]. Consequently, target receptor ACE2 can only be addressed, if the surface protein changes its conformation to the active state.

In that regard, Wang et al. [143] proposed magnetic DNA "nanoclaws" for the early cancer diagnosis through detection of circulating tumor cells. They achieved a flexible claw morphology by rolling circle amplification and hybridization of DNA probes. The magnetic nanoclaws were able to capture target cells in a mixture with off-target cells with a 95% efficiency and 85% purity due to the high availability of the displayed antibodies, contrary to spherical control NPs. This was confirmed with clinical samples, demonstrating that a simple ligand surface attachment is insufficient to exploit the potential of heteromultivalency.

The exact definition of the expression patterns of the targeted receptors is also an element that can enable an optimal particle design. Gunawan et al. [130,144,145] carried out several studies with immunoliposomes functionalized with antibodies targeting ICAM and *E*-selectin on activated endothelial cells. The formulation was optimized to achieve a cooperative effect of the two ligands with a 1:1 ratio when lipid rafts were present on the cells [144]. However, the maximum binding of the final NPs varied tremendously with the transient expression of the targets. Also, Levine and Kokkoli [129] demonstrated that PEGylated liposomes targeting two different cancer biomarkers, integrin $\alpha_5\beta_1$ and $\alpha_6\beta_4$, with equal ligand numbers achieved enhanced binding to cells with equal and high receptor expressions, but not to cells with different expression patterns. These results can be an obstacle for the clinical translation of such systems, due to the individuality of each disease and patient. Nevertheless, the disease biomarker variability, especially in tumors and metastasis, can also open new applications for heteromultivalent NPs. By targeting more than one receptor, the temporary downregulation of one of them can be overcome by binding to the second one [146,147]. In this context, Peiris et al. [148] demonstrated that metastasis targeting can be improved by functionalizing particles with up to four different ligands. The authors found that in a triple-negative breast cancer model, two-ligand particles produced highly variable results depending on the animal while four-ligand particles achieved consistent results with 7% of the initial dose reaching even in subclinical metastasis.

A disadvantage of adding targeting capabilities is that it can complicate a system's design to a high extent making its clinical translation difficult [149], as the ligand dynamics can highly differ from its single-ligand counterparts. In combination, ligands can hold different roles than when they are separately presented. This was demonstrated by Nie et al. [10] when functionalizing PEI polyplexes with B6 and a RGD-motif to target the tumoral TfR and integrins, respectively. Even though the authors aimed for a synergistic ligand effect they discovered that it was not additive. RGD, a targeting ligand known to cause NP internalization, mediated cellular attachment whereas B6 binding resulted in particle uptake. These results shed light on the different dynamic that the combination of two ligands can generate, which often does not equal the sum of the individual effects. Furthermore, they can result contradictory. A recent study combining two ligands promoting anti-angiogenic and antitumoral activity, showed a paradoxical stimulation of cell survival due to the activation of an additional pathway when both ligands bound simultaneously [150].

Lastly, it has to be considered that due to the complexity of heteromultivalent systems, *in vitro* results often do not correlate with *in vivo* findings. This was the case for PEGylated liposomes developed for tumor angiogenesis imaging targeting integrin $\alpha v\beta 3$ and galectin-1 with RGD and galectin-1-specific anginex, respectively [151]. Even though the dual targeted formulations showed a superior targeting *in vitro* than single-ligand formulations, both particle types showed similar tumor accumulations. Additionally, they differed in their distribution with the heteromultivalent formulations being found in the tumor endothelium and the single-targeted liposomes in the vessel lumen [152]. Sawant et al. [153] also detected that *in vivo* their TF- and 2C5 monoclonal antibody-functionalized NPs showed little improvement in targeting efficiency compared to single-ligand formulations. It is particularly noteworthy that for the majority of heteromultivalent systems there are no *in vivo* studies available (Table 3).

Taken all together, these results demonstrate that the virus mimicking heteromultivalency is a promising concept. However, every detail of the particle design (ligand density, ligand ratio, ligand arrangement) and its application (target expression levels, pattern variations) must be systematically studied and combined to achieve the sought-after targeting and specificity goals.

3.3. Stepwise heteromultivalent ligand display

Even though (hetero)multivalent display of ligands on a particle surface has been extensively investigated over the past years for the development of targeted nanomaterials, it has yet failed to achieve the desired results. In two widely cited meta-analyses of tumor-targeted NP studies, Wilhelm et al. and Dai et al. concluded, that the vast majority of both non-functionalized and targeted nanomaterials failed to

substantially reach their target regions [161,162]. While the exact numbers of calculated levels for NP delivery efficiency and their implications have since been extensively discussed [163], it is undoubted, that NP targeting strategies including (hetero)multivalent ligand presentation have so far only shown moderate clinical translation. In that regard, one obstacle indisputably lies in the fact that, despite being virus-inspired, (hetero)multivalent approaches mostly fail to entirely mimic the viral host cell recognition process, which is decidedly more complex [7,77]. Viruses not only heteromultivalently bind distinct membrane receptors, but they do so in a sequential manner [77]. Examples for this are the HIV type 1 binding consecutively to the CD4 and the chemokine receptor [164] or adenoviruses attaching to the coxsackie and adenovirus receptor (CAR) and integrins [165,166]. If the presentation of ligands by heteromultivalent NPs is simultaneous, any cell expressing either of the target receptors is able to bind the particles. For instance, the independent binding of different tissues by each ligand was demonstrated for RGD and TF targeted polyplexes intended for the treatment of choroidal neovascularization [167] and for p-selectin and αvβ3 integrin targeting NPs used for breast cancer treatment [147]. Overall, this translates into a poor particle specificity and target accumulation. This shortcoming of nanomaterials can be surmounted by a stepwise heteromultivalent approach with a virus-like sequential ligand presentation (Fig. 3). In some studies, different ligands are coupled to a NPs surface for its sequential presentation, in that one of them enables cellular targeting, and the second one directs the particle to intracellular compartments, such as mitochondria [168] or the nucleus [169]. Nevertheless, the ligands are ubiquitously present on the particle surface and therefore cannot decrease nonspecific particle accumulation. Our group recently showed, that mimicking the stepwise host cell recognition of influenza A viruses highly increases the target cell specificity of nanomaterials [74]. Influenza A viruses display hemagglutinin on their envelope, which requires activation by an enzyme on the host cell membrane. Activated virus particles can then bind to sialic acid, that triggers cell uptake [170]. To mimic this enzyme-mediated recognition, angiotensin-I (Ang-I) was coupled to biocompatible PEG-PLA block copolymer NPs with a PLGA-stabilized core [171]. Ang-I probed the target cells for the presence of angiotensin converting enzyme (ACE), which upon binding cleaved the two last amino acids, releasing angiotensin-II (Ang-II). The interaction of Ang-II with the Gq-coupled receptor angiotensin-II type 1 receptor (AT1R), as an agonist triggered endocytosis [172]. This principle was designed to identify with high specificity mesangial cells, as they play a crucial role in the development of diabetic nephropathy [173]. This renal complication is suffered by 50% of the 425 million diabetic patients worldwide [174] and lacks specific treatment options. The translation of the influenza A recognition principle enabled synthetic NPs to specifically identify mesangial cells in co-culture mixtures where they made up only 10%.

Furthermore, we improved the system incorporating an additional viral cell recognition step, the initial cell attachment [175]. As discussed above, viruses often attach to the host-cell surface to increase the viral concentration and initiate receptor recruitment. It does not mediate internalization of the virus particle, but it has been shown to be a decisive step during the infection process [78]. In order to mimic the attachment while still maintaining specificity, an antagonist for the AT1R, losartan carboxylic acid (EXP3174), was coupled to the particles. EXP3174 decorated NPs were previously shown to attach to the cell membrane, but not mediate internalization [72,176]. The close mimicking of the viral host cell recognition, through a first attachment, followed by an enzymatic activation and concluded by an agonist-receptor binding (Fig. 4A) enabled a 5- or 15-fold higher accumulation of particles in mesangial cells *in vivo* than NPs lacking the attachment principle or any viral traits, respectively (Fig. 4B). As there are a plethora of ectoenzymes available, this design principle could be expanded to numerous other cell types involved in the development of diseases.

In addition, we decided to even further extend the applicability of the system, namely to cell types lacking suitable ectoenzymes. We therefore introduced a modified recognition concept that was inspired by the cell infiltration strategy of human adenovirus (AdV) [177]. In order to mimic the stepwise virus-cell interplay of AdV, we implemented a sequential display of two ligands, that was based on the steric shielding of the second, uptake-mediating ligand [178]. While initial cell attachment of the NP was also mediated *via* binding of EXP3174 to the AT1R, final NP endocytosis was initiated through a cyclic RGD sequence that activated the integrin receptor $\alpha_v\beta_3$. However, as the second RGD ligand was attached in closer proximity to the NP core, it could only activate

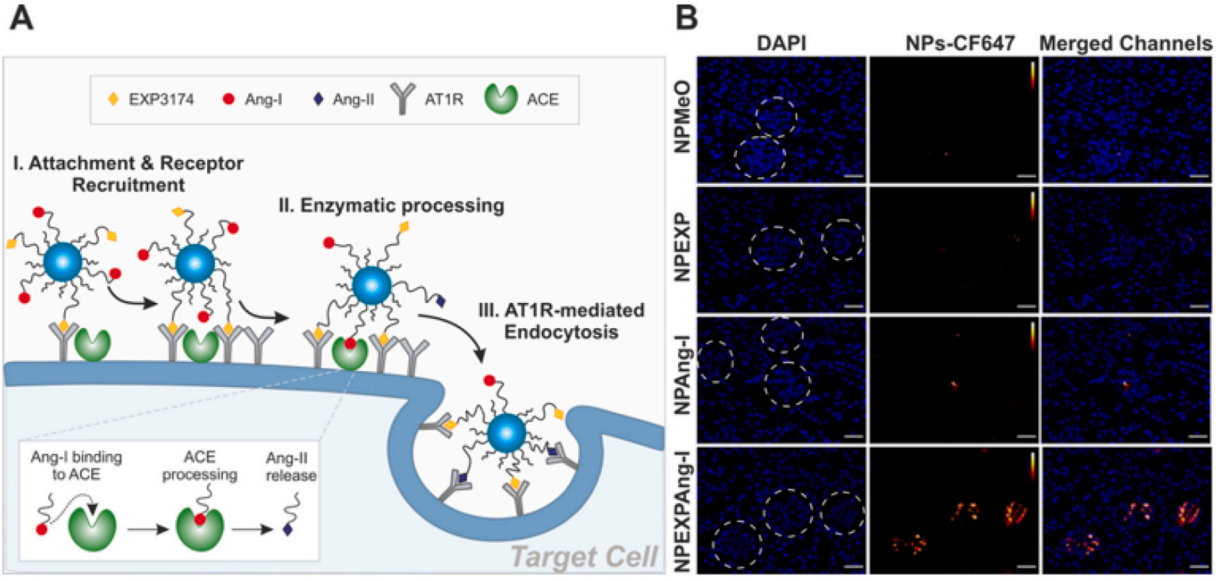

Fig. 4. Virus mimetic cell recognition strategies. (A) Illustration of the initial receptor attachment and sequential target cell recognition and internalization of virus-mimetic NPs (NPEXPAng-I). (B) *In vivo* glomerular distribution and mesangial cell targeting. NPs mimicking the viral cell attachment and multistep recognition (NPEXPAng-I) show a high glomerular accumulation. Elimination of the attachment-mediating ligand reduces the targeting potential (NPAng-I). Control particles with no ligand (NPMeO) or only able to attach (NPEXP) show no glomerular localization. Adapted with permission from [175]. Copyright 2020, Advanced Science published by Wiley-VCH Verlag & Co. KGaA. https://doi.org/10.1002/advs.201903204

the integrin after a previous binding of the AT1R and a resulting spatial approach of the NP to the cell surface. This two-step ligand display led to a significantly enhanced target cell selectivity of resulting NPs [178]. Additionally, *in vivo* accumulation in target mesangial cells was comparable to the influenza A mimetic system, thereby proving the potential of both virus-mimetic concepts.

These results demonstrate that apparently minor steps in the virus host-cell recognition such as a stepwise ligand presentation play crucial roles in their infectivity. Furthermore, their translation into robust synthetic nanomaterials can extraordinarily increase their specificity and targeting capabilities and open new research paths to further improve nanomaterial design.

4. Stimuli responsiveness

Viruses have evolved to respond to external stimuli, such as enzymes, reduction, or changes in the pH value, during their infection process [7]. This stimuli-responsiveness has been implemented in the newer generation of nanocarriers as it enables exploiting the specific disease environment to achieve a more effective and specific targeting. Particles can be designed to switch their surface charge, unmask active targeting ligands or shed their coating in response to pH variations, redox- or enzyme activity (Table 4). Following this trend in recent years nanocarriers have been becoming more complex and "smarter" by incorporating multiple stimuli responsive elements. Even though generally not exactly mimicking specific viruses, such systems aim at allowing for a higher control of the particle fate in the organism (Fig. 5), inspired by the viral cycle.

Despite stimuli-responsive nanomaterials being reviewed in the past [179], due to the high number of publications in this fields over the last 3 years we will give a brief overview and discuss the newest systems.

4.1. Single-stimuli-responsive systems

The pathological characteristics of therapeutically relevant tissues can be used to increase the targeting efficiency of nanocarriers. Enzyme-responsive systems that target enzymes linked to a specific disease are an example of this [180]. The enzymes most commonly addressed are the matrix metalloproteinases (MMPs) [181], which can be found in the extracellular tumor medium for example. They have been used to unveil PEG-shielded ligands protected during circulation [182–186], or to induce a morphology change [187–189], increasing the targeting potential of NPs. Other enzymes, such as legumain, which is upregulated in tumors in correlation with their malignancy [190], have also been targeted to unveil shielded ligands, like TAT [191], in a site-specific manner. Enzymes associated with drug-resistant bacterial strains, such as Penicillin G amidase (PGA) and β-lactamase (BLA) [192] or *P. aeruginosa* elastase [193], can also be used as targets to achieve a selective delivery of antimicrobial agents. Lastly, the above-mentioned influenza A mimetic NP concept of our group also depends on an enzymatic cleavage of ligand precursor Ang-I in order to initiate final NP uptake *via* Ang-II mediated activation of AT1R [74,175]. Enzyme-responsive systems have long been adopted for the controlled delivery of drugs [42,100,184,194].

As an alternative approach to enzymes, linkers or tethers with pH-responsive functionalities can be introduced in the particle design, to shield ligands during blood circulation, and increase their targeting once an acidic environment is reached [195–198]. Furthermore, pH-responsiveness can be used to initiate cargo release in acidic intracellular compartments or tumor milieus [199–201]. It can also be adopted to mimic the viral trait of endosomal escape [202,203] which is mediated by membrane fusion or disruption, for enveloped and non-enveloped viruses [204], respectively. The endolysosomal escape of non-enveloped viruses was mimicked by Song et al. [205] with NPs prepared from pH-sensitive hydrazone bond-containing polyurethane. After target-specific cell internalization, upon exposure to acidic pH the particles underwent charge reversal, core exposure and induced endosome rupture. This viral trait has also been implemented in synthetic nanomaterials through additional mechanisms, such as membrane fusion, osmotic disruption, particle swelling and membrane destabilization [206] or the incorporation of viral and virus-mimetic peptide sequences related to endosomal escape [207,208].

Lastly, Redox-responsive systems show great potential as drug delivery systems [209] in disease with elevated reactive oxygen species (ROS), such as cancer [210,211] or respiratory viral infections [212]. They can be used to induce a site-specific drug release, as shown by Jian et al. [213]. The authors emulated the viral capability of overcoming barriers, such as the BBB, with virus-sized polymerosomes encapsulating

Table 4
Single-stimuli responsive nanomaterials.

Stimulus	Effect	Target	NP	*In vivo*	Therapy/Cargo	Ref.
Enzymatic	Ligand unveiling	MMP-2	PEG-PCL NPs	A549 tumor (mouse)	Curcumin	[182]
		MMP-7	PEG NPs	–	siRNA	[183]
		MMP-9	PEG Quantum dots	BxPC-3 tumor (mouse)	GEM	[184]
		MMP-2	PEG NPs	lung tumor (mouse)	PTX	[185]
		"-"	PEG Liposomes	–	–	[186]
		Legumain	Liposomes	4 T1 tumor (mouse)	DOX	[191]
	Ligand activation	ACE	PEG-PLA/PLGA NPs	–	–	[74,175]
	Morphology change	MMP	Peptide NPs	HT-1080 tumor (mouse)	Pt(II)	[187]
		MMP-2/9	Peptide/Polymer NPs	Myocardial infarct (rat)	–	[188]
		MMP	Norbornene/Peptide NPs	HT-1080 tumor (mouse)	PTX	[189]
		Bacterial PGA/BLA	Polymer NPs	–	Antibiotics	[192]
		Bacterial elastase	PEI-Peptide NPs	–	PEI	[193]
pH	Ligand unveiling	Acidic Tumor environment	Dendritic lipopeptide NPs	4 T1 tumor (mouse)	DOX	[195]
		"-"	PEG copolymer NPs	HepG2 tumor (mouse)	"-"	[198]
	Charge inversion	"-"	Silica NPs	–	"-"	[196]
	Cargo release	Acidic endosome	Dendritic lipopeptide NPs	–	DNA	[199]
		Tumor lysosome	Polymeric micelles	–	DOX	[200]
		"-"	Dendritic peptide NPs	SKOV3/R tumor (mouse)	"-"	[201]
	Endosomal escape	Acidic endosome	PEG Liposomes	–	DNA	[202]
		"-"	Polymer NPs	–	Asiatic acid	[203]
		"-"	PEG-Polymer NPs	SKOV3 tumor (mouse)	DOX	[205]
Redox	Cargo release	Reductive tumor cytoplasm	Polmyerosomes	U87-MG tumor (mouse)	Saporin	[213]

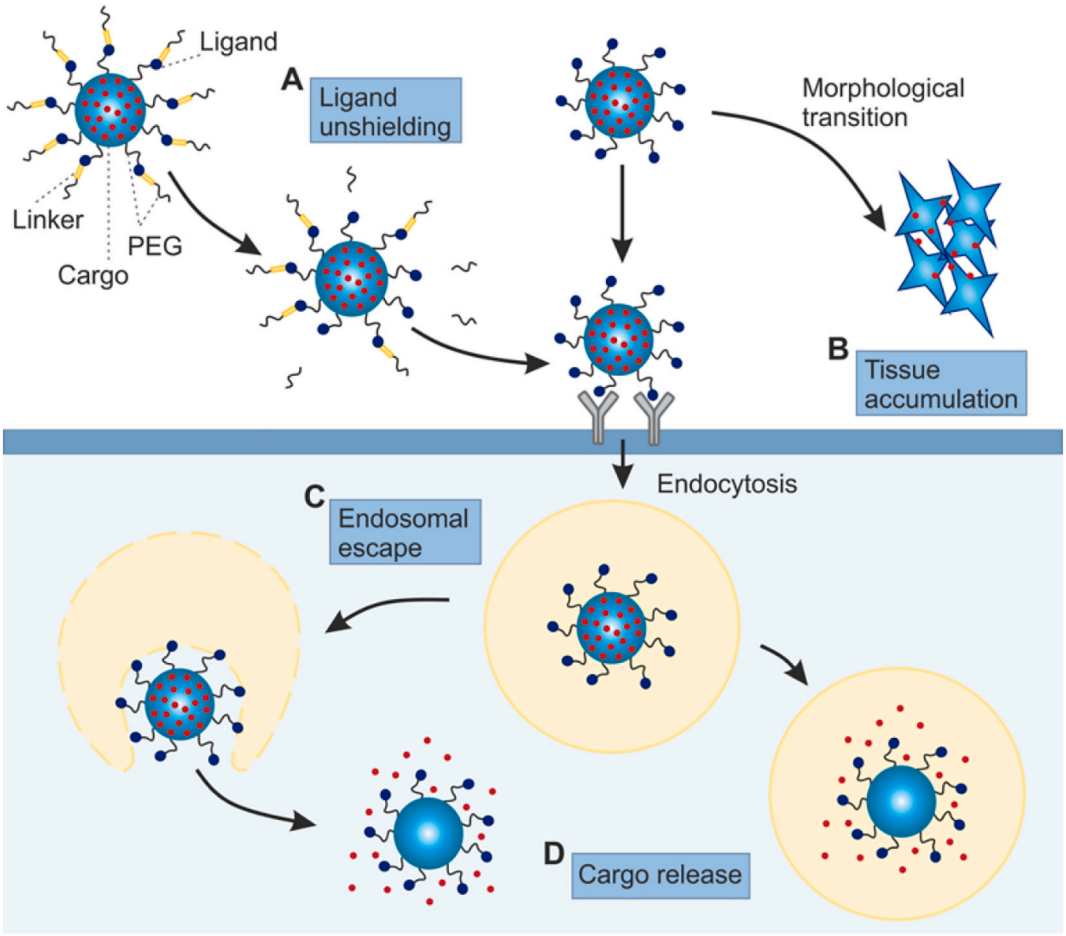

Fig. 5. Effect of stimuli responsiveness in targeted virus-mimetic NPs. (A) NPs with PEG protected ligands are subjected to ligand unshielding through enzymatic, pH or redox-responsive linker cleavage at the target site. (B) NPs undergo morphological transition due to specific enzymatic processing or temperature variation and accumulate in a specific tissue, such as sites of bacterial infection or tumors. (C) After NP cellular uptake, endosomal escape is triggered by pH mediated membrane disruption (D) Cargo release from NPs is initiated after response to pH, redox-, or enzymatic stimuli in different intracellular compartments.

the toxin saporin, which is highly degradable *in vivo*. The particles were functionalized with angiopep-2, a high affinity ligand towards the low-density lipoprotein receptor-related protein-1 (LRP-1). Due to their redox responsiveness, upon reaching intracellular environments the particles were able to release their payload. After administration in glioblastoma-bearing mice, particles were able to accumulate at the target through LRP-1-mediated BBB transcytosis and increase survival rate through tumor inhibition.

4.2. Multiresponsive systems

Particles that respond to a single stimulus hold great advantages regarding targeting efficiency. However, in recent years nanomaterials are being designed so that they respond to a combination of stimuli. These multiresponsive systems allow to mimic the continuous changes that viruses undergo during their infection cycle. They also enable targeting a higher variety of diseases with increased specificity. Additionally, they provide a more precise control of particle fate upon administration.

Some systems present sequential responsiveness to the same type of stimuli, as for example, the multiple targeting of both extracellular and intracellular enzymes. Han et al. [184] used this concept and achieved specific *in vivo* tumor targeting, by unveiling of a PEG-ylated ligand by MMP-9 and controlled drug by cathepsin-B, present in the tumor environment and lysosomes, respectively. Another approach is the dual redox-responsiveness, which was employed by He et al. [214] to increase *in vivo* delivery of nucleic acids to tumor cell with polyplexes that, like viruses, are subject to sequential unshielding and unpacking steps: first after cellular attachment or internalization, and second to enable genome release after endosomal escape.

Other systems are responsive to a combination of different stimuli. The association of MMP- and reactive oxygen species (ROS)-responsiveness enabled Daniel et al. [215] to use amphiphilic polymer NPs in inflammatory diseases, such as myocardial infarction, arthritis, ischemia and atherosclerosis, where both are upregulated. With this design approach they achieved specific *in vivo* targeting of ischemic skeletal muscle [216], avoiding off-target accumulation in healthy muscle and regulating macrophage internalization [217].

The increase in NP specificity achieved by multiresponsive systems has the potential to reduce therapy-associated toxicity. Zhang et al. [218] developed a polycaprolacton and PEG delivery system connected by redox-responsive azo bonds that were disintegrated by azoreductase after sialic acid-mediated internalization in hepatocellular carcinoma cells. Camptothecin release due to disulfide bond breakage was triggered in the presence of high concentrations of glutathione [218]. A combination of active targeting with the two-step stimuli-responsive drug release achieved a good *in vivo* targeting with an efficient tumor therapy. Similarly, Li et al. [219] developed NPs composed of hydroxyethyl starch (HES) coupled to paclitaxel (PTX) through a redox-sensitive disulfide bond. During circulation particles underwent a size reduction due to HES degradation by α-amylase, which promoted their extravasation to tumors. The cleavage of the disulfide bond in high

redox potential tumor environments unloaded the particles´ cargo. Stimuli responsive NPs enable increased *in vivo* targeting specificity and site-controlled drug release. Additionally, when combining responses to multiple stimuli, the sequential transformation stepsviruses undergo during their infection process can be mimicked. Furthermore, due to the myriad of developed materials with transversal application, the therapy options for difficultly targetable diseases are broadened.

5. Cargo release and cell-to-cell spreading

A fundament for the perpetuation of the viral cycle is their ability to replicate and spread from cell to cell [220]. After a successful host cell infiltration *via* above described mechanisms, viruses thereby initially release their genome (RNA/DNA), which is subsequently replicated and translated into further virus components such as protein envelopes, leading to the assembly of numerous new copies of the viral particle (Fig. 1). For obvious reasons, synthetic nanoparticles, in contrast, cannot be (to date) reproduced within the target cell. However, this limitation is only of minor importance since the central aspect of nanomedicine is not the particle reproduction but drug delivery into or the NP-assisted therapy of targeted cells. In that regard, most approaches discussed in this review (Tables 1–4) present nanoparticles that were loaded with the "usual suspects", *i.e.* cytotoxic substances such as doxorubicin or paclitaxel to treat severe tumor diseases. Even though therapeutic efficiency was thereby oftentimes considerably improved compared to the application of a free drug, these classic nanotherapeutic concepts suffer the widely discussed limitation, that generally, only small doses of therapeutic substances can be encapsulated in the currently available nanoparticulate systems. Consequently, most clinically translated NP drug delivery approaches are based on the administration of highly potent chemotherapeutic agents for only a very limited range of mostly malignant tumor diseases [221]. In that regard, the mimicry of viral cargo, *i.e.* the delivery of DNA or RNA components could offer a substantial expansion of currently treatable diseases as a nucleic acid based therapy generally requires only minor concentrations compared to classical therapy options [222,223]. Also, above described viral strategies to protect its cargo and deliver it to the necessary intracellular compartments could be a highly promising model to maximize the therapeutic effect of these gene delivery approaches.

As the viral infectivity is to a large extent based on the ability to disseminate from the initial target cell and spread across the surrounding tissue, bestowing NPs with this trait may also allow to lower dosages and enforce valuable properties in applications, such as cancer treatment. Several years ago, Lee et al. [224] developed a virus mimetic delivery vehicle capable of disseminating from cell to cell. It consisted on a core-shell nanogel loaded with DOX. The poly(l-histidine-*co*-phenylalanine) core was covered by a PEG shell, linked to bovine serum albumin (BSA) molecules. To achieve a specific *in vitro* targeting to tumor cells, folate molecules were conjugated to the BSA. Upon exposure of the nanogels to different pH values, they were able to shrink and expand due to their pH sensitive core, varying between 55 nm at pH 7.4 and 355 nm at pH 6.4. After "infection" of the target cells, DOX-mediated apoptosis was induced, and the nanogels were released in to the medium ready to target the next cell. This DOX apoptosis-derived approach to induce cell spreading was also used by Cui et al. [225]. They additionally enhanced the *in vivo* penetration in tumors by NP hyaluronidase release under acidic tumor conditions, which is able to cleave HA in the extracellular matrix and reduces the NP size. However, a limitation of this infective mechanism is the amount of DOX loaded in the nanocarriers, since it is responsible for cell death and NP release. Fang et al. [226] developed magnetoresponsive nanocapsules composed of an iron oxide core and a tumor targeting lactoferrin shell. The anticancer drug-loaded NPs were able to release therapeutic agents whilst concomitantly producing intense heat after an external high frequency magnetic field was applied. Particles were released after cell death and migrated to neighboring cells. With this dual *in vivo* treatment mechanism, the need of a drug-induced effect for particle spreading is minimized. Another option to achieve particle spreading was shown by Zhang et al. who developed a DOX carrier system composed of dendritic peptides, which under acidic pH conditions revealed arginine rich domains that induced membrane-breaking activity [201]. The problem can be further evaded when the NPs are able to bind to the cell cytoskeleton in order to disseminate to neighboring cells, as was shown recently by Dalmau-Mena et al. [227]. Their *in vitro* approach was based on the way viruses bind to the microtubule motor to disseminate and replicate. Gold NPs were modified with viral peptides that bind dynein, a microtubule motor proteins which are used for transport by several viruses [228]. Internalized particles were able to move through the cytosol after dynein binding and progress to neighboring cells through cell projections, reducing the particle loss to extracellular compartments.

Overall mimicking the viral transmission shows great potential, especially in the field of oncology where the therapy would enormously benefit from the dose reductions enabled by these technologies. Nevertheless, an improvement of the specificity of the targeting mechanisms would pose a great advantage, as it would facilitate a much wider range of applications. Meanwhile, local therapy seems to be the ideal use of such "infective" NPs, reducing the risk of off target effects.

6. Towards an artificial virus?

A comprehensive examination of the viral characteristics has promoted the design of particles that mimic different aspects of a virus' natural behavior (Fig. 6). In that regard, one could argue, that in many cases, viruses do not necessarily have to reach extraordinary levels of targeting efficiency, as already a minor fraction of successful viral particles can be sufficient to induce an infection due to the viral capability to replicate upon host cell entry. While this is undoubtedly true, numerous viruses nevertheless possess remarkable strategies to maximize their target accumulation and the implementation of single viral traits has already improved several aspects of nanomaterials' performance.

However, even though this fundamental research has considerably advanced our knowledge and has provided the foundations for particle optimization, none of the described concepts has reached clinical translation so far, one impediment that has been found to be critical for the failure of numerous nanomedicines. Therefore, it is crucial to discuss critical parameters for a successful bench-to-bedside transition of promising virus-mimetic concepts. In that regard, Hua et al. excellently reviewed current challenges for the translational development of nanomedicine approaches in general [221].

One critical aspect that the authors identified, was that many concepts initially focused too much on a few specific formulation aspects such as novel receptor-specific ligands or other highly developed NP components instead of concentrating on the actual biological target and the entirety of respective structural requirements to reach this site of action. Accordingly, we believe that a holistic approach, *i.e.* the development of an "artificial virus" instead of merely equipping NPs with single viral traits, may hold more promise for a successful clinical translation of virus-inspired nanomaterials.

In that regard, the combination of structural features, such as shape and surface properties, with ligand mediated cell recognition and stimuli responsiveness has recently led to the development of formulations that are almost an exact synthetic replica of viruses. In publications such as the one by Lee et al. [29] we can see that this provides huge advantages regarding targeting capability. In their work they prepared a synthetic duplicate of the RABV by exactly matching its size, shape and surface glycoprotein. Silica-coated gold nanorods, with elongated morphology equal to the RABV were chosen to increase the cellular receptor interaction. Their close imitation of the RABV properties enabled a virus-like *in vivo* behavior which could suppress brain tumors after irradiation. Due to their viral surface ligands the particles interact with the virus-used targeted receptors, but the perfect combination with an exact

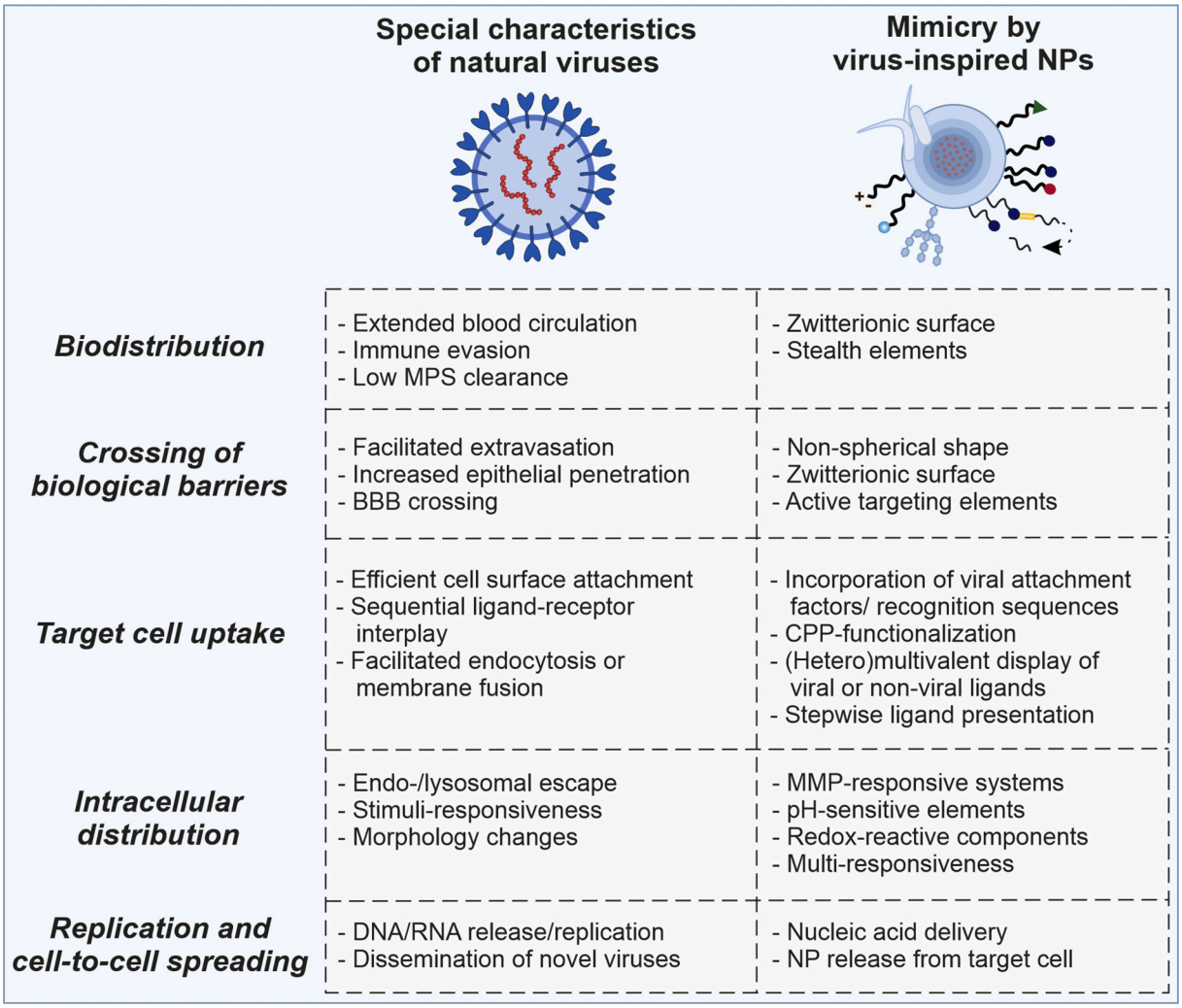

Fig. 6. Viral characteristics associated with overcoming critical obstacles in biological media and their possible mimicry by virus-inspired NPs.

virus-like shape and size potentiates its effect. Also the work published by Mable et al. [229] where the morphology and pH-responsiveness of the Dengue virus (DV) was mimicked with copolymer vesicles points towards the same conclusions. By imitating the framboidal morphology the DV adopts upon transition from the 28 °C mosquito vector to the 37 °C human host [230] and its additional pH-induced transformation that allows for endosomal escape, they were able to address SR-B1 overexpressing triple-negative breast cancer cells for which there are currently no targeted therapies. More so, their formulation did not accumulate in healthy or SR-B1-negative cells. The authors attributed the *in vitro* targeting specificity to a combination of the ligand and the Dengue-mimicking rough surface, which was associated with higher targeting efficiency through membrane deformation [229]. These examples support our assessment, that the holistic implementation of viral properties on NPs to create an "artificial virus" may help to increase the therapies' specificity and effectivity, as individual traits seem insufficient to achieve these goals. We can probably look forward to formulations further implementing multiple viral traits to achieve the perfect "synthetic virus", which may surmount the alarming low specificity and target cell accumulation that nanomaterials achieve up to date [161,162].

An important question in this regard is if there will be a single universal "artificial virus formulation" only subjected to slight modifications depending on the application, or if viruses will be mimicked in accordance with their natural targets. The latter is a frequently used approach. For example, for brain targeting the RABV is often used as a model [29,85], for its capability of crossing the BBB. Another example is the addressing of hepatic cells with particles mimicking the HBV [80–82]. However, to expand the applicability to therapeutically relevant cells not naturally addressed by viruses the first approach may be a better fit. This is reinforced by the focus on high tunability of the formulations being developed. Indisputably, due to disease individuality an exact tailoring of the formulation is essential.

Apart from the structural considerations for virus-inspired NPs, cargo selection will also play a central role for the feasibility of clinical translation. In that regard, possible drug candidates not only have to possess the necessary physicochemical characteristics for sufficient encapsulation, but also have a pharmaceutical profile, that would actually benefit from virus-inspired delivery options. As already mentioned above, nucleic acid-based systems thereby rank among the most promising candidates [222,223], as they most closely resemble the actual viral cargo.

A widely discussed challenge for sufficient clinical adaptation is also the lack of realistic *in vitro* and *in vivo* models. In that regard, we believe that the translation of new nanomaterials including virus-inspired approaches will eventually only be successful, if a central focus is placed on realistically mimicking central physiological aspects during both *in vitro* and *in vivo* testing. This includes aspects like the implementation of physiological cell culture and NP incubation conditions [231] or the use of suitable animal models with a realistic pathophysiology. These

considerations are particularly important for virus-mimetic concepts, as they are based on a refined adaptation to multiple influencing factors such as immune recognition, the penetration of physiological barriers or the responsiveness to external physicochemical stimuli.

Once virus-inspired materials have proven to be successful, another possible impediment for a clinical and later industrial scale-up will doubtlessly be the considerable structural complexity, that is oftentimes needed to incorporate multiple viral traits. The higher the intricacy of the particle design, the higher the difficulty for its precise characterization, large-scale manufacturing and regulation. In that regard, it is encouraging, that intensive research has begun to use safe, non-toxic and FDA-approved materials for their developed formulations.

Nevertheless, additional comprehensive research is needed in an exciting field where only the pillars have been set.

7. Conclusion

The implementation of viral features on NPs is a feasible endeavor that has substantially influenced and improved the design of therapeutic nanomaterials. Future investigations in the formulation field incorporating viral traits using a more holistic approach may solve the specificity and accumulation problems NPs face to date. Overall, it is reasonable to say that viruses can be considered as a great source of inspiration for nanomaterial design with enormous potential in the field of targeted drug delivery.

Declaration of Competing Interest

There are no conflicts to declare.

Acknowledgements

Financial support from the German Research Foundation (DFG), Grant Number GO 565/17-3, is gratefully acknowledged.

References

[1] M. Rahman, S. Laurent, N. Tawil, L.'.H. Yahia, M. Mahmoudi, Protein-Nanoparticle Interactions: The Bio-Nano Interface, Springer, Berlin, Heidelberg, 2013.
[2] K. Abstiens, S. Maslanka Figueroa, M. Gregoritza, A.M. Goepferich, Interaction of functionalized nanoparticles with serum proteins and its impact on colloidal stability and cargo leaching, Soft Matter 15 (2019) 709–720, https://doi.org/10.1039/c8sm02189a.
[3] Y.K. Lee, E.-J. Choi, T.J. Webster, S.-H. Kim, D. Khang, Effect of the protein corona on nanoparticles for modulating cytotoxicity and immunotoxicity, Int. J. Nanomedicine 10 (2015) 97–113, https://doi.org/10.2147/IJN.S72998.
[4] V. Mirshafiee, M. Mahmoudi, K. Lou, J. Cheng, M.L. Kraft, Protein corona significantly reduces active targeting yield, Chem. Commun. (Camb.) 49 (2013) 2557–2559, https://doi.org/10.1039/c3cc37307j.
[5] P.P. Karmali, D. Simberg, Interactions of nanoparticles with plasma proteins: implication on clearance and toxicity of drug delivery systems, Expert Opin. Drug Deliv. 8 (2011) 343–357, https://doi.org/10.1517/17425247.2011.554818.
[6] H. Meng, W. Leong, K.W. Leong, C. Chen, Y. Zhao, Walking the line: the fate of nanomaterials at biological barriers, Biomaterials 174 (2018) 41–53, https://doi.org/10.1016/j.biomaterials.2018.04.056.
[7] M. Marsh, A. Helenius, Virus entry: open sesame, Cell 124 (2006) 729–740, https://doi.org/10.1016/j.cell.2006.02.007.
[8] C.E. Dunbar, K.A. High, J.K. Joung, D.B. Kohn, K. Ozawa, M. Sadelain, Gene therapy comes of age, Science 359 (2018), https://doi.org/10.1126/science.aan4672.
[9] S.-D. Li, L. Huang, Non-viral is superior to viral gene delivery, J. Control. Release 123 (2007) 181–183, https://doi.org/10.1016/j.jconrel.2007.09.004.
[10] Y. Nie, D. Schaffert, W. Rödl, M. Ogris, E. Wagner, M. Günther, Dual-targeted polyplexes: one step towards a synthetic virus for cancer gene therapy, J. Control. Release 152 (2011) 127–134, https://doi.org/10.1016/j.jconrel.2011.02.028.
[11] D. Raoult, S. Audic, C. Robert, C. Abergel, P. Renesto, H. Ogata, B. La Scola, M. Suzan, J.-M. Claverie, The 1.2-megabase genome sequence of Mimivirus, Science 306 (2004) 1344–1350, https://doi.org/10.1126/science.1101485.
[12] J. Cui, T.E. Schlub, E.C. Holmes, An allometric relationship between the genome length and virion volume of viruses, J. Virol. 88 (2014) 6403–6410, https://doi.org/10.1128/JVI.00362-14.
[13] S. Maslanka Figueroa, D. Fleischmann, S. Beck, A. Goepferich, Thermodynamic, spatial and methodological considerations for the manufacturing of therapeutic polymer nanoparticles, Pharm. Res. 37 (2020), https://doi.org/10.1007/s11095-020-2783-4.
[14] A. Albanese, P.S. Tang, W.C.W. Chan, The effect of nanoparticle size, shape, and surface chemistry on biological systems, Annu. Rev. Biomed. Eng. 14 (2012) 1–16, https://doi.org/10.1146/annurev-bioeng-071811-150124.
[15] C.H.J. Choi, J.E. Zuckerman, P. Webster, M.E. Davis, Targeting kidney mesangium by nanoparticles of defined size, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 6656–6661, https://doi.org/10.1073/pnas.1103573108.
[16] H.S. Choi, W. Liu, P. Misra, E. Tanaka, J.P. Zimmer, B. Itty Ipe, M.G. Bawendi, J. V. Frangioni, Renal clearance of quantum dots, Nat. Biotechnol. 25 (2007) 1165–1170, https://doi.org/10.1038/nbt1340.
[17] C. Zhou, M. Long, Y. Qin, X. Sun, J. Zheng, Luminescent gold nanoparticles with efficient renal clearance, Angew. Chem. Int. Ed. Eng. 50 (2011) 3168–3172, https://doi.org/10.1002/anie.201007321.
[18] J.E. Zuckerman, M.E. Davis, Targeting therapeutics to the glomerulus with nanoparticles, Adv. Chronic Kidney Dis. 20 (2013) 500–507, https://doi.org/10.1053/j.ackd.2013.06.003.
[19] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (2015) 941–951, https://doi.org/10.1038/nbt.3330.
[20] M.F. Bachmann, G.T. Jennings, Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns, Nat. Rev. Immunol. 10 (2010) 787–796, https://doi.org/10.1038/nri2868.
[21] V. Manolova, A. Flace, M. Bauer, K. Schwarz, P. Saudan, M.F. Bachmann, Nanoparticles target distinct dendritic cell populations according to their size, Eur. J. Immunol. 38 (2008) 1404–1413, https://doi.org/10.1002/eji.200737984.
[22] C. Lico, P. Giardullo, M. Mancuso, E. Benvenuto, L. Santi, S. Baschieri, A biodistribution study of two differently shaped plant virus nanoparticles reveals new peculiar traits, Colloids Surf. B: Biointerfaces 148 (2016) 431–439, https://doi.org/10.1016/j.colsurfb.2016.09.019.
[23] P.C. Roberts, R.W. Compans, Host cell dependence of viral morphology, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 5746–5751.
[24] A. Mahmud, D.E. Discher, Lung vascular targeting through inhalation delivery: insight from filamentous viruses and other shapes, IUBMB Life 63 (2011) 607–612, https://doi.org/10.1002/iub.481.
[25] Y. Geng, P. Dalhaimer, S. Cai, R. Tsai, M. Tewari, T. Minko, D.E. Discher, Shape effects of filaments versus spherical particles in flow and drug delivery, Nat. Nanotechnol. 2 (2007) 249–255, https://doi.org/10.1038/nnano.2007.70.
[26] K.L. Lee, L.C. Hubbard, S. Hern, I. Yildiz, M. Gratzl, N.F. Steinmetz, Shape matters: the diffusion rates of TMV rods and CPMV icosahedrons in a spheroid model of extracellular matrix are distinct, Biomater. Sci. 1 (2013), https://doi.org/10.1039/C3BM00191A.
[27] A. Hernandez-Garcia, M.A. Cohen Stuart, R. de Vries, Templated co-assembly into nanorods of polyanions and artificial virus capsid proteins, Soft Matter 14 (2017) 132–139, https://doi.org/10.1039/c7sm02012k.
[28] X. Jiang, W. Qu, D. Pan, Y. Ren, J.-M. Williford, H. Cui, E. Luijten, H.-Q. Mao, Plasmid-templated shape control of condensed DNA-block copolymer nanoparticles, Adv. Mater. Weinheim. 25 (2013) 227–232, https://doi.org/10.1002/adma.201202932.
[29] C. Lee, H.S. Hwang, S. Lee, B. Kim, J.O. Kim, K.T. Oh, E.S. Lee, H.-G. Choi, Y. S. Youn, Rabies virus-inspired silica-coated gold nanorods as a photothermal therapeutic platform for treating brain tumors, Adv. Mater. Weinheim. 29 (2017), https://doi.org/10.1002/adma.201605563.
[30] J. Perez-Juste, I. Pastoriza-Santos, L. Liz-Marzan, P. MULVANEY, Gold nanorods: synthesis, characterization and applications, Coord. Chem. Rev. 249 (2005) 1870–1901, https://doi.org/10.1016/j.ccr.2005.01.030.
[31] S. Andersson, The structure of virus capsids, Z. Anorg. Allg. Chem. 634 (2008) 2161–2170, https://doi.org/10.1002/zaac.200800214.
[32] N.P. Truong, M.R. Whittaker, C.W. Mak, T.P. Davis, The importance of nanoparticle shape in cancer drug delivery, Expert Opin. Drug Deliv. 12 (2015) 129–142, https://doi.org/10.1517/17425247.2014.950564.
[33] R. Fernandes, D.H. Gracias, Self-folding polymeric containers for encapsulation and delivery of drugs, Adv. Drug Deliv. Rev. 64 (2012) 1579–1589, https://doi.org/10.1016/j.addr.2012.02.012.
[34] M.G. Mateu, Structure and Physics of Viruses: An Integrated Textbook, Springer, Dordrecht, 2013.
[35] M.Y. Chen, A. Hoffer, P.F. Morrison, J.F. Hamilton, J. Hughes, K.S. Schlageter, J. Lee, B.R. Kelly, E.H. Oldfield, Surface properties, more than size, limiting convective distribution of virus-sized particles and viruses in the central nervous system, J. Neurosurg. 103 (2005) 311–319, https://doi.org/10.3171/jns.2005.103.2.0311.
[36] N. Banerjee, S. Mukhopadhyay, Viral glycoproteins: biological role and application in diagnosis, Virusdisease 27 (2016) 1–11, https://doi.org/10.1007/s13337-015-0293-5.
[37] Y. Niu, M. Yu, S.B. Hartono, J. Yang, H. Xu, H. Zhang, J. Zhang, J. Zou, A. Dexter, W. Gu, C. Yu, Nanoparticles mimicking viral surface topography for enhanced cellular delivery, Adv. Mater. Weinheim. 25 (2013) 6233–6237, https://doi.org/10.1002/adma.201302737.
[38] F. Wang, P. Liu, L. Sun, C. Li, V.A. Petrenko, A. Liu, Bio-mimetic nanostructure self-assembled from Au@Ag heterogeneous nanorods and phage fusion proteins for targeted tumor optical detection and photothermal therapy, Sci. Rep. 4 (2014) 6808, https://doi.org/10.1038/srep06808.
[39] X. Cai, R. Jin, J. Wang, D. Yue, Q. Jiang, Y. Wu, Z. Gu, Bioreducible fluorinated peptide dendrimers capable of circumventing various physiological barriers for highly efficient and safe gene delivery, ACS Appl. Mater. Interfaces 8 (2016) 5821–5832, https://doi.org/10.1021/acsami.5b11545.

[40] X. Sun, M. Li, Y. Yang, H. Jia, W. Liu, Carrier-free nanodrug-based virus-surface-mimicking nanosystems for efficient drug/gene co-delivery, Biomater. Sci. 6 (2018) 3300–3308, https://doi.org/10.1039/c8bm01033a.
[41] W. Wang, P. Wang, X. Tang, A.A. Elzatahry, S. Wang, D. Al-Dahyan, M. Zhao, C. Yao, C.-T. Hung, X. Zhu, T. Zhao, X. Li, F. Zhang, D. Zhao, Facile synthesis of uniform virus-like mesoporous silica nanoparticles for enhanced cellular internalization, ACS Cent. Sci. 3 (2017) 839–846, https://doi.org/10.1021/acscentsci.7b00257.
[42] S. Liu, J. Yang, H. Jia, H. Zhou, J. Chen, T. Guo, Virus spike and membrane-lytic mimicking nanoparticles for high cell binding and superior endosomal escape, ACS Appl. Mater. Interfaces 10 (2018) 23630–23637, https://doi.org/10.1021/acsami.8b06934.
[43] Liang Xu, Peter Frederik, Kathleen F. Pirollo, Wen-Hua Tang, Antonina Rait, Lai-Man Xiang, Weiqun Huang, Idalia Cruz, Yuzhi Yin, Esther H. Chang, Self-Assembly of a Virus-Mimicking Nanostructure System for Efficient Tumor-Targeted Gene Delivery, 2002. Vol. 13.
[44] D.J. Vigerust, V.L. Shepherd, Virus glycosylation: role in virulence and immune interactions, Trends Microbiol. 15 (2007) 211–218, https://doi.org/10.1016/j.tim.2007.03.003.
[45] H.-D. Klenk, R. Wagner, Dagmar Heuer, T. Wolff, Importance of hemagglutinin glycosylation for the biological functions of influenza virus, Virus Res. 82 (2002) 73–75.
[46] J.N. Reitter, R.E. Means, R.C. Desrosiers, A role for carbohydrates in immune evasion in AIDS, Nat. Med. 4 (1998) 679–684.
[47] T. Tokatlian, B.J. Read, C.A. Jones, D.W. Kulp, S. Menis, J.Y.H. Chang, J. M. Steichen, S. Kumari, J.D. Allen, E.L. Dane, A. Liguori, M. Sangesland, D. Lingwood, M. Crispin, W.R. Schief, D.J. Irvine, Innate immune recognition of glycans targets HIV nanoparticle immunogens to germinal centers, Science 363 (2019) 649–654, https://doi.org/10.1126/science.aat9120.
[48] L. Li, T. Zheng, T. Wang, Z. Zhang, T. Gong, X. Sun, Virus envelope-like self-assembled nanoparticles based on α-CD/PEG for antigens targeting to dendritic cells, J. Biomed. Nanotechnol. 13 (2017) 1490–1499, https://doi.org/10.1166/jbn.2017.2441.
[49] S.R. Pinnapireddy, M. Raafat El Assy, P. Schlote, U. Bakowsky, Glycosylated artificial virus-like hybrid vectors for advanced gene delivery, Polymers (Basel) 11 (2019), https://doi.org/10.3390/polym11020243.
[50] K. Jain, P. Kesharwani, U. Gupta, N.K. Jain, A review of glycosylated carriers for drug delivery, Biomaterials 33 (2012) 4166–4186, https://doi.org/10.1016/j.biomaterials.2012.02.033.
[51] H.J. Byeon, Q. Le Thao, S. Lee, S.Y. Min, E.S. Lee, B.S. Shin, H.-G. Choi, Y.S. Youn, Doxorubicin-loaded nanoparticles consisted of cationic- and mannose-modified-albumins for dual-targeting in brain tumors, J. Control. Release 225 (2016) 301–313, https://doi.org/10.1016/j.jconrel.2016.01.046.
[52] M.D. Tate, E.R. Job, Y.-M. Deng, V. Gunalan, S. Maurer-Stroh, P.C. Reading, Playing hide and seek: how glycosylation of the influenza virus hemagglutinin can modulate the immune response to infection, Viruses 6 (2014) 1294–1316, https://doi.org/10.3390/v6031294.
[53] K.-S. Chang, J. Jiang, Z. Cai, G. Luo, Human apolipoprotein e is required for infectivity and production of hepatitis C virus in cell culture, J. Virol. 81 (2007) 13783–13793, https://doi.org/10.1128/JVI.01091-07.
[54] K. Ezzat, M. Pernemalm, S. Pålsson, T.C. Roberts, P. Järver, A. Dondalska, B. Bestas, M.J. Sobkowiak, B. Levänen, M. Sköld, E.A. Thompson, O. Saher, O. K. Kari, T. Lajunen, E. Sverremark Ekström, C. Nilsson, Y. Ishchenko, T. Malm, M. J.A. Wood, U.F. Power, S. Masich, A. Lindén, J.K. Sandberg, J. Lehtiö, A.-L. Spetz, S. El Andaloussi, The viral protein corona directs viral pathogenesis and amyloid aggregation, Nat. Commun. 10 (2019) 2331, https://doi.org/10.1038/s41467-019-10192-2.
[55] F. Alexis, E. Pridgen, L.K. Molnar, O.C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol. Pharm. 5 (2008) 505–515, https://doi.org/10.1021/mp800051m.
[56] N.M. Gulati, P.L. Stewart, N.F. Steinmetz, Bioinspired shielding strategies for nanoparticle drug delivery applications, Mol. Pharm. 15 (2018) 2900–2909, https://doi.org/10.1021/acs.molpharmaceut.8b00292.
[57] A.S. Pitek, A.M. Wen, S. Shukla, N.F. Steinmetz, The protein corona of plant virus nanoparticles influences their dispersion properties, cellular interactions, and in vivo fates, Small 12 (2016) 1758–1769, https://doi.org/10.1002/smll.201502458.
[58] C. Leng, H.-C. Hung, S. Sun, D. Wang, Y. Li, S. Jiang, Z. Chen, Probing the surface hydration of nonfouling zwitterionic and PEG materials in contact with proteins, ACS Appl. Mater. Interfaces 7 (2015) 16881–16888, https://doi.org/10.1021/acsami.5b05627.
[59] S. Ashraf, J. Park, M.A. Bichelberger, K. Kantner, R. Hartmann, P. Maffre, A. H. Said, N. Feliu, J. Lee, D. Lee, G.U. Nienhaus, S. Kim, W.J. Parak, Zwitterionic surface coating of quantum dots reduces protein adsorption and cellular uptake, Nanoscale 8 (2016) 17794–17800, https://doi.org/10.1039/c6nr05805a.
[60] S. Chen, J. Zheng, L. Li, S. Jiang, Strong resistance of phosphorylcholine self-assembled monolayers to protein adsorption: insights into nonfouling properties of zwitterionic materials, J. Am. Chem. Soc. 127 (2005) 14473–14478, https://doi.org/10.1021/ja054169u.
[61] D. Maiolo, P. Del Pino, P. Metrangolo, W.J. Parak, F. Baldelli Bombelli, Nanomedicine delivery: does protein corona route to the target or off road? Nanomedicine (London) 10 (2015) 3231–3247, https://doi.org/10.2217/nnm.15.163.
[62] J. Witten, T. Samad, K. Ribbeck, Selective permeability of mucus barriers, Curr. Opin. Biotechnol. 52 (2018) 124–133, https://doi.org/10.1016/j.copbio.2018.03.010.
[63] S.K. Lai, E. O'Hanlon, S. Harrold, S.T. Man, Y.-Y. Wang, R. Cone, J. Hanes, Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus, PNAS 104 (2007) 1482–1487.
[64] L.M. Ensign, R. Cone, J. Hanes, Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers, Adv. Drug Deliv. Rev. 64 (2012) 557–570, https://doi.org/10.1016/j.addr.2011.12.009.
[65] L.M. Ensign, B.C. Tang, Y.-Y. Wang, T.A. Tse, T. Hoen, R. Cone, J. Hanes, Mucus-penetrating nanoparticles for vaginal drug delivery protect against herpes simplex virus, Sci. Transl. Med. 4 (2012), 138ra79, https://doi.org/10.1126/scitranslmed.3003453.
[66] C. Liu, H. Xu, Y. Sun, X. Zhang, H. Cheng, S. Mao, Design of virus-mimicking polyelectrolyte complexes for enhanced oral insulin delivery, J. Pharm. Sci. 108 (2019) 3408–3415, https://doi.org/10.1016/j.xphs.2019.05.034.
[67] X. Zhu, J. Wu, W. Shan, Z. Zhou, M. Liu, Y. Huang, Sub-50 nm nanoparticles with biomimetic surfaces to sequentially overcome the mucosal diffusion barrier and the epithelial absorption barrier, Adv. Funct. Mater. 26 (2016) 2728–2738, https://doi.org/10.1002/adfm.201505000.
[68] W. Shan, Y. Cui, M. Liu, L. Wu, Y. Xiang, Q. Guo, Z. Zhang, Y. Huang, Systematic evaluation of the toxicity and biodistribution of virus mimicking mucus-penetrating DLPC-NPs as oral drug delivery system, Int. J. Pharm. 530 (2017) 89–98, https://doi.org/10.1016/j.ijpharm.2017.07.061.
[69] J. Wu, Y. Zheng, M. Liu, W. Shan, Z. Zhang, Y. Huang, Biomimetic viruslike and charge reversible nanoparticles to sequentially overcome mucus and epithelial barriers for oral insulin delivery, ACS Appl. Mater. Interfaces 10 (2018) 9916–9928, https://doi.org/10.1021/acsami.7b16524.
[70] A. Verma, F. Stellacci, Effect of surface properties on nanoparticle-cell interactions, Small 6 (2010) 12–21, https://doi.org/10.1002/smll.200901158.
[71] J. Grove, M. Marsh, The cell biology of receptor-mediated virus entry, J. Cell Biol. 195 (2011) 1071–1082, https://doi.org/10.1083/jcb.201108131.
[72] R. Hennig, K. Pollinger, A. Veser, M. Breunig, A. Goepferich, Nanoparticle multivalency counterbalances the ligand affinity loss upon PEGylation, J. Control. Release 194 (2014) 20–27, https://doi.org/10.1016/j.jconrel.2014.07.062.
[73] W. Hild, K. Pollinger, A. Caporale, C. Cabrele, M. Keller, N. Pluym, A. Buschauer, R. Rachel, J. Tessmar, M. Breunig, A. Goepferich, G protein-coupled receptors function as logic gates for nanoparticle binding and cell uptake, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 10667–10672, https://doi.org/10.1073/pnas.0912782107.
[74] S. Maslanka Figueroa, A. Veser, K. Abstiens, D. Fleischmann, S. Beck, A. Goepferich, Influenza A Virus Mimetic Nanoparticles Trigger Selective Cell Uptake, Proc. Natl. Acad. Sci. U. S. A, States of America, 2019, https://doi.org/10.1073/pnas.1902563116.
[75] J. Zhou, A.V. Kroll, M. Holay, R.H. Fang, L. Zhang, Biomimetic nanotechnology toward personalized vaccines, Adv. Mater. Weinheim. 32 (2020), e1901255, https://doi.org/10.1002/adma.201901255.
[76] S. Chattopadhyay, J.-Y. Chen, H.-W. Chen, C.-M.J. Hu, Nanoparticle vaccines adopting virus-like features for enhanced immune potentiation, Nanotheranostics 1 (2017) 244–260, https://doi.org/10.7150/ntno.19796.
[77] S. Boulant, M. Stanifer, P.-Y. Lozach, Dynamics of virus-receptor interactions in virus binding, signaling, and endocytosis, Viruses 7 (2015) 2794–2815, https://doi.org/10.3390/v7062747.
[78] J.C. Jones, E.A. Turpin, H. Bultmann, C.R. Brandt, S. Schultz-Cherry, Inhibition of influenza virus infection by a novel antiviral peptide that targets viral attachment to cells, J. Virol. 80 (2006) 11960–11967, https://doi.org/10.1128/JVI.01678-06.
[79] W. Rubas, A.C. Banerjea, H. Gallati, P.P. Speiser, W.K. Joklik, Incorporation of the reovirus M cell attachment protein into small unilamellar vesicles: incorporation efficiency and binding capability to L929 cells in vitro, J. Microencapsul. 7 (1990) 385–395, https://doi.org/10.3109/02652049009021848.
[80] Q. Liu, M. Somiya, M. Iijima, K. Tatematsu, S.'i. Kuroda, A hepatitis B virus-derived human hepatic cell-specific heparin-binding peptide: identification and application to a drug delivery system, Biomater. Sci. 7 (2018) 322–335, https://doi.org/10.1039/c8bm01134f.
[81] X. Zhang, Q. Zhang, Q. Peng, J. Zhou, L. Liao, X. Sun, L. Zhang, T. Gong, Hepatitis B virus preS1-derived lipopeptide functionalized liposomes for targeting of hepatic cells, Biomaterials 35 (2014) 6130–6141, https://doi.org/10.1016/j.biomaterials.2014.04.037.
[82] M. Somiya, S. 'i. Kuroda, Development of a virus-mimicking nanocarrier for drug delivery systems: the bio-nanocapsule, Adv. Drug Deliv. Rev. 95 (2015) 77–89, https://doi.org/10.1016/j.addr.2015.10.003.
[83] B.B. Finlay, G. McFadden, Anti-immunology: evasion of the host immune system by bacterial and viral pathogens, Cell 124 (2006) 767–782, https://doi.org/10.1016/j.cell.2006.01.034.
[84] J. Jung, M. Somiya, S.-Y. Jeong, E.K. Choi, S.'i. Kuroda, Low immunogenic bio-nanocapsule based on hepatitis B virus escape mutants, Nanomedicine 14 (2018) 595–600, https://doi.org/10.1016/j.nano.2017.11.017.
[85] L. You, J. Wang, T. Liu, Y. Zhang, X. Han, T. Wang, S. Guo, T. Dong, J. Xu, G. J. Anderson, Q. Liu, Y.-Z. Chang, X. Lou, G. Nie, Targeted brain delivery of rabies virus glycoprotein 29-modified Deferoxamine-loaded nanoparticles reverses functional deficits in parkinsonian mice, ACS Nano 12 (2018) 4123–4139, https://doi.org/10.1021/acsnano.7b08172.
[86] H.J. Jang, E.J. Jeong, K.Y. Lee, Carbon dioxide-generating PLG nanoparticles for controlled anti-cancer drug delivery, Pharm. Res. 35 (2018) 59, https://doi.org/10.1007/s11095-018-2359-8.
[87] H. Derakhshankhah, S. Jafari, Cell penetrating peptides: a concise review with emphasis on biomedical applications, Biomed. Pharmacother. 108 (2018) 1090–1096, https://doi.org/10.1016/j.biopha.2018.09.097.

[88] E. Koren, V.P. Torchilin, Cell-penetrating peptides: breaking through to the other side, Trends Mol. Med. 18 (2012) 385–393, https://doi.org/10.1016/j.molmed.2012.04.012.

[89] S. Fawell, J. Seery, Y. Daikh, C. Moore, L.L. Chen, B. Pepinsky, J. Barsoum, Tat-mediated delivery of heterologous proteins into cells, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 664–668.

[90] X. Qi, T. Droste, C.C. Kao, Cell-penetrating peptides derived from viral capsid proteins, Mol. Plant Microbe In. 24 (2011) 25–36.

[91] V.P. Torchilin, Tat peptide-mediated intracellular delivery of pharmaceutical nanocarriers, Adv. Drug Deliv. Rev. 60 (2008) 548–558, https://doi.org/10.1016/j.addr.2007.10.008.

[92] L. Pan, Q. He, J. Liu, Y. Chen, M. Ma, L. Zhang, J. Shi, Nuclear-targeted drug delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles, J. Am. Chem. Soc. 134 (2012) 5722–5725, https://doi.org/10.1021/ja211035w.

[93] S. Santra, H. Yang, D. Dutta, J.T. Stanley, P.H. Holloway, W. Tan, B.M. Moudgil, R.A. Mericle, TAT conjugated, FITC doped silica nanoparticles for bioimaging applications, Chem. Commun. (Camb.) (2004) 2810–2811, https://doi.org/10.1039/b411916a.

[94] P. Wunderbaldinger, L. Josephson, R. Weissleder, Tat peptide directs enhanced clearance and hepatic permeability of magnetic nanoparticles, Bioconjug. Chem. 13 (2002) 264–268, https://doi.org/10.1021/bc015563u.

[95] M. Lewin, N. Carlesso, C.-H. Tung, X.-W. Tang, D. Cory, D.T. Scadden, R. Weissleder, Tat peptide-derivatized magnetic nanoparticles allow in vivo tracking and recovery of progenitor cells, Nat. Biotechnol. 18 (2000) 410–414.

[96] M.D. Phan, H. Kim, S. Lee, C.-J. Yu, B. Moon, K. Shin, HIV peptide-mediated binding behaviors of nanoparticles on a lipid membrane, Langmuir 33 (2017) 2590–2595, https://doi.org/10.1021/acs.langmuir.6b04234.

[97] J.M. de La Fuente, C.C. Berry, Tat peptide as an efficient molecule to translocate gold nanoparticles into the cell nucleus, Bioconjug. Chem. 16 (2005) 1176–1180.

[98] L. Liu, K. Guo, J. Lu, S.S. Venkatraman, D. Luo, K.C. Ng, E.-A. Ling, S. Moochhala, Y.-Y. Yang, Biologically active core/shell nanoparticles self-assembled from cholesterol-terminated PEG-TAT for drug delivery across the blood-brain barrier, Biomaterials 29 (2008) 1509–1517, https://doi.org/10.1016/j.biomaterials.2007.11.014.

[99] Y. Liu, H. Wang, K.-i. Kamei, M. Yan, K.-J. Chen, Q. Yuan, L. Shi, Y. Lu, H.-R. Tseng, Delivery of intact transcription factor by using self-assembled supramolecular nanoparticles, Angew. Chem. 123 (2011) 3114–3118, https://doi.org/10.1002/ange.201005740.

[100] X.-B. Xiong, A. Lavasanifar, Traceable multifunctional micellar nanocarriers for cancer-targeted co-delivery of MDR-1 siRNA and doxorubicin, ACS Nano 5 (2011) 5202–5213, https://doi.org/10.1021/nn2013707.

[101] K.S. Rao, M.K. Reddy, J.L. Horning, V. Labhasetwar, TAT-conjugated nanoparticles for the CNS delivery of anti-HIV drugs, Biomaterials 29 (2008) 4429–4438, https://doi.org/10.1016/j.biomaterials.2008.08.004.

[102] X. Gao, S. Li, F. Ding, H. Fan, L. Shi, L. Zhu, J. Li, J. Feng, X. Zhu, C. Zhang, Rapid detection of exosomal MicroRNAs using virus-mimicking fusogenic vesicles, Angew. Chem. Int. Ed. Eng. 58 (2019) 8719–8723, https://doi.org/10.1002/anie.201901997.

[103] R. Hennig, A. Veser, S. Kirchhof, A. Goepferich, Branched polymer–drug conjugates for multivalent blockade of angiotensin II receptors, Mol. Pharm. 12 (2015) 3292–3302, https://doi.org/10.1021/acs.molpharmaceut.5b00301.

[104] E.C. Dreaden, B.E. Gryder, L.A. Austin, B.A. Tene Defo, S.C. Hayden, M. Pi, L. D. Quarles, A.K. Oyelere, M.A. El-Sayed, Antiandrogen gold nanoparticles dual-target and overcome treatment resistance in hormone-insensitive prostate cancer cells, Bioconjug. Chem. 23 (2012) 1507–1512, https://doi.org/10.1021/bc300158k.

[105] E.H. Lim, N. Danthi, M. Bednarski, K.C.P. Li, A review: integrin alphavbeta3-targeted molecular imaging and therapy in angiogenesis, Nanomedicine 1 (2005) 110–114, https://doi.org/10.1016/j.nano.2005.03.008.

[106] F. Danhier, A. Le Breton, V. Préat, RGD-based strategies to target alpha(v) beta(3) integrin in cancer therapy and diagnosis, Mol. Pharm. 9 (2012) 2961–2973, https://doi.org/10.1021/mp3002733.

[107] B. Lepenies, J. Lee, S. Sonkaria, Targeting C-type lectin receptors with multivalent carbohydrate ligands, Adv. Drug Deliv. Rev. 65 (2013) 1271–1281, https://doi.org/10.1016/j.addr.2013.05.007.

[108] J. Yoo, C. Park, G. Yi, D. Lee, H. Koo, Active targeting strategies using biological ligands for nanoparticle drug delivery systems, Cancers (Basel) 11 (2019), https://doi.org/10.3390/cancers11050640.

[109] A.M. Alkilany, L. Zhu, H. Weller, A. Mews, W.J. Parak, M. Barz, N. Feliu, Ligand density on nanoparticles: a parameter with critical impact on nanomedicine, Adv. Drug Deliv. Rev. 143 (2019) 22–36, https://doi.org/10.1016/j.addr.2019.05.010.

[110] A.O. Saeed, J.P. Magnusson, E. Moradi, M. Soliman, W. Wang, S. Stolnik, K. J. Thurecht, S.M. Howdle, C. Alexander, Modular construction of multifunctional bioresponsive cell-targeted nanoparticles for gene delivery, Bioconjug. Chem. 22 (2011) 156–168, https://doi.org/10.1021/bc100149g.

[111] A. Fakhari, A. Baoum, T.J. Siahaan, K.B. Le, C. Berkland, Controlling ligand surface density optimizes nanoparticle binding to ICAM-1, J. Pharm. Sci. 100 (2011) 1045–1056, https://doi.org/10.1002/jps.22342.

[112] D.R. Elias, A. Poloukhtine, V. Popik, A. Tsourkas, Effect of ligand density, receptor density, and nanoparticle size on cell targeting, Nanomedicine 9 (2013) 194–201, https://doi.org/10.1016/j.nano.2012.05.015.

[113] S. Maslanka Figueroa, D. Fleischmann, S. Beck, A. Goepferich, The effect of ligand mobility on the cellular interaction of multivalent nanoparticles, Macromol. Biosci. 303 (2020) 1900427, https://doi.org/10.1002/mabi.201900427.

[114] Z. Poon, S. Chen, A.C. Engler, H.-i. Lee, E. Atas, G. von Maltzahn, S.N. Bhatia, P. T. Hammond, Ligand-clustered "patchy" nanoparticles for modulated cellular uptake and in vivo tumor targeting, Angew. Chem. Int. Ed. Eng. 49 (2010) 7266–7270, https://doi.org/10.1002/anie.201003445.

[115] H. Chen, H. Paholak, M. Ito, K. Sansanaphongpricha, W. Qian, Y. Che, D. Sun, 'Living' PEGylation on gold nanoparticles to optimize cancer cell uptake by controlling targeting ligand and charge densities, Nanotechnology 24 (2013) 355101, https://doi.org/10.1088/0957-4484/24/35/355101.

[116] K. Abstiens, M. Gregoritza, A.M. Goepferich, Ligand density and linker length are critical factors for multivalent nanoparticle-receptor interactions, ACS Appl. Mater. Interfaces 11 (2019) 1311–1320, https://doi.org/10.1021/acsami.8b18843.

[117] P.L. Stewart, C.Y. Chiu, S. Huang, T. Muir, Y. Zhao, B. Chait, P. Mathias, G. R. Nemerow, Cryo-EM visualization of an exposed RGD epitope on adenovirus that escapes antibody neutralization, EMBO J. 16 (1997) 1189–1198.

[118] C.Y. Chiu, P. Mathias, G.R. Nemerow, P.L. Stewart, Structure of adenovirus complexed with its internalization receptor, αvβ5Integrin, J. Virol. 73 (1999) 6759–6768.

[119] M.J. Goldman, J.M. Wilson, Expression of alpha v beta 5 integrin is necessary for efficient adenovirus-mediated gene transfer in the human airway, J. Virol. 69 (1995) 5951–5958.

[120] Q.K.T. Ng, M.K. Sutton, P. Soonsawad, L. Xing, H. Cheng, T. Segura, Engineering clustered ligand binding into nonviral vectors: alphavbeta3 targeting as an example, Mol. Ther. 17 (2009) 828–836, https://doi.org/10.1038/mt.2009.11.

[121] E. Moradi, D. Vllasaliu, M. Garnett, F. Falcone, S. Stolnik, Ligand density and clustering effects on endocytosis of folate modified nanoparticles, RSC Adv. 2 (2012) 3025, https://doi.org/10.1039/c2ra01168a.

[122] C.L. Modery-Pawlowski, A.S. Gupta, Heteromultivalent ligand-decoration for actively targeted nanomedicine, Biomaterials 35 (2014) 2568–2579, https://doi.org/10.1016/j.biomaterials.2013.12.047.

[123] H. Gao, Perspectives on dual targeting delivery systems for brain tumors, J. NeuroImmune Pharmacol. 12 (2017) 6–16, https://doi.org/10.1007/s11481-016-9687-4.

[124] Y. Liu, Q. Chen, M. Xu, G. Guan, W. Hu, Y. Liang, X. Zhao, M. Qiao, D. Chen, H. Liu, Single peptide ligand-functionalized uniform hollow mesoporous silica nanoparticles achieving dual-targeting drug delivery to tumor cells and angiogenic blood vessel cells, Int. J. Nanomedicine 10 (2015) 1855–1867, https://doi.org/10.2147/IJN.S75098.

[125] A.S. Gupta, Nanomedicine approaches in vascular disease: a review, Nanomedicine 7 (2011) 763–779, https://doi.org/10.1016/j.nano.2011.04.001.

[126] Q. Xu, Y. Liu, S. Su, W. Li, C. Chen, Y. Wu, Anti-tumor activity of paclitaxel through dual-targeting carrier of cyclic RGD and transferrin conjugated hyperbranched copolymer nanoparticles, Biomaterials 33 (2012) 1627–1639, https://doi.org/10.1016/j.biomaterials.2011.11.012.

[127] S. Bhattacharyya, J.A. Khan, G.L. Curran, J.D. Robertson, R. Bhattacharya, P. Mukherjee, Efficient delivery of gold nanoparticles by dual receptor targeting, Adv. Mater. Weinheim. 23 (2011) 5034–5038, https://doi.org/10.1002/adma.201102287.

[128] M.-Z. Zhang, C. Li, B.-Y. Fang, M.-H. Yao, Q.-Q. Ren, L. Zhang, Y.-D. Zhao, High transfection efficiency of quantum dot-antisense oligonucleotide nanoparticles in cancer cells through dual-receptor synergistic targeting, Nanotechnology 25 (2014) 255102, https://doi.org/10.1088/0957-4484/25/25/255102.

[129] R.M. Levine, E. Kokkoli, Dual-ligand α5β1 and α6β4 integrin targeting enhances gene delivery and selectivity to cancer cells, J. Control. Release 251 (2017) 24–36, https://doi.org/10.1016/j.jconrel.2017.02.017.

[130] R.C. Gunawan, D. Almeda, D.T. Auguste, Complementary targeting of liposomes to IL-1α and TNF-α activated endothelial cells via the transient expression of VCAM1 and E-selectin, Biomaterials 32 (2011) 9848–9853, https://doi.org/10.1016/j.biomaterials.2011.08.093.

[131] M. Shadidi, M. Sioud, Selective targeting of cancer cells using synthetic peptides, Drug Resist. Updat. 6 (2003) 363–371, https://doi.org/10.1016/j.drup.2003.11.002.

[132] K.C. Tjandra, P. Thordarson, Multivalency in drug delivery-when is it too much of a good thing? Bioconjug. Chem. 30 (2019) 503–514, https://doi.org/10.1021/acs.bioconjchem.8b00804.

[133] H. He, Y. Li, X.-R. Jia, J. Du, X. Ying, W.-L. Lu, J.-N. Lou, Y. Wei, PEGylated poly (amidoamine) dendrimer-based dual-targeting carrier for treating brain tumors, Biomaterials 32 (2011) 478–487, https://doi.org/10.1016/j.biomaterials.2010.09.002.

[134] K. Laginha, D. Mumbengegwi, T. Allen, Liposomes targeted via two different antibodies: assay, B-cell binding and cytotoxicity, Biochim. Biophys. Acta 1711 (2005) 25–32, https://doi.org/10.1016/j.bbamem.2005.02.007.

[135] S. Angioletti-Uberti, Exploiting receptor competition to enhance nanoparticle binding selectivity, Phys. Rev. Lett. 118 (2017) 68001, https://doi.org/10.1103/PhysRevLett.118.068001.

[136] M. Delguste, C. Zeippen, B. Machiels, J. Mast, L. Gillet, D. Alsteens, Multivalent binding of herpesvirus to living cells is tightly regulated during infection, Sci. Adv. 4 (2018).

[137] C.B. Wilen, J.C. Tilton, R.W. Doms, HIV: cell binding and entry, Cold Spring Harbor Perspect. Med. 2 (2012), https://doi.org/10.1101/cshperspect.a006866.

[138] Q.-S. Xia, H.-M. Ding, Y.-Q. Ma, Can dual-ligand targeting enhance cellular uptake of nanoparticles? Nanoscale 9 (2017) 8982–8989, https://doi.org/10.1039/c7nr01020f.

[139] Y. Liu, Y. Hui, R. Ran, G.-Z. Yang, D. Wibowo, H.-F. Wang, A.P.J. Middelberg, C.-X. Zhao, Synergetic combinations of dual-targeting ligands for enhanced in vitro

and in vivo tumor targeting, Adv. Healthc. Mater. 7 (2018), e1800106, https://doi.org/10.1002/adhm.201800106.
[140] M.C. Lo Giudice, F. Meder, E. Polo, S.S. Thomas, K. Alnahdi, S. Lara, K.A. Dawson, Constructing bifunctional nanoparticles for dual targeting: improved grafting and surface recognition assessment of multiple ligand nanoparticles, Nanoscale 8 (2016) 16969–16975, https://doi.org/10.1039/c6nr05478a.
[141] M. Gui, W. Song, H. Zhou, J. Xu, S. Chen, Y. Xiang, X. Wang, Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding, Cell Res. 27 (2017) 119–129, https://doi.org/10.1038/cr.2016.152.
[142] T. Tang, M. Bidon, J.A. Jaimes, G.R. Whittaker, S. Daniel, Coronavirus membrane fusion mechanism offers a potential target for antiviral development, Antivir. Res. 178 (2020) 104792, https://doi.org/10.1016/j.antiviral.2020.104792.
[143] Z. Wang, W. Qin, J. Zhuang, M. Wu, Q. Li, C. Fan, Y. Zhang, Virus-mimicking cell capture using Heterovalency magnetic DNA Nanoclaws, ACS Appl. Mater. Interfaces 11 (2019) 12244–12252, https://doi.org/10.1021/acsami.8b21998.
[144] R.C. Gunawan, D.T. Auguste, Immunoliposomes that target endothelium in vitro are dependent on lipid raft formation, Mol. Pharm. 7 (2010) 1569–1575, https://doi.org/10.1021/mp9003095.
[145] R.C. Gunawan, D.T. Auguste, The role of antibody synergy and membrane fluidity in the vascular targeting of immunoliposomes, Biomaterials 31 (2010) 900–907, https://doi.org/10.1016/j.biomaterials.2009.09.107.
[146] G. Covarrubias, F. He, S. Raghunathan, O. Turan, P.M. Peiris, W.P. Schiemann, E. Karathanasis, Effective treatment of cancer metastasis using a dual-ligand nanoparticle, PLoS One 14 (2019), e0220474, https://doi.org/10.1371/journal.pone.0220474.
[147] E. Doolittle, P.M. Peiris, G. Doron, A. Goldberg, S. Tucci, S. Rao, S. Shah, M. Sylvestre, P. Govender, O. Turan, Z. Lee, W.P. Schiemann, E. Karathanasis, Spatiotemporal targeting of a dual-ligand nanoparticle to cancer metastasis, ACS Nano 9 (2015) 8012–8021, https://doi.org/10.1021/acsnano.5b01552.
[148] P.M. Peiris, F. He, G. Covarrubias, S. Raghunathan, O. Turan, M. Lorkowski, B. Gnanasambandam, C. Wu, W.P. Schiemann, E. Karathanasis, Precise targeting of cancer metastasis using multi-ligand nanoparticles incorporating four different ligands, Nanoscale 10 (2018) 6861–6871, https://doi.org/10.1039/c8nr02513d.
[149] Z. Cheng, A. Al Zaki, J.Z. Hui, V.R. Muzykantov, A. Tsourkas, Multifunctional nanoparticles: cost versus benefit of adding targeting and imaging capabilities, Science 338 (2012) 903–910, https://doi.org/10.1126/science.1226338.
[150] T. Jia, J. Choi, J. Ciccione, M. Henry, A. Mehdi, J. Martinez, B. Eymin, G. Subra, J.-L. Coll, Heteromultivalent targeting of integrin αvβ3 and neuropilin 1 promotes cell survival via the activation of the IGF-1/insulin receptors, Biomaterials 155 (2018) 64–79, https://doi.org/10.1016/j.biomaterials.2017.10.042.
[151] E. Kluza, D.W.J. van der Schaft, P.A.I. Hautvast, W.J.M. Mulder, K.H. Mayo, A. W. Griffioen, G.J. Strijkers, K. Nicolay, Synergistic targeting of alphavbeta3 integrin and galectin-1 with heteromultivalent paramagnetic liposomes for combined MR imaging and treatment of angiogenesis, Nano Lett. 10 (2010) 52–58, https://doi.org/10.1021/nl902659g.
[152] E. Kluza, I. Jacobs, S.J.C.G. Hectors, K.H. Mayo, A.W. Griffioen, G.J. Strijkers, K. Nicolay, Dual-targeting of αvβ3 and galectin-1 improves the specificity of paramagnetic/fluorescent liposomes to tumor endothelium in vivo, J. Control. Release 158 (2012) 207–214, https://doi.org/10.1016/j.jconrel.2011.10.032.
[153] R.R. Sawant, A.M. Jhaveri, A. Koshkaryev, F. Qureshi, V.P. Torchilin, The effect of dual ligand-targeted micelles on the delivery and efficacy of poorly soluble drug for cancer therapy, J. Drug Target. 21 (2013) 630–638, https://doi.org/10.3109/1061186X.2013.789032.
[154] P. Sapra, T.M. Allen, Improved outcome when B-cell lymphoma is treated with combinations of immunoliposomal anticancer drugs targeted to both the CD19 and CD20 epitopes, Clin. Cancer Res. 10 (2004) 2530–2537.
[155] F. Pastorino, C. Brignole, D. Di Paolo, B. Nico, A. Pezzolo, D. Marimpietri, G. Pagnan, F. Piccardi, M. Cilli, R. Longhi, D. Ribatti, A. Corti, T.M. Allen, M. Ponzoni, Targeting liposomal chemotherapy via both tumor cell-specific and tumor vasculature-specific ligands potentiates therapeutic efficacy, Cancer Res. 66 (2006) 10073–10082, https://doi.org/10.1158/0008-5472.CAN-06-2117.
[156] J.M. Saul, A.V. Annapragada, R.V. Bellamkonda, A dual-ligand approach for enhancing targeting selectivity of therapeutic nanocarriers, J. Control. Release 114 (2006) 277–287, https://doi.org/10.1016/j.jconrel.2006.05.028.
[157] K. Mack, R. Rüger, S. Fellermeier, O. Seifert, R.E. Kontermann, Dual targeting of tumor cells with bispecific single-chain Fv-immunoliposomes, Antibodies 1 (2012) 199–214, https://doi.org/10.3390/antib1020199.
[158] X. Li, H. Zhou, L. Yang, G. Du, A.S. Pai-Panandiker, X. Huang, B. Yan, Enhancement of cell recognition in vitro by dual-ligand cancer targeting gold nanoparticles, Biomaterials 32 (2011) 2540–2545, https://doi.org/10.1016/j.biomaterials.2010.12.031.
[159] S. Dixit, K. Miller, Y. Zhu, E. McKinnon, T. Novak, M.E. Kenney, A.-M. Broome, Dual receptor-targeted theranostic nanoparticles for localized delivery and activation of photodynamic therapy drug in glioblastomas, Mol. Pharm. 12 (2015) 3250–3260, https://doi.org/10.1021/acs.molpharmaceut.5b00216.
[160] C. Jang, J.H. Lee, A. Sahu, G. Tae, The synergistic effect of folate and RGD dual ligand of nanographene oxide on tumor targeting and photothermal therapy in vivo, Nanoscale 7 (2015) 18584–18594, https://doi.org/10.1039/c5nr05067g.
[161] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (2016) 16014, https://doi.org/10.1038/natrevmats.2016.14.
[162] Q. Dai, S. Wilhelm, D. Ding, A.M. Syed, S. Sindhwani, Y. Zhang, Y.Y. Chen, P. MacMillan, W.C.W. Chan, Quantifying the ligand-coated nanoparticle delivery to cancer cells in solid tumors, ACS Nano 12 (2018) 8423–8435, https://doi.org/10.1021/acsnano.8b03900.
[163] Y.-H. Cheng, C. He, J.E. Riviere, N.A. Monteiro-Riviere, Z. Lin, Meta-analysis of nanoparticle delivery to tumors using a physiologically based pharmacokinetic modeling and simulation approach, ACS Nano 14 (2020) 3075–3095, https://doi.org/10.1021/acsnano.9b08142.
[164] E.A. Berger, P.M. Murphy, J.M. Farber, Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease, Annu. Rev. Immunol. 17 (1999) 657–700, https://doi.org/10.1146/annurev.immunol.17.1.657.
[165] G.R. Nemerow, P.L. Stewart, Role of alpha(v) integrins in adenovirus cell entry and gene delivery, Microbiol. Mol. Biol. Rev. 63 (1999) 725–734.
[166] E. Li, D. Stupack, G.M. Bokoch, G.R. Nemerow, Adenovirus endocytosis requires actin cytoskeleton reorganization mediated by rho family GTPases, J. Virol. 72 (1998) 8806–8812.
[167] S.R. Singh, H.E. Grossniklaus, S.J. Kang, H.F. Edelhauser, B.K. Ambati, U. B. Kompella, Intravenous transferrin, RGD peptide and dual-targeted nanoparticles enhance anti-VEGF intraceptor gene delivery to laser-induced CNV, Gene Ther. 16 (2009) 645–659, https://doi.org/10.1038/gt.2008.185.
[168] M.S. Chan, L.S. Liu, H.M. Leung, P.K. Lo, Cancer-cell-specific mitochondria-targeted drug delivery by dual-ligand-functionalized nanodiamonds circumvent drug resistance, ACS Appl. Mater. Interfaces 9 (2017) 11780–11789, https://doi.org/10.1021/acsami.6b15954.
[169] D. Chen, B. Li, S. Cai, P. Wang, S. Peng, Y. Sheng, Y. He, Y. Gu, H. Chen, Dual targeting luminescent gold nanoclusters for tumor imaging and deep tissue therapy, Biomaterials 100 (2016) 1–16, https://doi.org/10.1016/j.biomaterials.2016.05.017.
[170] C. Peitsch, H.-D. Klenk, W. Garten, E. Böttcher-Friebertshäuser, Activation of influenza a viruses by host proteases from swine airway epithelium, J. Virol. 88 (2014) 282–291, https://doi.org/10.1128/JVI.01635-13.
[171] S.C. Owen, D.P.Y. Chan, M.S. Shoichet, Polymeric micelle stability, Nano Today 7 (2012) 53–65, https://doi.org/10.1016/j.nantod.2012.01.002.
[172] G. Bkaily, S. Sleiman, J. Stephan, C. Asselin, S. Choufani, M. Kamal, D. Jacques, F. Gobeil, P. D'Orléans-Juste, Angiotensin II AT1 receptor internalization, translocation and de novo synthesis modulate cytosolic and nuclear calcium in human vascular smooth muscle cells, Can. J. Physiol. Pharmacol. 81 (2003) 274–287, https://doi.org/10.1139/y03-007.
[173] T.Q. Nguyen, R. Goldschmeding, The mesangial cell in diabetic nephropathy, in: J.J. Roelofs, L. Vogt (Eds.), Diabetic Nephropathy: Pathophysiology and Clinical Aspects, Springer International Publishing, Cham, 2019, pp. 143–151.
[174] International Diabetes Federation, IDF Diabetes Atlas, IDF Diabetes Atlas 8, 2017, pp. 1–50.
[175] S. Maslanka Figueroa, D. Fleischmann, S. Beck, P. Tauber, R. Witzgall, F. Schweda, A. Goepferich, Nanoparticles mimicking viral cell recognition strategies are superior transporters into mesangial cells, Adv. Sci. (2020), 1903204, https://doi.org/10.1002/advs.201903204.
[176] R. Hennig, A. Ohlmann, J. Staffel, K. Pollinger, A. Haunberger, M. Breunig, F. Schweda, E.R. Tamm, A. Goepferich, Multivalent nanoparticles bind the retinal and choroidal vasculature, J. Control. Release 220 (2015) 265–274, https://doi.org/10.1016/j.jconrel.2015.10.033.
[177] S. Luisoni, U.F. Greber, Biology of Adenovirus Cell Entry, 2016, pp. 27–58.
[178] D. Fleischmann, S. Maslanka Figueroa, S. Beck, K. Abstiens, R. Witzgall, F. Schweda, P. Tauber, A. Goepferich, Adenovirus-mimetic nanoparticles: sequential ligand-receptor interplay as a universal tool for enhanced in vitro/in vivo cell identification, ACS Appl. Mater. Interfaces (2020), https://doi.org/10.1021/acsami.0c10057.
[179] S. Wang, P. Huang, X. Chen, Stimuli-responsive programmed specific targeting in nanomedicine, ACS Nano 10 (2016) 2991–2994, https://doi.org/10.1021/acsnano.6b00870.
[180] Q. Yao, L. Kou, Y. Tu, L. Zhu, MMP-responsive 'Smart' drug delivery and tumor targeting, Trends Pharmacol. Sci. 39 (2018) 766–781, https://doi.org/10.1016/j.tips.2018.06.003.
[181] C.J. Malemud, Matrix metalloproteinases (MMPs) in health and disease: an overview, Front. Biosci. 11 (2006) 1696–1701, https://doi.org/10.2741/1915.
[182] F. Guo, J. Wu, W. Wu, D. Huang, Q. Yan, Q. Yang, Y. Gao, G. Yang, PEGylated self-assembled enzyme-responsive nanoparticles for effective targeted therapy against lung tumors, J. Nanobiotechnol. 16 (2018) 57, https://doi.org/10.1186/s12951-018-0384-8.
[183] H. Li, M. Miteva, K.C. Kirkbride, M.J. Cheng, C.E. Nelson, E.M. Simpson, M. K. Gupta, C.L. Duvall, T.D. Giorgio, Dual MMP7-proximity-activated and folate receptor-targeted nanoparticles for siRNA delivery, Biomacromolecules 16 (2015) 192–201, https://doi.org/10.1021/bm501394m.
[184] H. Han, D. Valdepérez, Q. Jin, B. Yang, Z. Li, Y. Wu, B. Pelaz, W.J. Parak, J. Ji, Dual enzymatic reaction-assisted gemcitabine delivery systems for programmed pancreatic cancer therapy, ACS Nano 11 (2017) 1281–1291, https://doi.org/10.1021/acsnano.6b05541.
[185] L. Zhu, T. Wang, F. Perche, A. Taigind, V.P. Torchilin, Enhanced anticancer activity of nanopreparation containing an MMP2-sensitive PEG-drug conjugate and cell-penetrating moiety, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 17047–17052, https://doi.org/10.1073/pnas.1304987110.
[186] L. Zhu, P. Kate, V.P. Torchilin, Matrix metalloprotease 2-responsive multifunctional liposomal nanocarrier for enhanced tumor targeting, ACS Nano 6 (2012) 3491–3498, https://doi.org/10.1021/nn300524f.
[187] M.T. Proetto, C.E. Callmann, J. Cliff, C.J. Szymanski, D. Hu, S.B. Howell, J. E. Evans, G. Orr, N.C. Gianneschi, Tumor retention of enzyme-responsive Pt(II) drug-loaded nanoparticles imaged by nanoscale secondary ion mass spectrometry and fluorescence microscopy, ACS Cent. Sci. 4 (2018) 1477–1484, https://doi.org/10.1021/acscentsci.8b00444.

[188] M.M. Nguyen, A.S. Carlini, M.-P. Chien, S. Sonnenberg, C. Luo, R.L. Braden, K. G. Osborn, Y. Li, N.C. Gianneschi, K.L. Christman, Enzyme-responsive nanoparticles for targeted accumulation and prolonged retention in heart tissue after myocardial infarction, Adv. Mater. Weinheim. 27 (2015) 5547–5552, https://doi.org/10.1002/adma.201502003.
[189] C.E. Callmann, C.V. Barback, M.P. Thompson, D.J. Hall, R.F. Mattrey, N. C. Gianneschi, Therapeutic enzyme-responsive nanoparticles for targeted delivery and accumulation in tumors, Adv. Mater. Weinheim. 27 (2015) 4611–4615, https://doi.org/10.1002/adma.201501803.
[190] C. Liu, C. Sun, H. Huang, K. Janda, T. Edgington, Overexpression of legumain in tumors is significant for invasion/metastasis and a candidate enzymatic target for prodrug therapy, Cancer Res. 63 (2003) 2957–2964.
[191] Z. Liu, M. Xiong, J. Gong, Y. Zhang, N. Bai, Y. Luo, L. Li, Y. Wei, Y. Liu, X. Tan, R. Xiang, Legumain protease-activated TAT-liposome cargo for targeting tumours and their microenvironment, Nat. Commun. 5 (2014) 4280, https://doi.org/10.1038/ncomms5280.
[192] Y. Li, G. Liu, X. Wang, J. Hu, S. Liu, Enzyme-responsive polymeric vesicles for bacterial-strain-selective delivery of antimicrobial agents, Angew. Chem. Int. Ed. Eng. 55 (2016) 1760–1764, https://doi.org/10.1002/anie.201509401.
[193] I. Insua, E. Liamas, Z. Zhang, A.F.A. Peacock, A.M. Krachler, F. Fernandez-Trillo, Enzyme-responsive polyion complex (PIC) nanoparticles for the targeted delivery of antimicrobial polymers, Polym. Chem. 7 (2016) 2684–2690, https://doi.org/10.1039/c6py00146g.
[194] Q. Hu, P.S. Katti, Z. Gu, Enzyme-responsive nanomaterials for controlled drug delivery, Nanoscale 6 (2014) 12273–12286, https://doi.org/10.1039/c4nr04249b.
[195] Z. Zhang, X. Zhang, X. Xu, Y. Li, Y. Li, D. Zhong, Y. He, Z. Gu, Virus-inspired mimics based on dendritic lipopeptides for efficient tumor-specific infection and systemic drug delivery, Adv. Funct. Mater. 25 (2015) 5250–5260, https://doi.org/10.1002/adfm.201502049.
[196] Z.-Y. Li, Y. Liu, J.-J. Hu, Q. Xu, L.-H. Liu, H.-Z. Jia, W.-H. Chen, Q. Lei, L. Rong, X.-Z. Zhang, Stepwise-acid-active multifunctional mesoporous silica nanoparticles for tumor-specific nucleus-targeted drug delivery, ACS Appl. Mater. Interfaces 6 (2014) 14568–14575, https://doi.org/10.1021/am503846p.
[197] E. Vivès, J. Schmidt, A. Pèlegrin, Cell-penetrating and cell-targeting peptides in drug delivery, Biochim. Biophys. Acta 1786 (2008) 126–138, https://doi.org/10.1016/j.bbcan.2008.03.001.
[198] H. Gao, T. Cheng, J. Liu, J. Liu, C. Yang, L. Chu, Y. Zhang, R. Ma, L. Shi, Self-regulated multifunctional collaboration of targeted nanocarriers for enhanced tumor therapy, Biomacromolecules 15 (2014) 3634–3642, https://doi.org/10.1021/bm5009348.
[199] M. Xu, Y. Chen, P. Banerjee, L. Zong, L. Jiang, Dendritic cells targeting and pH-responsive multi-layered nanocomplexes for smart delivery of DNA vaccines, AAPS PharmSciTech 18 (2017) 2618–2625, https://doi.org/10.1208/s12249-017-0741-1.
[200] L. Jiang, Y. Liang, Q. Huo, Y. Pu, W. Lu, S. Han, J. Cao, B. He, Y. Sun, Viral capsids mimicking based on pH-sensitive biodegradable polymeric micelles for efficient anticancer drug delivery, J. Biomed. Nanotechnol. 14 (2018) 1409–1419, https://doi.org/10.1166/jbn.2018.2587.
[201] X. Zhang, X. Xu, Y. Li, C. Hu, Z. Zhang, Z. Gu, Virion-like membrane-breaking nanoparticles with tumor-activated cell-and-tissue dual-penetration conquer impermeable cancer, Adv. Mater. Weinheim. 30 (2018), e1707240, https://doi.org/10.1002/adma.201707240.
[202] K. Sasaki, K. Kogure, S. Chaki, Y. Nakamura, R. Moriguchi, H. Hamada, R. Danev, K. Nagayama, S. Futaki, H. Harashima, An artificial virus-like nano carrier system: enhanced endosomal escape of nanoparticles via synergistic action of pH-sensitive fusogenic peptide derivatives, Anal. Bioanal. Chem. 391 (2008) 2717–2727, https://doi.org/10.1007/s00216-008-2012-1.
[203] S. Wannasarit, S. Wang, P. Figueiredo, C. Trujillo, F. Eburnea, L. Simón-Gracia, A. Correia, Y. Ding, T. Teesalu, D. Liu, R. Wiwattanapatapee, H.A. Santos, W. Li, A virus-mimicking pH-responsive acetalated dextran-based membrane-active polymeric nanoparticle for intracellular delivery of antitumor therapeutics, Adv. Funct. Mater. 29 (2019) 1905352, https://doi.org/10.1002/adfm.201905352.
[204] D. Mudhakir, H. Harashima, Learning from the viral journey: how to enter cells and how to overcome intracellular barriers to reach the nucleus, AAPS J. 11 (2009) 65–77, https://doi.org/10.1208/s12248-009-9080-9.
[205] N. Song, L. Zhou, J. Li, Z. Pan, X. He, H. Tan, X. Wan, J. Li, R. Ran, Q. Fu, Inspired by nonenveloped viruses escaping from endo-lysosomes: a pH-sensitive polyurethane micelle for effective intracellular trafficking, Nanoscale 8 (2016) 7711–7722, https://doi.org/10.1039/c6nr00859c.
[206] S.A. Smith, L.I. Selby, A.P.R. Johnston, G.K. Such, The endosomal escape of nanoparticles: toward more efficient cellular delivery, Bioconjug. Chem. 30 (2019) 263–272, https://doi.org/10.1021/acs.bioconjchem.8b00732.
[207] Y.W. Cho, J.-D. Kim, K. Park, Polycation gene delivery systems: escape from endosomes to cytosol, J. Pharm. Pharmacol. 55 (2003) 721–734.
[208] C. Plank, B. Oberhauser, K. Mechtler, C. Koch, E. Wagner, The influence of endosome-disruptive peptides on gene transfer using synthetic virus-like gene transfer system, J. Biol. Chem. 269 (1984).
[209] R.L. McCarley, Redox-responsive delivery systems, Annu Rev Anal Chem (Palo Alto, Calif) 5 (2012) 391–411, https://doi.org/10.1146/annurev-anchem-062011-143157.
[210] X. Guo, Y. Cheng, X. Zhao, Y. Luo, J. Chen, W.-E. Yuan, Advances in redox-responsive drug delivery systems of tumor microenvironment, J. Nanobiotechnol. 16 (2018) 74, https://doi.org/10.1186/s12951-018-0398-2.
[211] T.P. Szatrowski, C.F. Nathan, Production of large amounts of hydrogen peroxide by human tumor cells, Cancer Res. 51 (1991) 794–798.
[212] O.A. Khomich, S.N. Kochetkov, B. Bartosch, A.V. Ivanov, Redox biology of respiratory viral infections, Viruses 10 (2018), https://doi.org/10.3390/v10080392.
[213] Y. Jiang, W. Yang, J. Zhang, F. Meng, Z. Zhong, Protein toxin chaperoned by LRP-1-targeted virus-mimicking vesicles induces high-efficiency glioblastoma therapy in vivo, Adv. Mater. Weinheim. 30 (2018), e1800316, https://doi.org/10.1002/adma.201800316.
[214] Y. He, Y. Nie, G. Cheng, L. Xie, Y. Shen, Z. Gu, Viral mimicking ternary polyplexes: a reduction-controlled hierarchical unpacking vector for gene delivery, Adv. Mater. Weinheim. 26 (2014) 1534–1540, https://doi.org/10.1002/adma.201304592.
[215] K.B. Daniel, C.E. Callmann, N.C. Gianneschi, S.M. Cohen, Dual-responsive nanoparticles release cargo upon exposure to matrix metalloproteinase and reactive oxygen species, Chem. Commun. (Camb.) 52 (2016) 2126–2128, https://doi.org/10.1039/c5cc09164k.
[216] J.L. Ungerleider, J.K. Kammeyer, R.L. Braden, K.L. Christman, N.C. Gianneschi, Enzyme-targeted nanoparticles for delivery to ischemic skeletal muscle, Polym. Chem. 8 (2017) 5212–5219, https://doi.org/10.1039/C7PY00568G.
[217] L. Adamiak, M.A. Touve, C.L.M. LeGuyader, N.C. Gianneschi, Peptide brush polymers and nanoparticles with enzyme-regulated structure and charge for inducing or evading macrophage cell uptake, ACS Nano 11 (2017) 9877–9888, https://doi.org/10.1021/acsnano.7b03686.
[218] L. Zhang, Y. Wang, X. Zhang, X. Wei, X. Xiong, S. Zhou, Enzyme and redox dual-triggered intracellular release from actively targeted polymeric micelles, ACS Appl. Mater. Interfaces 9 (2017) 3388–3399, https://doi.org/10.1021/acsami.6b14078.
[219] Y. Li, H. Hu, Q. Zhou, Y. Ao, C. Xiao, J. Wan, Y. Wan, H. Xu, Z. Li, X. Yang, α-amylase- and redox-responsive nanoparticles for tumor-targeted drug delivery, ACS Appl. Mater. Interfaces 9 (2017) 19215–19230, https://doi.org/10.1021/acsami.7b04066.
[220] W. Mothes, N.M. Sherer, J. Jin, P. Zhong, Virus cell-to-cell transmission, J. Virol. 84 (2010) 8360–8368, https://doi.org/10.1128/JVI.00443-10.
[221] S. Hua, M.B.C. de Matos, J.M. Metselaar, G. Storm, Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization, Front. Pharmacol. 9 (2018) 790, https://doi.org/10.3389/fphar.2018.00790.
[222] H. Shen, X. Huang, J. Min, S. Le, Q. Wang, X. Wang, A.A. Dogan, X. Liu, P. Zhang, M.S. Draz, J. Xiao, Nanoparticle delivery systems for DNA/RNA and their potential applications in nanomedicine, Curr. Top. Med. Chem. 19 (2019) 2507–2523, https://doi.org/10.2174/1568026619666191024170212.
[223] I. Lostale-Seijo, J. Montenegro, Synthetic materials at the forefront of gene delivery, Nat. Rev. Chem. 2 (2018) 258–277.
[224] E.S. Lee, D. Kim, Y.S. Youn, K.T. Oh, Y.H. Bae, A virus-mimetic nanogel vehicle, Angew. Chem. 120 (2008) 2452–2455, https://doi.org/10.1002/ange.200704121.
[225] T. Cui, Z. Yan, H. Qin, Y. Sun, J. Ren, X. Qu, A sequential target-responsive nanocarrier with enhanced tumor penetration and neighboring effect in vivo, Small 15 (2019), e1903323, https://doi.org/10.1002/smll.201903323.
[226] J.-H. Fang, Y.-T. Lee, W.-H. Chiang, S.-H. Hu, Magnetoresponsive virus-mimetic nanocapsules with dual heat-triggered sequential-infected multiple drug-delivery approach for combinatorial tumor therapy, Small 11 (2015) 2417–2428, https://doi.org/10.1002/smll.201402969.
[227] I. Dalmau-Mena, P. Del Pino, B. Pelaz, M.Á. Cuesta-Geijo, I. Galindo, M. Moros, J. M. de La Fuente, C. Alonso, Nanoparticles engineered to bind cellular motors for efficient delivery, J. Nanobiotechnol. 16 (2018) 33, https://doi.org/10.1186/s12951-018-0354-1.
[228] M. Martínez-Moreno, I. Navarro-Lérida, F. Roncal, J.P. Albar, C. Alonso, F. Gavilanes, I. Rodríguez-Crespo, Recognition of novel viral sequences that associate with the dynein light chain LC8 identified through a pepscan technique, FEBS Lett. 544 (2003) 262–267, https://doi.org/10.1016/S0014-5793(03)00516-7.
[229] C.J. Mable, I. Canton, O.O. Mykhaylyk, B. Ustbas Gul, P. Chambon, E. Themistou, S.P. Armes, Targeting triple-negative breast cancer cells using Dengue virus-mimicking pH-responsive framboidal triblock copolymer vesicles, Chem. Sci. 10 (2019) 4811–4821, https://doi.org/10.1039/C8SC05589K.
[230] F.A. Rey, Two hosts, two structures, Nature 497 (2013) 443.
[231] Y.Y. Chen, A.M. Syed, P. MacMillan, J.V. Rocheleau, W.C.W. Chan, Flow rate affects nanoparticle uptake into endothelial cells, Adv. Mater. Weinheim. 32 (2020), e1906274, https://doi.org/10.1002/adma.201906274.