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Nanotechnology-Mediated Drug Delivery for the Treatment of Obesity and Its Related Comorbidities

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Obesity is a serious health issue affecting humanity on a global scale. Recognized by the American Medical Association as a chronic disease, the incidence of obesity continues to grow at an accelerating rate and obesity has become one of the major threats to human health. Excessive weight gain is tied to metabolic syndrome, which is shown to increase the risk of chronic diseases, such as heart disease and type 2 diabetes, taxing an already overburdened healthcare system and increasing mortality worldwide. Available treatments such as bariatric surgery and pharmacotherapy are often accompanied by adverse side effects and poor patient compliance. Nanotechnology, an emerging technology with a wide range of biomedical applications, has provided an unprecedented opportunity to improve the treatment of many diseases, including obesity. This review provides an introduction to obesity and obesity-related comorbidities. The most recent developments of nanotechnology-based drug delivery strategies are highlighted and discussed. Additionally, challenges and consideration for the development of nanoformulations with translational potential are discussed. The overall objective of this review is to enhance the understanding of the design and development of nanomedicine for treatments of obesity and related comorbidities.

1. Introduction

Obesity is a deadly condition; ≈4.5 million deaths worldwide were estimated to have been caused by overweightness and obesity in 2013.[1] The World Health Organization (WHO) estimated that in 2010, over 700 million youth and adults worldwide were obese, and 2 billion individuals were overweight.[2] It is overwhelmingly clear that obesity has become a health crisis globally. People with a body mass index (BMI, mass in kilograms divided by the square of the height in meters) above 30 kg m^{-2} are considered obese.[3,4] The American Medical Association has classified obesity as a reversible and preventable chronic disease, which is accompanied by a host of related deadly comorbidities including type 2 diabetes, heart disease, and several types of cancers.[5] Particularly, diabetic disorders and cardiovascular diseases are the most common comorbidities associated with obesity.

The causes of obesity are complex and multivariate. Broadly speaking, behavior and genetics appear to be the major factors that cause obesity.[6] Current treatments for obesity focus on lifestyle changes, reducing energy consumption and increasing energy expenditure. Other than lifestyle adjustments such as exercise and diet modification, current clinical strategies to treat obesity give priority to pharmacotherapy, including the drugs orlistat and lorcaserin, and surgical interventions in the form of bariatric surgeries. However, these conventional treatments have side effects which call out for their improvement.[7] Notably, there are challenges concerning the bioavailability and effective delivery of antiobesity drugs (particularly nucleic acid-based therapeutics) which must be addressed for their successful incorporation into delivery systems.[8]

To overcome these drawbacks, nanotechnology presents promising methods to improve drug encapsulation, protect the payload from degradation, improve solubility, and target specific disease areas.[9] Additionally, the delivery challenges associated with nucleic acid-based therapeutics including small interfering Ribonucleic acid (siRNA), messenger Ribonucleic acid (mRNA), short hairpin Ribonucleic acid (shRNA), antisense oligonucleotides, and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) components can be addressed via encapsulation into nanoparticles.[10] Advancements in nanomedicine research have led to methods that reduce toxicity, improve biocompatibility, prolong the half-life of drugs, and reduce side effects through modifying nanoparticle properties.[11] In the last decade, researchers have published articles featuring promising applications of nanotechnology including nanoparticles and nanopatches inducing the browning of adipocytes to

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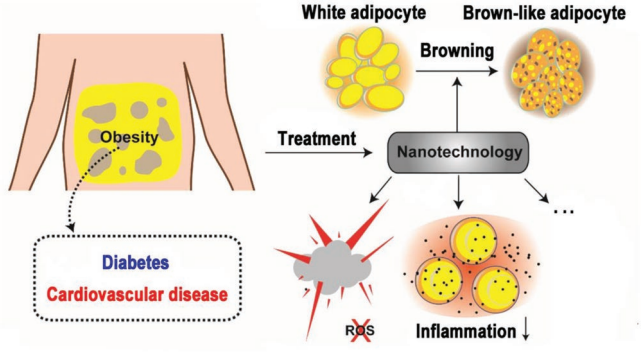

Figure 1. Schematic of nanotechnology in the treatment of obesity and related diseases. This figure shows an overview of nanotechnology mediated treatments of obesity and related diseases, including techniques such as the conversion of white adipose tissue (WAT) to brown adipose tissue (BAT), reducing reactive oxygen species (ROS), and lowering inflammation.

increase fat loss, as well as for the targeted treatment of obesity, diabetes, and heart disease.[12]

In Section 1 of this review, we will give an introductory review of the physiology of obesity and its related comorbidities such as diabetes and heart disease. The mechanisms and potential treatment targets recently reported in the literature will be discussed for each subject. Section 2 will summarize the recent nanotechnological advances for the treatment of obesity, diabetes, and heart disease and their different mechanisms of action (**Figure 1**). Finally, the scientific, technical, and regulatory challenges of developing nanomedicines to treat these diseases are discussed in Section 3. More importantly, in Section 4 we will also give a brief perspective of nanotechnology and how it can be used in combination with other delivery systems, which will help improve the treatment and targeting efficiency of nanomedicines. In addition, we summarize the current technologies and their in treating obesity and related disease in recent articles (**Table 1**).

2. Mechanisms of Obesity and Potential Targets

The interactions between genetic, environmental, and psychosocial factors determine body weight and fat deposition. In terms of behavior, a person's diet (especially the high-fat "Western" diet), low physical activity, unfavorable energy balance (if calorie consumption exceeds expenditure), and use of some medications are all factors that influence obesity.[13] This leads to the storage of excess energy as lipids in white adipose tissue (WAT).[14] Strategies aiming to dissipate this excess energy have attracted continuing interest, and one of the most studied mechanisms is WAT browning, during which white adipocytes are converted into brown fat cells.[15] Brown adipose tissue (BAT) is generated through the expression of uncoupling protein 1 and induces energy expenditure through thermogenesis within WAT.[16] Considerable numbers of browning agents and techniques have been investigated, including drugs, foods, gene ablation, and transgene methods.[17] Obesity often leads to the excessive production of reactive oxygen species,[18] and therefore changes the redox equilibrium of the cellular microenvironment.[19] Oxidative stress damages cellular structures and generates inflammation and adipokines,[20] which in turn further contributes to the development of obesity. Obesity is closely associated with inflammation, which is tied to insulin resistance and type 2 diabetes.[21] Obesity-related inflammation often presents as metaflammation, defined as chronic inflammation regulated by metabolic cells in response to excess nutrients and energy.[22] Studies have shown that disruption of the link between obesity and its related comorbidities can suppress inflammatory signaling through knocking out key pathways, including components of the NF-κB and c-Jun N-terminal kinase pathways,[23] as well as numerous other pro-inflammatory signaling molecules, scaffolding proteins, and cytokines in obese mice.[24]

In terms of genetics, several genes have been proven to be positively correlated with obesity. Li et al. found the dominant role of FTO and TMEM18 as genes involved in increasing the risk of obesity.[25] Furthermore, Chambers et al. carried out a GWAS of over 12 000 individuals and identified MC4r as a locus which contributes to obesity.[26] Luo et al. also found that the C2-domain protein AIDA-mediated

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Table 1. Current technologies and their use in obesity and related diseases.

Technology	Materials	Disease	Advantages	Ref.
NPs, injection	Dextran	Type II Diabetes/heart diseases	Efficiency, specificity, reduce side effects for nontargeted tissues	[47]
	PLGA	Obesity (browning)	Enable sustained local release of a Notch inhibitor; Localized NP retention; Browning of adipocytes; Biocompatible and biocompatible polymers	[45]
	YSK05, cholesterol, and mPEG-DMG	Type 2 diabetes	Nontoxic delivery of siRNA to silence gene expression	[84]
	PLGA, PVA	Obesity–reduce inflammation	Reduce side effects of rosiglitazone drug	[85]
	PLGA, PEG	Obesity (browning)	Passive/active targeting, minimize side-effects	[12b]
	Egg yolk phosphatidylcholine, PEG, peptide	Obesity	Passive targeting via peptide to vascular network	[86]
	oligopeptide (ATS-9R)	Type 2 diabetes	Gene silencing, reduce whole body inflammation	[87]
	Egg yolk phosphatidylcholine (EPC), cholesterol	Type 2 diabetes	Multivalent active targeting and passive targeting, reducing weight gain via the control of adipose function	[88]
	Egg yolk phosphatidylcholine (EPC), cholesterol, peptide-conjugated PEG-lipid	Obesity–weight loss	Prevents protein from being cleared from circulation, protects protein, reduces side-effects, nontoxic to liver, inhibition of neovascularization via apoptosis/necrosis of endothelial cells in WF	[89]
	MSN, PCL	Obesity	Study found that obesity interferes with biodistribution of nanoparticles—opposite of normal uptake occurs	[12d]
	LITA	Obesity – liver lipid accumulation	Passive targeting, increase bioavailability of drug, controlled delivery, separation of peripheral and central effects of drug	[90]
	Zinc oxide	Type 2 diabetes	Prevent progression to type 2 diabetes	[91]
	Porous silicon	MI	Targeting, biodegradable	[92]
	Polynorbornene, peptide	MI	Targeting, prolonged retention	[93]
	PLGA	MI	Targeting, reduce side effects, lower effective dose	[94]
	PLGA	Heart disease	Local delivery, drug stabilization and solubilization, prolonged and controllable drug release profiles	[95]
Nanogel, injection	CHC	Diabetes	Controlled biodegradation, controlled insulin release, cytocompatible	[96]
NPs, oral delivery	GLP-1	Type 2 diabetes	Oral absorption, prolonged period of treatment	[97]
	Chitosan, gamma-PGA	Diabetes	Increase oral bioavailability of insulin	[98]
Microneedle patch	Silk, PVA	Diabetes	Self-administration, miniaturization, pain-free administration, drug delivery, drug stability, noninvasive	[99]
	85% PVA, 10% dextran, 5% CMC	Diabetes	Biocompatible, nontoxic, high transdermal bioavailability, applicable to variety of protein/peptide medications, painless administration, noninvasive	[100]
	HA	Heart disease	Sustained delivery, safe and convenient delivery	[101]
	HA	Obesity–weight loss (browning)	Lower dose, localized treatment, painless, bloodless, high drug integrity, low side-effects, amenability for home-based self-administration	[102]
Microneedle patch with NPs	Dextran, HA	Type II diabetes	Efficiency, reduce side effect	[12a]
	HA	Obesity–weight loss	Improves lipolysis, overcome bioavailability issues, circumvent the first-pass hepatic metabolism, and provide controlled delivery for consistent plasma level of the drug	[103]
	PVP/PVA	Diabetes	Fast response, excellent biocompatibility, and painless administration	[104]
	Alginate	Type 2 diabetes	Enhance the mechanical strength of MN, painless and noninvasive transdermal administration	[105]

endoplasmic-reticulum-associated degradation system may represent an "antithrifty" mechanism mediating the downregulation of enzymes for intestinal fat absorption and systemic fat storage.[27] Two typical gene-silencing strategies to treat obesity have been reported recently. SREBP, a sterol regulatory element-binding protein, is involved in activation of cholesterol production-related genes, the development of diabetic hepatic steatosis as well as carbohydrate-induced hypertriglyceridemia.[28] Meanwhile, fatty acid-binding proteins (FABPs) influence fatty-acid uptake and lipid storage in adipocytes through the regulation of diverse lipid signals.[29] Therefore, silencing the expression of SREBP or FABPs may potentially provide therapeutic effect for diseases such as obesity, diabetes, and atherosclerosis that will be discussed in the following sections.

3. Nanotechnology as a Treatment for Obesity

Traditionally, the treatment of obesity is centered around diet, physical exercises, and variation of lifestyle, yet increasingly, medical intervention is becoming a significant treatment.[30] Current clinical treatments of obesity focus on pharmacotherapy treatments and surgical interventions.[7] The most common antiobesity drugs include orlistat, lorcaserin, liraglutide, phentermine-topiramate, and naltrexone-bupropion.[31] Each of these drugs is accompanied by a host of side effects. Common adverse reactions of these pharmacotherapy drugs include gastrointestinal discomfort or pain, nausea, insomnia, constipation, headaches, and vomiting.[32] Bariatric surgeries have proven to be significantly more effective in reducing BMI than pharmacotherapies. The three main types or bariatric surgery are gastric banding, Roux-en-Y gastric bypass, and vertical sleeve gastrectomy.[33] These treatments, however, are often accompanied by adverse side effects including intestinal bleeding, and in rare cases, suicide.[34] Nanotechnology has become a promising solution to the drawbacks of currently available therapies due to their superior properties, which include specific cellular targeting, protection of therapeutics from physiological degradation, as well as sustained release of therapeutic.[35] Nanotechnology therefore represents a revolutionary technology that can reduce side effects and increase the efficacy of antiobesity therapies as well as treat related comorbidities.

3.1. Nanoparticle-Based Obesity Therapies

Nanoparticles (NPs) feature tremendous qualities such as large surface-to-volume ratio, ability to encapsulate drugs, and tunable surface chemistry, which make them very attractive delivery vehicles to treat many diseases.[36] Surface modification with targeting ligands allow for navigation of the complex in vivo environment through active targeting, their small size allows for passive targeting of tissues, and novel formulations have shown the capability for controlled drug release, which underscores their growing numbers of use in modern medicine.[37] Nanoparticle therapeutics can be divided into several broad categories, including the inorganic class, the lipid class, and the polymer class. Each category of NP has unique properties which factor into decisions about their use.

3.2. Inorganic Nanoparticles

Inorganic nanoparticles, including gold GNPs, iron oxide, mesoporous silica (MSNs), and calcium phosphate nanoparticles are extensively implicated with the treatment of obesity, and either serve as delivery vectors for therapeutic agents, or directly treat obesity by virtue of their superior physicochemical properties. Thovhogi et al. functionalized GNPs with a synthetic adipose homing peptide (AHP) for targeted delivery to the WAT of rats with obesity. Compared to rats treated with GNPs alone, those treated with AHP-GNPs had a much higher concentration of Au in WATs.[38] Although in vivo degradation and toxicity-related experiments of AHP-GNPs were not mentioned in this research, it is a promising platform for targeted delivery of antiobesity therapeutics using gold nanoparticles with good loading capacity. The utilization of inorganic nanoparticles with inherent properties which benefit the treatment of obesity can reduce adverse side effects and simplify treatment procedures. For example, taking advantage of the magnetocaloric effect of superparamagnetic iron oxide nanoparticles, Marinozzi et al. exploited a hyperthermia treatment to modulate the lipid content of 3T3 adipocytes after nanoparticle uptake. This treatment achieved a significant delipidation lasting more than 24 h without cell death, damage or dedifferentiation, representing a physiologically mild strategy to safely counteract obesity.[39] Further experiments in vivo are necessary to ensure that the magnetic field can overcome somatic barriers to stimulate heat production reliably in nanoparticles. Since increased oxidative stress has been shown to contribute to obesity, Rocca et al. developed antioxidative cerium oxide nanoparticles as a potential pharmaceutical approach against obesity. Cerium oxide nanoparticles inhibit adipogenesis through reducing both mRNA transcription of related genes and triglyceride accumulation, resulting in reduced weight and lowered insulin, leptin, glucose, and triglycerides in blood plasma.[40] In general, inorganic nanoparticles show a broad applicability for the treatment of obesity due to their dual role as carrier and therapeutic agent, which also indicates a possibility for synergistic therapy. Even though they have many advantageous qualities, inorganic nanoparticles have some potential concerns; they are less compatible in bodily environments and display slower degradation rates in comparison with other delivery systems. Therefore, different aspects of in vivo research should be carried out to further explore their preclinical safety.

3.3. Lipid Nanoparticles

Lipid nanoparticles are biocompatible, form bilayers to encapsulate payloads, and fuse with the cell membrane to deliver payloads.[41] Lipid nanoparticles are ideal delivery vectors for drugs that require improved solubility, due to amphiphilic components in their structure. Numerous approaches have been developed to solve the poor bioavailability of antiobesity drugs

due to their nonideal aqueous solubility. For example, to overcome poor solubility and bioavailability of trans-resveratrol (R), an antiobesity drug that induces browning in WAT, Zu et al. synthesized R encapsulated lipid nanocarriers (R-nano), and R encapsulated liposomes (R-lipo). Nanoencapsulation of R-nano and R-lipo increased the aqueous solubility and stability of R, as well as the uptake by 3T3-L1 cells, leading to enhanced browning activities of R and improved efficiency of obesity treatment.[42] However, the therapeutic features as well as molecular mechanisms of R-nano and R-lipo should be thoroughly characterized before they are clinically translated to methods of obesity treatment. Additionally, Sullivan et al. encapsulated nuclear factor-κB inhibitor curcumin (curcusomes) with egg phosphatidylcholine (Northern Lipids) coated Ag. In the case of a leptin deficient (*ob/ob*) mouse model, curcusome nanoparticles targeting hepatic tumor necrosis factor (TNF)/inducible nitric oxide synthase-producing dendritic cells (Tip-DCs) and adipose tissue macrophages showed reduction of NF-κB/RelA DNA binding activity, therefore reducing TNF and increasing interleukin-4 production. The results suggest a promising treatment for insulin resistance in obese mice by targeting inflammatory DCs.[43] Considering the possible instability of lipid nanoparticles in the gastrointestinal tract, the administration protocol should also be carefully designed to ensure that the desirable therapeutic effects are not outweighed by side effects the treatment may cause. Most of these studies rely on parenteral administration, which usually shows poor patient compliance; therefore, transdermal approaches, including microneedles and patches, could be an ideal alternative and will be discussed in further detail.

3.4. Polymer Nanoparticles

Polymer NPs show diverse chemistries and physical characteristics and allow for easy modification of their physiochemical properties.[44] In terms of treating obesity, NP therapeutics are currently being explored with great results. Zhang and co-workers fabricated two peptide-functionalized poly(lactide-coglycolide)-*b*-poly(ethylene glycol) (PLGA-*b*-PEG) copolymer nanoparticle platforms to deliver peroxisome proliferator-activated receptor gamma activator rosiglitazone (Rosi) and prostaglandin E2 analog (16,16-dimethyl PGE2) (**Figure 2**). These nanoparticle drugs combined with angiogenesis targeting peptides and two browning agents showed effective transformation of WAT into BAT and further proves the synergistic effect of combining targeting agents with browning agents. This targeted strategy may pave the way for further treatments for obesity and metabolic syndrome.[12b] Furthermore, Jiang et al. showed that dibenzazepine (DBZ)-loaded poly(lactide-*co*-glycolide) NPs could stimulate browning in white adipose tissue of obese mice (**Figure 3**).[45] Notably, focal injection of DBZ-NPs into the inguinal WAT reduces off-target side effects and promotes localized sustained release of

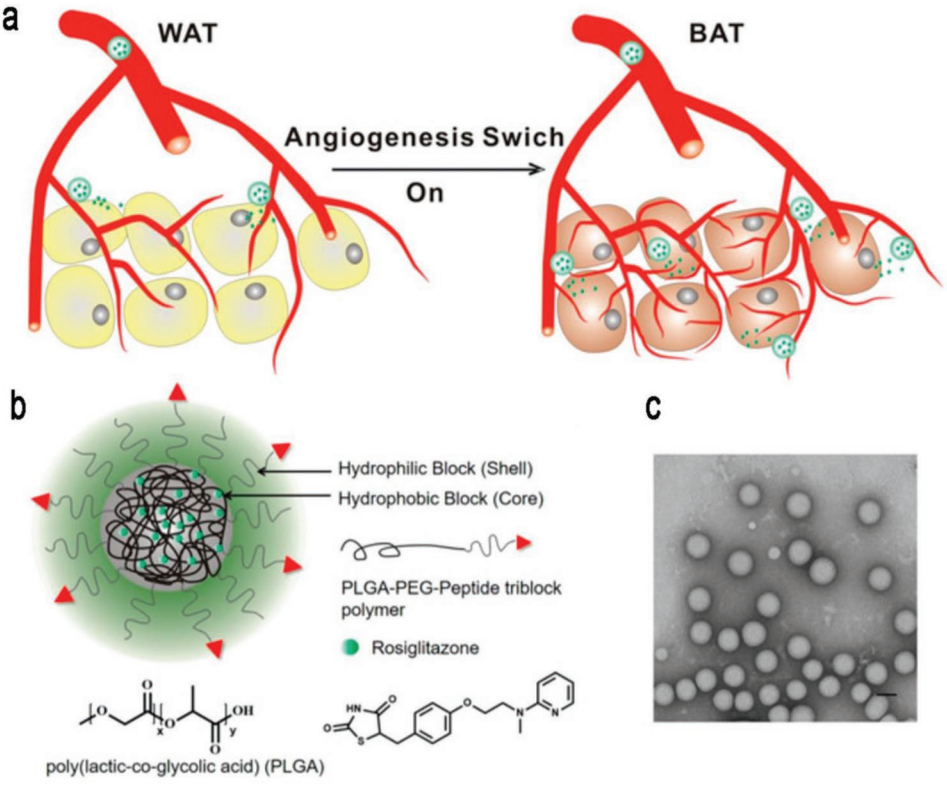

Figure 2. NP design and characterization. a) A schematic representation of the WAT browning process through a positive feedback drug delivery system. Released Rosi and PGE2 promote transformation of WAT into brown-like adipose tissue and stimulate angiogenesis. This facilitates the homing of targeted NPs to adipose angiogenic vessels, thereby amplifying their delivery and hence expediting the WAT browning process. b) Chemical structure of PLGA-*b*-PEG-peptide/rosiglitazone NPs. Reproduced with permission.[12b] Copyright 2018, PNAS.

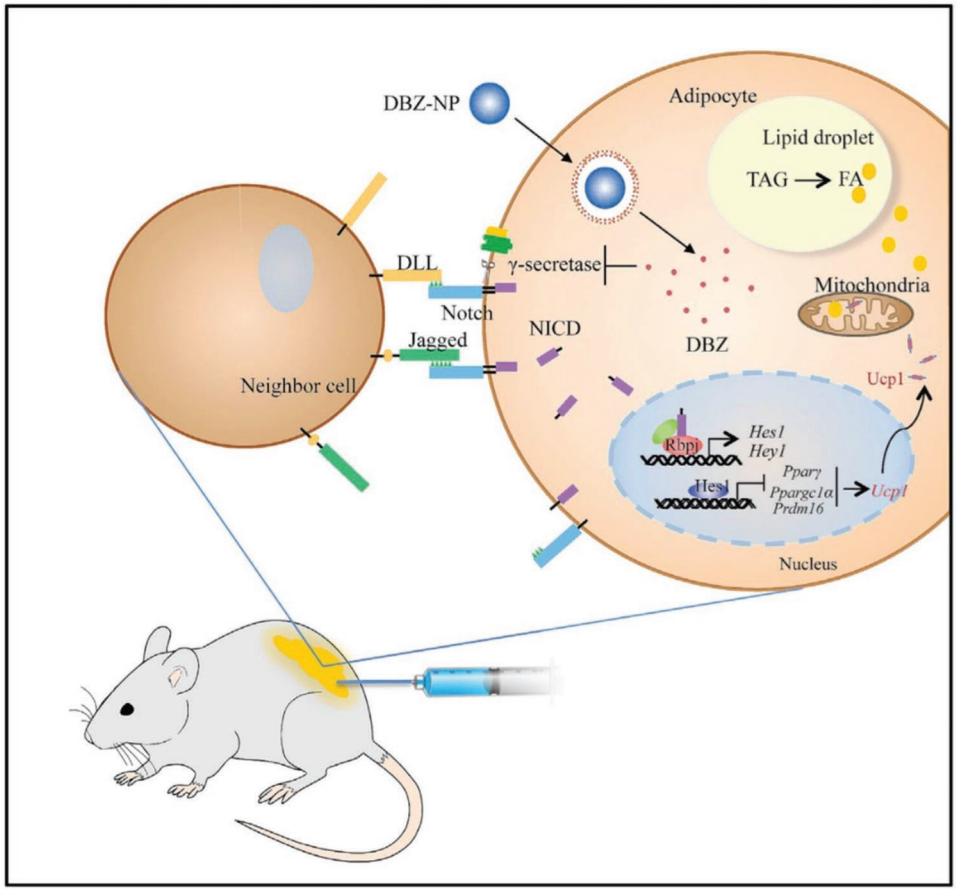

Figure 3. Schematic illustration of DBZ-releasing NPs for intracellular induction of browning through inhibition of notch signaling after local injection into inguinal WAT. Reproduced with permission.[45] Copyright 2017, Elsevier.

Notch inhibitor DBZ promote browning. It was suggested that these DBZ-NPs could efficiently cause Notch inhibition at a dosage 50 times lower than i.p. injection, and ten times lower than microsphere delivery methods. The application of FDA-approved PLGA provides a simple method for local delivery to induce browning of WAT. However, further modifications with functional moieties, such as targeting molecules, may enhance biointeraction between adipose tissue and nanoparticles for improved therapeutic effects.

Compared to synthetic polymer NPs, natural polymer NPs are amenable to modification, are biodegradable, present low toxicity and are not expensive to produce,[46] which make them great candidates for drug delivery in the treatment of obesity. In Ma et al. research, dextran (which can be effectively and specifically internalized by macrophage cells) was modified with contrast agents, fluorophores and anti-inflammatory drugs for the multifunctional treatment of obesity. More than 63% of dextran conjugates accumulated in visceral adipose tissue 24 h after parenteral administration and these nanoparticles were then taken up by M1 macrophages through receptor-mediated endocytosis. As a result, intracellular release of drug inhibited the generation of proinflammatory signals, thus inhibiting critical factors leading to obesity and related diseases (**Figure 4**).[47] The delivery components in this research are all approved by the FDA, which makes them feasible for clinical applications. Further studies, including dosage analysis, long-term treatment efficacy as well as studies on obesity-related complications should also be performed in order for clinical translation to proceed.

3.5. Self-Assembled Peptides as Nanocarriers

Peptides have been proven as attractive nonviral vectors for delivery of therapeutic genes due to their capability to overcome delivery barriers, including specific cell binding, cell-penetration, and cytosolic transport,[48] which can be applied to the treatment of gene-related diseases like obesity. Won et al. exploited an adipocyte-targeting sequence and 9-arginine (ATS-9R) that specifically binds to prohibitin, which is located on the surface of adipocytes. ATS-9R was then internalized into endothelial cells of adipose tissue after biorecognition. Furthermore, a therapeutic gene, shFABP4, was constructed and formed an oligopeptide complex with ATS-9R through electrostatic interaction-mediated self-assembly (ATS-9R/shFABP4). ATS-9R/shFABP4 was proven to be a safe therapy for obesity and obesity-related metabolic syndromes (**Figure 5**).[49] ATS-9R, serving as the targeting moiety, displays promise, and could be applied to other gene therapies for obesity treatment. Eldredge et al. delivered siRNA to primary adipocytes and hepatocytes using dendritic peptide bolaamphiphiles (bolas), which consists of two L-histidine and

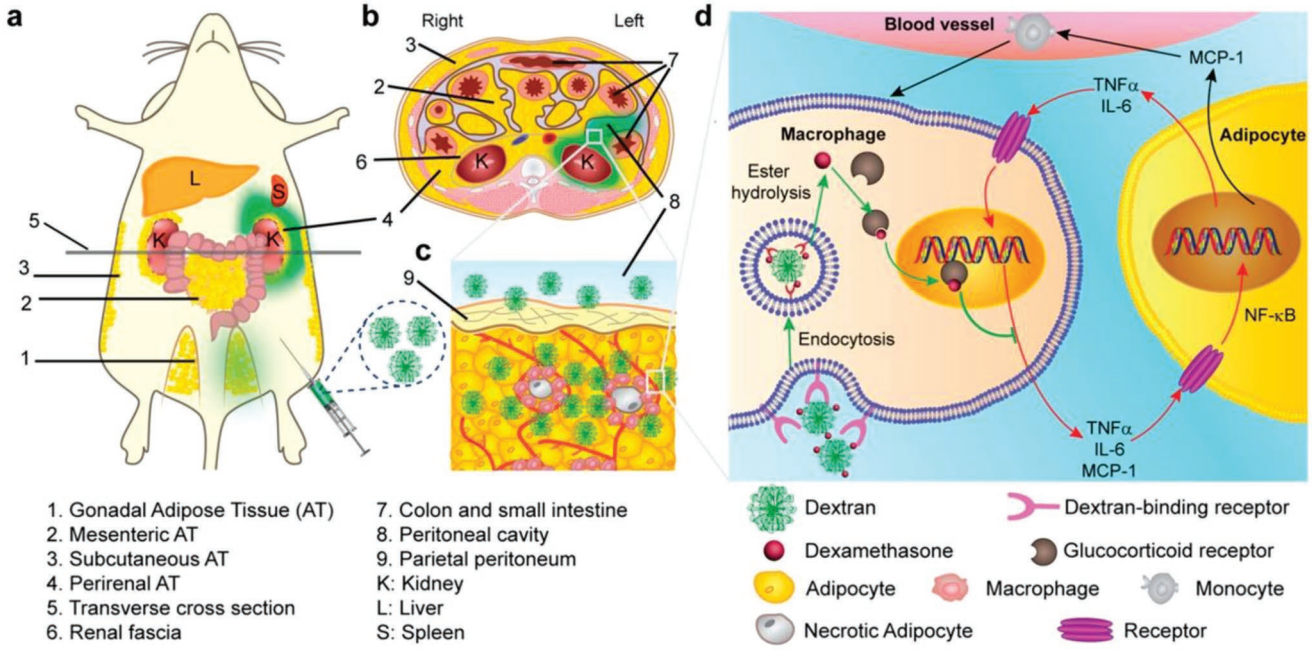

Figure 4. Proposed mechanism of dextran–dexamethasone conjugate accumulation in obese visceral adipose tissue, macrophage uptake, and uncoupling of the paracrine loop between M1 macrophages and adipocytes: a) dextran conjugates (green color) accumulate in the left perirenal adipose tissue (AT) and left gonadal AT after intraperitoneal left-side injection in obese mouse. The anatomical depiction shows mice, which have one mesenteric, two perirenal, and two gonadal AT depots. b) Transverse cross-section of mouse abdomen showing green dextran solution location after administration to the peritoneal cavity. c) Rapid association of dextran conjugate with M1 macrophages in inflamed AT is enabled by transport across the peritoneum to directly access interstitial cells. d) Simplified summary of inhibition of paracrine loop between M1 macrophages and adipocytes with dextran–dexamethasone conjugates. Reproduced with permission.[47] Copyright 2016, American Chemical Society.

L-tryptophan-modified L-lysine dendrons connected to a fluorocarbon core. The bolas-based delivery system achieved improved uptake by cells, endosomal escape, and stimuli-responsive release of siRNA, resulting in effective knockdown of GAPDH gene in primary adipocytes and hepatocytes without interfering with the metabolic activities of cells.[50] Although the biodistribution and in vivo efficiency of bola have not been definitively proven, bolas would potentially be a powerful vector for multigene analysis given its impact on lipid metabolism and energy balance using RNAi.

3.6. Microneedle Patches and Nanoparticle Hybrid Therapies

Microneedle patches provide a method for localized drug delivery and therefore may achieve maximum therapeutic effects with minimum dosage.[51] In order to treat obesity, the utilization of browning drugs with a microneedle patch was proposed and associated experiments were performed by Gu and co-workers Here, they fabricated degradable microneedle patches comprised of hyaluronic acid (HA) and embedded with rosiglitazone (Rosi) NPs. The Rosi NPs consisted of pH-sensitive acetal-modified dextran and coated with alginate, encapsulated with Rosi, glucose oxidase, and catalase payloads (**Figure 6**).[12a] The microneedles contain 121 needles in a 7×7 mm^2 patch with a center-to-center interval of 600 µm. Each microneedle was of a conical shape, with a depth of 800 and diameter of 300 µm at the base. In a diet-induced obesity in vivo mouse model, this patch enabled local browning of WAT, increasing energy expenditure and improving insulin sensitivity. Notably, patches only allowed the browning agent Rosi to be released in the targeted region and therefore minimized side effects on other organs.[12a,52] The combination of microneedle and nanoparticles integrates their respective efficacious characteristics. In this model, the delivery of therapeutic agents are optimized so that antiobesity drugs release at the expected location without interference of body fluids, which breaks barriers in terms of highly efficient administration of unstable, water-immiscible, and physiological environment-intolerant drugs.

4. Nanotechnology as a Treatment for Obesity-Related Comorbidities

Applying nanotechnology to human healthcare problems is certainly not restricted to the treatments of obesity that have been described above. Nanotechnology also has many additional applications in obesity-related comorbidities, such as type 2 diabetes and cardiovascular disease. The connection between obesity, diabetes, and cardiovascular disease can be clearly related through the metabolic syndrome. Metabolic syndrome brings together a whole host of symptoms and factors which increase the risk of cardiovascular disease and type 2 diabetes. Such symptoms include insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, and high blood pressure.[53] As all the symptoms are closely linked with

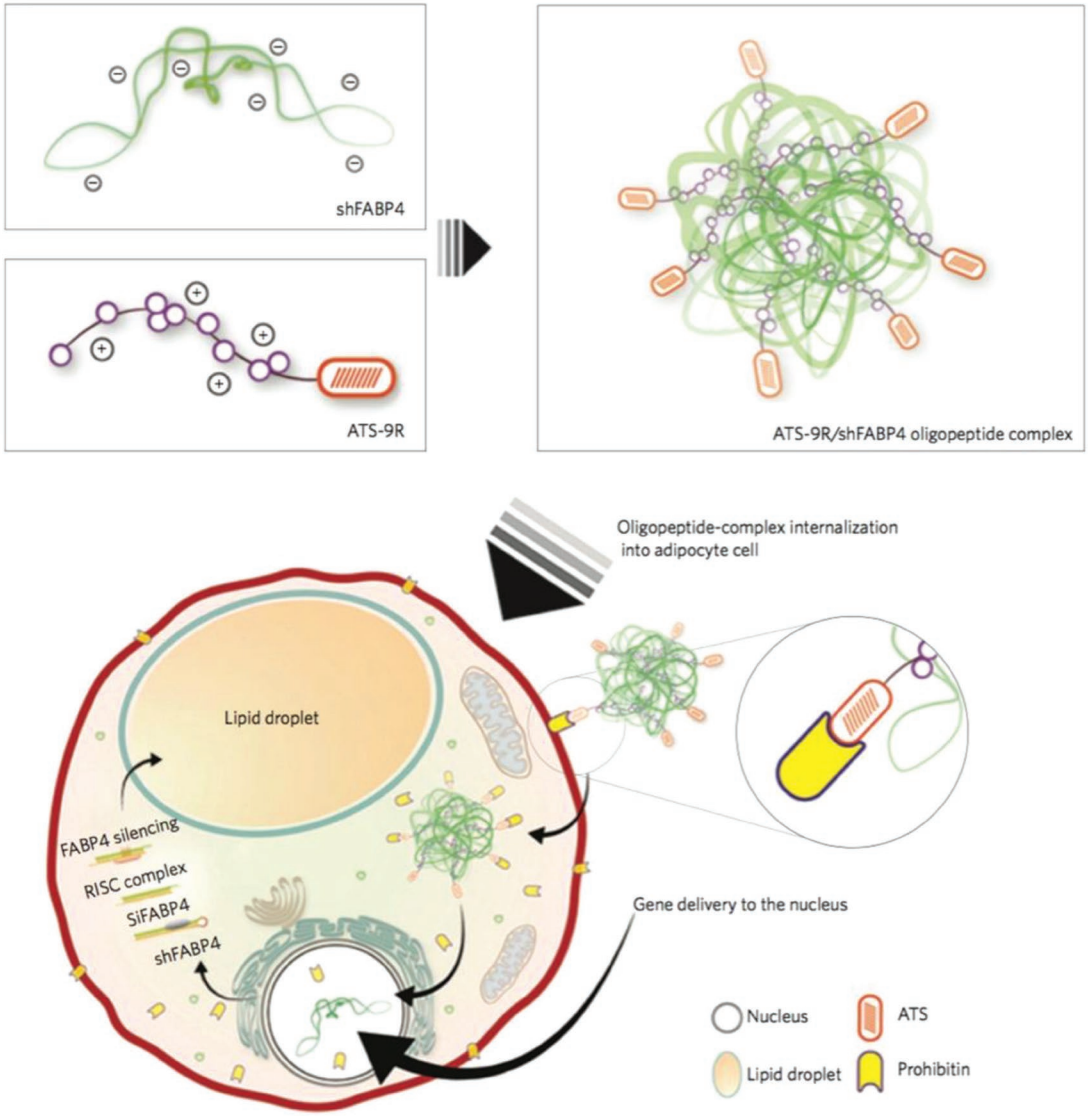

Figure 5. Mechanism of the targeted gene delivery to adipocytes by ATS-9R. Reproduced with permission.[49] Copyright 2016, Nature Publishing Group.

the initial development of obesity, the research shows a strong association between obesity, diabetes, and cardiovascular disease and thus has become a major focus of research.[54] Further details of how metabolic syndrome affects type 2 diabetes and cardiovascular disease has been extensively discussed in the literature.[55]

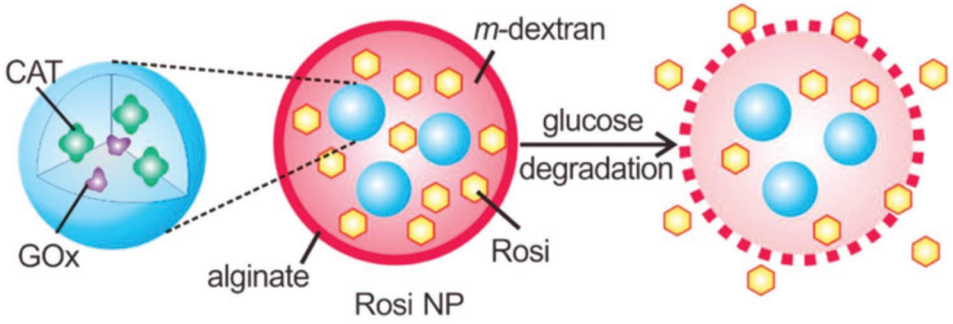

Figure 6. Schematic illustration of nanoparticles (NPs) encapsulating rosiglitazone (Rosi), glucose oxidase (GOx), and catalase (CAT) are prepared from pH-sensitive acetal-modified dextran and coated with alginate. Reproduced with permission.[12a] Copyright 2017, American Chemical Society.

4.1. Treatment of Type 2 Diabetes Using Nanotechnology

T2D, which accounts for the vast majority (90–95%) of diabetic individuals, is heavily correlated with obesity and can lead to many serious complications and diseases.[56] The cellular resistance to insulin which characterizes T2D results in increased blood glucose levels, leading to dysregulation of carbohydrate, lipid, and protein metabolism as well as β-cell malfunction.[57] As a result, T2D has become another massive problem for human health, and nanotechnology has great potential in addressing this problem. Current treatment strategies for T2D are bariatric surgery and insulin pump therapy (though mainly used for T1D in clinic, studies have shown efficacy of the insulin pump in T2D treatment). Insulin pump therapy is based on a store of insulin connected to a catheter which is installed subcutaneously. The pump along with a blood-glucose meter regularly monitors and releases insulin into the bloodstream according to several factors (mainly glycosylated hemoglobin A_{1c}, levels of the patient).[58] On the other hand, bariatric surgery works by restricting the amount of food that the digestive system can hold and induces the absorption disorder of nutrients. This mode of surgery has been established as a safer and more efficient alternative to the current drug treatments with a lower risk of complications and higher success rate.[33c,59]

Many efforts have been devoted to treating T2D using nanotechnology. Wang et al. synthesized a new highly intracellular stimuli-sensitive chitosan-graft-metformin (CS-MET) prodrug nanoparticle. This nanoparticle carries a short-hairpin RNA (shRNA) silencing sterol regulatory element-binding protein (SREBP), which is a major transcription factor involved in cholesterol and fatty acid metabolism. CS-MET/shSREBP nanocomplexes allow efficient delivery of metformin (which is commonly prescribed for T2D patients to attain glycemic control)[60] and also a gene payload simultaneously, leading to a synergistic therapeutic effect of reversing insulin resistance and alleviating the "fatty liver" phenotype. The study suggests a promising treatment for type 2 diabetes using prodrug nanoparticles.[61] For future studies, the addition of targeting moieties should be considered in this nanoparticle to optimize the targeting efficacy.

HA-NPs were shown to display great biocompatibility and receptor-binding properties, and HA self-assembles into nanocarriers for hydrophobic drug delivery.[62] Interestingly, Rho et al. showed that HA-NPs without encapsulated therapeutics accumulated in adipose tissue of diet-induced obesity mice, inhibit low molecular weight (LMW) HA binding to CD44, and decrease LMW HA-induced proinflammatory signaling through induction of CD44 clustering, leading to the normalization of blood glucose levels and insulin sensitivity in obese mice (**Figure 7**).[63] As a result, this nanoparticle could be a therapeutic agent for the treatment of T2D, targeting the links between adipose tissue inflammation and insulin resistance. The nanosystem discussed above attempts to treat T2D through targeting inflammatory signaling and immunoregulation which is notably different from the conventional treatment strategy of normalizing glucose levels with sustained insulin release or β-cell encapsulation for short-term or long-term treatment of diabetes. Nevertheless, synergistic effect may be achieved by combining insulin resistance-lowering strategies with controlled insulin release systems.

4.2. Treatment of Cardiovascular Disease Using Nanotechnology

Cardiovascular diseases are currently the leading cause of death worldwide, causing approximately about 17.7 million deaths

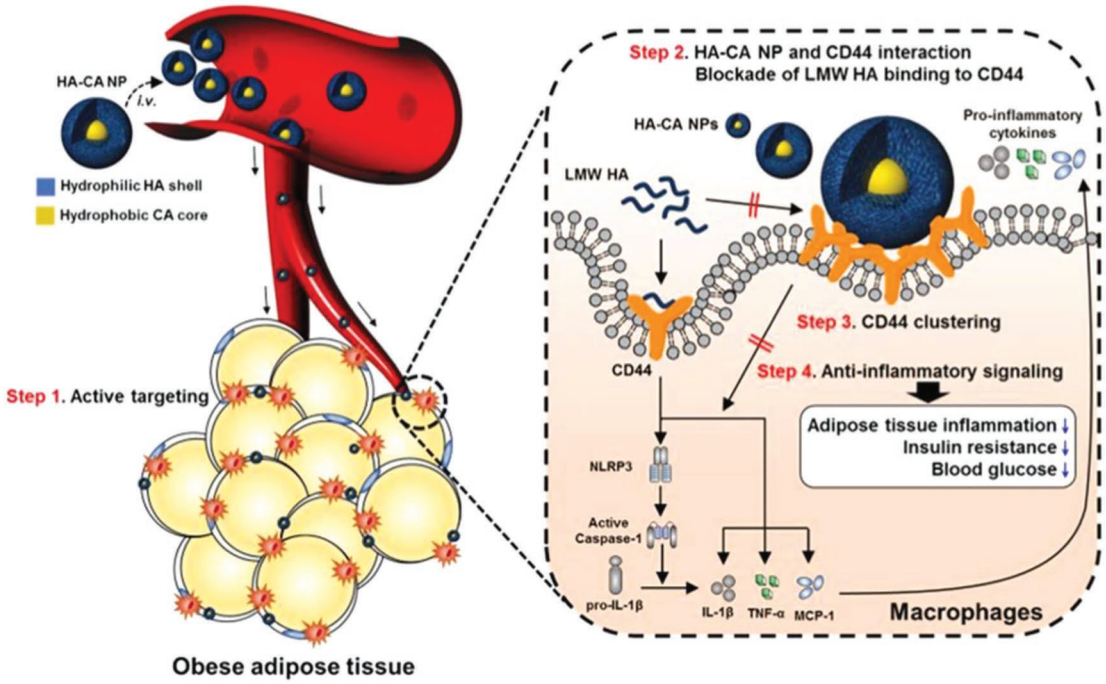

Figure 7. Schematic illustration of HA-CA NPs for treatment of type 2 diabetes. Reproduced with permission.[63] Copyright 2018, Elsevier.

each year.[64] Blood pressure is the most important link between increased BMI and cardiovascular disease, accounting for 31% of excess risk for coronary heart disease and 65% of excess risk for stroke.[65] Another important contributor, leptin levels, are related to increased blood pressure and involved in regulating activities like food intake, energy expenditure, and fat mass, which are responsible for the correlation between obesity and cardiovascular disease.[66] Obesity elevates not only the levels of blood lipid and blood glucose but also the buildup of fatty tissue which enhances vascular resistance and leads to a high risk of hypertension. Long-term heightened vascular resistance and hypertension raises the likelihood of ventricular hypertrophy, or enlargement of the heart.[67] In addition, the increased low-density lipoprotein cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels resulting from obesity contribute to a high risk of atherosclerosis.[68]

One of the most common treatments for cardiovascular disease in clinic is percutaneous coronary intervention (PCI). PCI is a nonsurgical procedure to open areas of the coronary artery blocked or narrowed by plaque buildup.[69] However, up to 40% of patients have been reported to develop periprocedural myonecrosis which causes left ventricular dysfunction or even death in severe cases after this surgery.[70] Another common treatment is coronary artery bypass grafting, a surgical procedure in which a healthy vein or artery is grafted to a blocked coronary artery so that the blood is able to bypass the area blocked by plaque.[71] After surgery, it is often accompanied by acute kidney injury because of inadequate blood flow to the kidneys resulting in kidney disfunction or even failure.[72]

Several emerging biomimetic nanocarriers have been used in the treatment of cardiovascular disease. It is hypothesized that apoptosis of macrophages and of smooth muscle cells play an important role in plaque rupture.[73] Marrache et al. constructed high-density synthetic lipoprotein-mimicking nanoparticles which target the mitochondrial membrane potential that occurs during apoptosis to detect "vulnerable plaque." The nanoparticles contain various agents including a core of biodegradable poly(lactic-*co*-glycolic acid), cholesteryl oleate, and triphenylphosphonium, which can detect the collapse of mitochondrial membrane potential. Moreover, the lipid layer was tailored with A-I mimetic 4F peptide to enhance the transport of cholesterol from the lesion. In addition, quantum dots (QDs) were incorporated in the core to improve optical imaging (**Figure 8**).[74] Moreover, synthetic HDL nanoparticles consisting of PLGA, lipids 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine/1,2-distearoyl-sn-glycero-3-phosphocholine and apolipoproteins were developed by Davidson and group.[75] This synthetic HDL was utilized by Zhang and co-workers for biomedical applications. Notably, results showed that HDL-PLGA nanoparticles accumulated in macrophages and monocytes within the aorta.[76] In conclusion, HDL-mimicking NPs show great potential for early detection of vulnerable plaques and as preventative therapies, which makes them attractive for atherosclerosis therapy. However, the components of this nanoparticle are not amenable to simple construction, which presents difficulties in scaling up production when translating to the clinic/bringing to market.

Additionally, Zhang et al. invented a new strategy to fabricate biomimetic nanoparticles coated with platelet membranes.

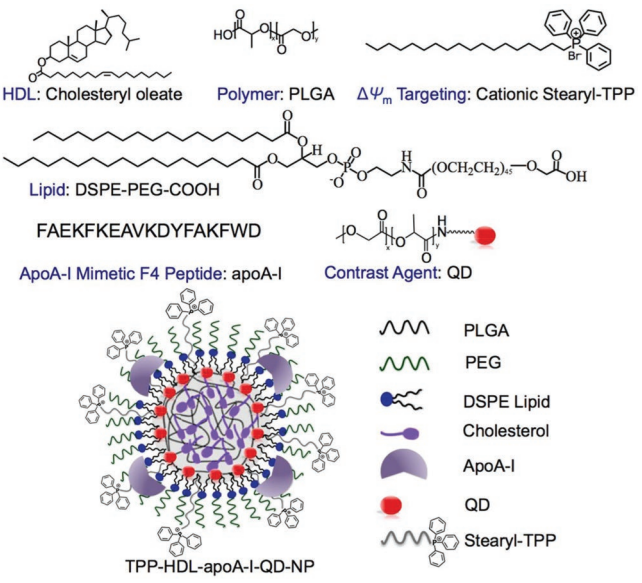

Figure 8. Schematic diagram of the mitochondria-targeted biodegradable HDL mimicking NP platform and various components. Reproduced with permission.[74] Copyright 2013, PNAS.

100 nm PLGA nanoparticles coated with platelet membranes (PNPs) can selectively deliver various biological motifs to damaged human and rodent vasculatures as well as display enhanced binding to platelet-adhering pathogens (**Figure 9**).[77] Furthermore, it was found that fabricated PNPs showed an impressive ability to bind different components of atherosclerotic plaques in vitro. These PNPs also showed an ability to bind not only areas with serious plaque formation, but correspondingly areas that display light plaque formation and preatherosclerotic areas.[78] The nanoparticle formulations described above are promising solutions for treating cardiovascular diseases, especially the targeted treatment of atherosclerotic diseases utilizing the natural atherosclerotic plaque-targeting abilities of HDL and platelet membranes, and all speak to the great ingenuity of NP therapies which are under development. However, the plaque elimination ability is weak or absent in both nanosystems, which is a concern as plaque elimination is important to prevent atherosclerosis progression. Therefore, the diagnostic and therapeutic functions should both be considered in the future design of these two nanoparticle systems.

4.3. Advantages and Limitations of Nanoparticle Therapies

Small molecule drugs without any carrier generally distribute indiscriminately throughout the body, which include both disease sites and healthy tissue. This is a problem particularly when toxic compounds are used as therapeutics. Surface modifications and innovative formulations of nanoparticles improve circulation time, bioavailability, biodistribution, pharmacokinetics, and safety profiles.[37a] However, even if the therapeutic is rendered safer due to NP encapsulation, off-target effects remain a big issue for effective delivery. Therefore, looking for effective targeting moieties is an urgently demanding issue. Although NPs have great qualities such as tunable surface

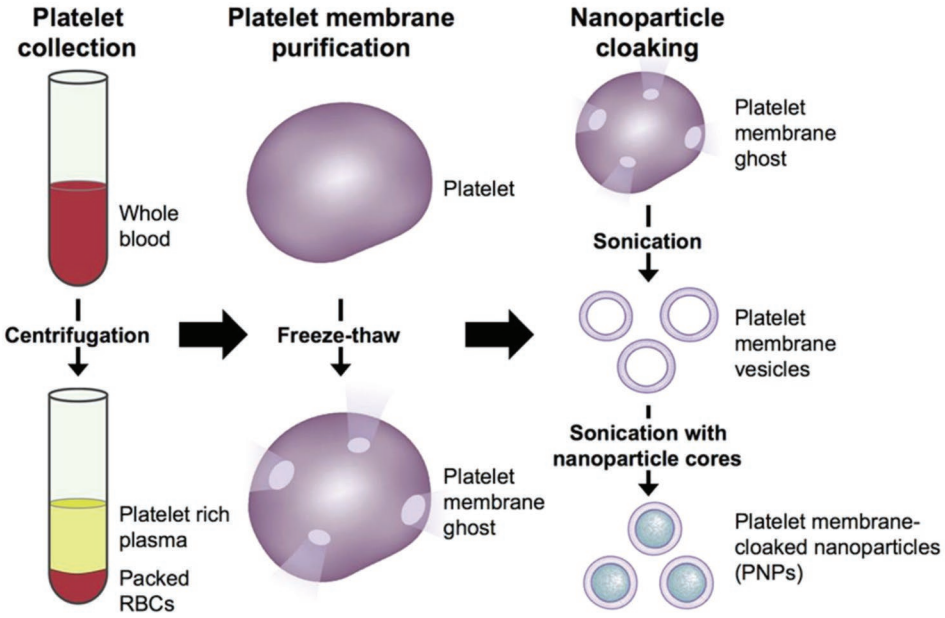

Figure 9. Schematic preparation of PNPs. Reproduced with permission.[77] Copyright 2015, Nature Publishing Group.

chemistry for targeting of tissues, and controlled drug release, a general issue with nanoparticles is that NP biodistribution primarily sequesters to the liver and spleen due to reticuloendothelial/mononuclear phagocyte system function. Notably, obesity can interfere with the distribution of nanoparticles. Due to the associated splenomegaly and complications of obesity, e.g., metabolic syndrome, smaller nanoparticles tend to deposit in the spleen, especially in obese patients.[79] The exact mechanism of such changes need to be studied for the safe administration of nanoparticle formulations. Additionally, the heterogeneities of vascular permeability in tissues and organs limits nanoparticle penetration and effectiveness.[80] Nevertheless, "stealth" coating with PEG-PLGA holds great potential in the delivery of drugs due to nonspecific, reticuloendothelial system-avoidance properties of PEG. For example, Zhang and co-workers constructed targeted nanoparticles composed of PEG-PLGA which showed higher accumulation in WAT and steady circulation in the blood.[12b]

5. Challenges and Perspective

Nanotechnologies which are utilized in the treatment of obesity have significantly advanced in recent years. Many nanomedicine-based strategies have shown promising curative effect in the lab phase for weight control via suppression of nutrient digestion and enhancement of energy expenditure.[81] Despite the many existing challenges, there is tremendous promise in nanomedicine. The continuous discovery of new molecular targets, our improved understanding of the pathophysiology of obesity, diabetes, and heart disease, as well as emerging molecular biological techniques will aid in the prevention and treatment of these diseases. The potential gene targets provide new directions for researchers to develop the next generation of nanomedicines targeting these obesity-related genes to improve therapeutic efficiency. For example, improved results may be achieved through targeted delivery systems or using gene-editing technologies such as a CRISPR/Cas9 system to knock down or knock out a specific target. Additionally, the microneedle patch-nanoparticle hybrid drug delivery system can overcome the biological barriers by combining nanotechnology with other therapeutic strategies.

While the arrival of nanotechnology presents many new opportunities, there remains much to be learned in the emerging field of nanomedicine for the treatment of obesity and related comorbidities, including prominent uncertainties in regard to optimal nanomedicine formulations, hurdles in manufacturing, regulation, and approval of nanomedicine for the clinic. Over the past decade, there has been an overabundance of successful NP preclinical studies, however as of 2017 only 15 passively targeted nanocarriers have been approved for clinical use, without a single nanomedicine passing into the clinical stage[82] due to (1) uncertain potential hazard of nanocarriers, (2) complex immunological/biological systems lead to limited understanding of their net effects on spatial kinetics of the therapeutic nanocarriers, and (3) there exist multiple challenges in scale-up and regulation. Rosenblum et al. note that challenges in design, such as scalability, and controllability of release should be addressed, as well the development of more predictive preclinical animal models and standardization guidelines in regard to nanomedicine are needed.[83] In addition to the technological challenges of nanoparticles discussed above, obstacles related to commercialization and approval of nanomedicines by the regulatory authorities are prominent hurdles that need to be overcome to bridge the bench-bed gap. Overall, it is essential to meticulously characterize biological barriers such as the reticuloendothelial system as well as the changes in the body due to obesity, T2D, and cardiovascular disease for their effects on the delivery process to be understood, as well as to continue building a

library of unique markers and targets for treatment. Design of nanotechnological components in the next generations of nanodelivery platforms will depend on the close interfacing of nanocarrier delivery systems and our growing knowledge of their strengths and limitations. As the demand for obesity treatment continues to grow in the coming years, these nanomedicines, properly developed, will certainly have a great opportunity to make a lasting impact on one of the deadly plagues of our time.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, *N. Engl. J. Med.* **2016**, *375*, 794.
[2] J. J. Heindel, R. Newbold, T. T. Schug, *Nat. Rev. Endocrinol.* **2015**, *11*, 653.
[3] B. E. Schneider, E. C. Mun, *Diabetes Care* **2005**, *28*, 475.
[4] V. S. Malik, W. C. Willett, F. B. Hu, *Nat. Rev. Endocrinol.* **2013**, *9*, 13.
[5] S. A. Fryhofer, *American Medical Association*, nd Web, December **2013**.
[6] C. Bouchard, *Am. J. Clin. Nutr.* **2010**, *91*, 1.
[7] a) A. S. Shah, D. D'Alessio, M. E. Ford-Adams, A. P. Desai, T. H. Inge, *Diabetes Care* **2016**, *39*, 934; b) P. M. O'neil, S. R. Smith, N. J. Weissman, M. C. Fidler, M. Sanchez, J. Zhang, B. Raether, C. M. Anderson, W. R. Shanahan, *Obesity* **2012**, *20*, 1426; c) S. U. Dombrowski, K. Knittle, A. Avenell, V. Araujo-Soares, F. F. Sniehotta, *BMJ* **2014**, *348*, g2646; d) S. R. Smith, N. J. Weissman, C. M. Anderson, M. Sanchez, E. Chuang, S. Stubbe, H. Bays, W. R. Shanahan, B. Modification, L. f. Overweight, O. M. S. Group, *N. Engl. J. Med.* **2010**, *363*, 245; e) L. Angrisani, A. Santonicola, P. Iovino, G. Formisano, H. Buchwald, N. Scopinaro, *Obes. Surg.* **2015**, *25*, 1822.
[8] a) S. M. Musthaba, S. Ahmad, A. Ahuja, J. Ali, S. Baboota, *Curr. Nanosci.* **2009**, *5*, 344; b) B. Yameen, W. I. Choi, C. Vilos, A. Swami, J. Shi, O. C. Farokhzad, *J. Controlled Release* **2014**, *190*, 485.
[9] a) J. Shi, A. R. Votruba, O. C. Farokhzad, R. Langer, *Nano Lett.* **2010**, *10*, 3223; b) J. Safari, Z. Zarnegar, *J. Saudi Chem. Soc.* **2014**, *18*, 85; c) Q. Hu, H. Li, L. Wang, H. Gu, C. Fan, *Chem. Rev.* **2018**, https://doi.org/10.1021/acs.chemrev.7b00663.
[10] a) P. Guo, *Nat. Nanotechnol.* **2010**, *5*, 833; b) P. Kesharwani, V. Gajbhiye, N. K. Jain, *Biomaterials* **2012**, *33*, 7138.
[11] W. Jiang, D. Rutherford, T. Vuong, H. Liu, *Bioact. Mater.* **2017**, *2*, 185.
[12] a) Y. Zhang, Q. Liu, J. Yu, S. Yu, J. Wang, L. Qiang, Z. Gu, *ACS Nano* **2017**, *11*, 9223; b) Y. Xue, X. Xu, X.-Q. Zhang, O. C. Farokhzad, R. Langer, *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 5552; c) Y. Liu, Z.-T. Cao, C.-F. Xu, Z.-D. Lu, Y.-L. Luo, J. Wang, *Biomaterials* **2018**, *172*, 92; d) C. de Jesus Felismino, E. Helal-Neto, F. L. Portilho, S. R. Pinto, F. Sancenón, R. Martínez-Máñez, A. de Assis Ferreira, S. V. da Silva, T. C. Barja-Fidalgo, R. Santos-Oliveira, *J. Controlled Release* **2018**, *281*, 11.
[13] J. M. Friedman, *Nature* **2000**, *404*, 632.
[14] H. Ohno, K. Shinoda, B. M. Spiegelman, S. Kajimura, *Cell Metab.* **2012**, *15*, 395.
[15] T. Montanari, N. Poscic, M. Colitti, *Obes. Rev.* **2017**, *18*, 495.
[16] N. Hironori, *Diabetes Metab. J.* **2013**, *37*, 85.
[17] J. Nedergaard, B. Cannon, *Cell Metab.* **2014**, *20*, 396.
[18] I. Bondia-Pons, L. Ryan, J. A. Martinez, *J. Physiol. Biochem.* **2012**, *68*, 701.
[19] E. Hopps, D. Noto, G. Caimi, M. R. Averna, *Nutr., Metab. Cardiovasc. Dis.* **2010**, *20*, 72.
[20] a) A. Fernandez-Sanchez, E. Madrigal-Santillan, M. Bautista, J. Esquivel-Soto, A. Morales-Gonzalez, C. Esquivel-Chirino, I. Durante-Montiel, G. Sanchez-Rivera, C. Valadez-Vega, J. A. Morales-Gonzalez, *Int. J. Mol. Sci.* **2011**, *12*, 3117; b) C. K. Roberts, K. K. Sindhu, *Life Sci.* **2009**, *84*, 705.
[21] a) G. S. Hotamisligil, *Nature* **2006**, *444*, 860; b) M. E. Kotas, R. Medzhitov, *Cell* **2015**, *160*, 816; c) C. N. Lumeng, A. R. Saltiel, *J. Clin. Invest.* **2011**, *121*, 2111; d) J. M. Olefsky, C. K. Glass, *Annu. Rev. Physiol.* **2010**, *72*, 219.
[22] M. F. Gregor, G. S. Hotamisligil, *Annu. Rev. Immunol.* **2011**, *29*, 415.
[23] J. Hirosumi, G. Tuncman, L. F. Chang, C. Z. Gorgun, K. T. Uysal, K. Maeda, M. Karin, G. S. Hotamisligil, *Nature* **2002**, *420*, 333.
[24] a) W. L. Holland, J. T. Brozinick, L. P. Wang, E. D. Hawkins, K. M. Sargent, Y. Q. Liu, K. Narra, K. L. Hoehn, T. A. Knotts, A. Siesky, D. H. Nelson, S. K. Karathanasis, G. K. Fontenot, M. J. Birnbaum, S. A. Summers, *Cell Metab.* **2007**, *5*, 167; b) G. S. Hotamisligil, *Cell* **2010**, *140*, 900; c) T. Nakamura, M. Furuhashi, P. Li, H. Cao, G. Tuncman, N. Sonenberg, C. Z. Gorgun, G. S. Hotamisligil, *Cell* **2010**, *140*, 338; d) B. Vandanmagsar, Y. H. Youm, A. Ravussin, J. E. Galgani, K. Stadler, R. L. Mynatt, E. Ravussin, J. M. Stephens, V. D. Dixit, *Nat. Med.* **2011**, *17*, 179.
[25] S. Li, J. H. Zhao, J. A. Luan, R. N. Luben, S. A. Rodwell, K.-T. Khaw, K. K. Ong, N. J. Wareham, R. J. Loos, *Am. J. Clin. Nutr.* **2010**, *91*, 184.
[26] J. C. Chambers, P. Elliott, D. Zabaneh, W. Zhang, Y. Li, P. Froguel, D. Balding, J. Scott, J. S. Kooner, *Nat. Genet.* **2008**, *40*, 716.
[27] H. Luo, M. Jiang, G. Lian, Q. Liu, M. Shi, T. Y. Li, L. Song, J. Ye, Y. He, L. Yao, C. Zhang, Z.-Z. Lin, C.-S. Zhang, T.-J. Zhao, W.-P. Jia, P. Li, S.-Y. Lin, S.-C. Lin, *Cell Metab.* **2018**, *27*, 843.
[28] a) J. L. Goldstein, R. A. DeBose-Boyd, M. S. Brown, *Cell* **2006**, *124*, 35; b) Y. A. Moon, G. S. Liang, X. F. Xie, M. Frank-Kamenetsky, K. Fitzgerald, V. Koteliansky, M. S. Brown, J. L. Goldstein, J. D. Horton, *Cell Metab.* **2012**, *15*, 240.
[29] M. Furuhashi, G. S. Hotamisligil, *Nat. Rev. Drug Discovery* **2008**, *7*, 489.
[30] P. Gonzalez-Muniesa, M. A. Martinez-Gonzalez, F. B. Hu, J. P. Despres, Y. Matsuzawa, R. J. F. Loos, L. A. Moreno, G. Bray, J. A. Martinez, *Nat. Rev. Dis. Primers* **2017**, *3*, 17034.
[31] K. Kaszubska, B. Budzynska, G. Biala, *Curr. Issues Pharm. Med. Sci.* **2016**, *29*, 57.
[32] G. Srivastava, C. M. Apovian, *Nat. Rev. Endocrinol.* **2018**, *14*, 12.

[33] a) H. Buchwald, Y. Avidor, E. Braunwald, M. D. Jensen, W. Pories, K. Fahrbach, K. Schoelles, *JAMA, J. Am. Med. Assoc.* **2004**, *292*, 1724; b) L. Sjöström, K. Narbro, C. D. Sjöström, K. Karason, B. Larsson, H. Wedel, T. Lystig, M. Sullivan, C. Bouchard, B. Carlsson, *N. Engl. J. Med.* **2007**, *357*, 741; c) G. Mingrone, S. Panunzi, A. De Gaetano, C. Guidone, A. Iaconelli, G. Nanni, M. Castagneto, S. Bornstein, F. Rubino, *Lancet* **2015**, *386*, 964.
[34] Y. Q. Zhang, J. C. Yu, L. Qiang, Z. Gu, *Sci. China: Life Sci.* **2018**, *61*, 373.
[35] X. Y. Xu, W. Ho, X. Q. Zhang, N. Bertrand, O. Farokhzad, *Trends Mol. Med.* **2015**, *21*, 223.
[36] M. A. Boles, D. Ling, T. Hyeon, D. V. Talapin, *Nat. Mater.* **2016**, *15*, 141.
[37] a) X. Xu, W. Ho, X. Zhang, N. Bertrand, O. Farokhzad, *Trends Mol. Med.* **2015**, *21*, 223; b) Y. H. Tsou, X. Q. Zhang, H. Zhu, S. Syed, X. Xu, *Small* **2017**, *13*, 1701921.
[38] N. Thovhogi, N. Sibuyi, M. Meyer, M. Onani, A. Madiehe, *J. Nanopart. Res.* **2015**, *17*, 112.
[39] M. R. Marinozzi, L. Pandolfi, M. Malatesta, M. Colombo, V. Collico, P. M.-J. Lievens, S. Tambalo, C. Lasconi, F. Vurro, F. Boschi, S. Mannucci, A. Sbarbati, D. Prosperi, L. Calderan, *Int. J. Biochem. Cell Biol.* **2017**, *93*, 62.
[40] A. Rocca, S. Moscato, F. Ronca, S. Nitti, V. Mattoli, M. Giorgi, G. Ciofani, *Nanomedicine* **2015**, *11*, 1725.
[41] H. Yin, R. L. Kanasty, A. A. Eltoukhy, A. J. Vegas, J. R. Dorkin, D. G. Anderson, *Nat. Rev. Genet.* **2014**, *15*, 541.
[42] Y. Zu, H. Overby, G. Ren, Z. Fan, L. Zhao, S. Wang, *Colloids Surf., B* **2018**, *164*, 414.
[43] S. K. Yekollu, R. Thomas, B. O'sullivan, *Diabetes* **2011**, *60*, 2928.
[44] Z.-W. Wu, C.-T. Chien, C.-Y. Liu, J.-Y. Yan, S.-Y. Lin, *J. Drug Targeting* **2012**, *20*, 551.
[45] C. Jiang, M. A. Cano-Vega, F. Yue, L. Kuang, N. Narayanan, G. Uzunalli, M. P. Merkel, S. Kuang, M. Deng, *Mol. Ther.* **2017**, *25*, 1718.
[46] N. C. Ngwuluka, N. A. Ochekpe, O. I. Aruoma, *Polymers* **2014**, *6*, 1312.
[47] L. Ma, T.-W. Liu, M. A. Wallig, I. T. Dobrucki, L. W. Dobrucki, E. R. Nelson, K. S. Swanson, A. M. Smith, *ACS Nano* **2016**, *10*, 6952.
[48] M. de Raad, E. A. Teunissen, E. Mastrobattista, *Nanomedicine* **2014**, *9*, 2217.
[49] Y.-W. Won, P. P. Adhikary, K. S. Lim, H. J. Kim, J. K. Kim, Y.-H. Kim, *Nat. Mater.* **2014**, *13*, 1157.
[50] A. C. Eldredge, M. E. Johnson, Y. Cao, L. Zhang, C. Zhao, Z. X. Liu, Q. Yang, Z. B. Guan, *Biomaterials* **2018**, *178*, 458.
[51] Y. Q. Zhang, J. C. Yu, D. Wen, G. J. Chen, Z. Gu, *Expert Opin. Drug Delivery* **2018**, *15*, 431.
[52] a) J. C. Clapham, J. R. Arch, M. Tadayyon, *Pharmacol. Ther.* **2001**, *89*, 81; b) A. Whittle, J. Relat-Pardo, A. Vidal-Puig, *Trends Pharmacol. Sci.* **2013**, *34*, 347; c) E. Colman, J. Golden, M. Roberts, A. Egan, J. Weaver, C. Rosebraugh, *N. Engl. J. Med.* **2012**, *367*, 1577.
[53] J. Kaur, *Cardiol. Res. Pract.* **2014**, *2014*, 943162.
[54] Y. Rochlani, N. V. Pothineni, S. Kovelamudi, J. L. Mehta, *Ther. Adv. Cardiovasc. Dis.* **2017**, *11*, 215.
[55] a) M. T. Hamilton, D. G. Hamilton, T. W. Zderic, *Diabetes* **2007**, *56*, 2655; b) B. Isomaa, P. Almgren, T. Tuomi, B. Forsén, K. Lahti, M. Nissén, M.-R. Taskinen, L. Groop, *Diabetes Care* **2001**, *24*, 683; c) H.-M. Lakka, D. E. Laaksonen, T. A. Lakka, L. K. Niskanen, E. Kumpusalo, J. Tuomilehto, J. T. Salonen, *JAMA, J. Am. Med. Assoc.* **2002**, *288*, 2709; d) J. B. Meigs, P. W. Wilson, C. S. Fox, R. S. Vasan, D. M. Nathan, L. M. Sullivan, R. B. D'agostino, *J. Clin. Endocrinol. Metabol.* **2006**, *91*, 2906; e) N. Esser, S. Legrand-Poels, J. Piette, A. J. Scheen, N. Paquot, *Diabetes Res. Clin. Pract.* **2014**, *105*, 141.
[56] S. B. Heymsfield, T. A. Wadden, *N. Engl. J. Med.* **2017**, *376*, 254.
[57] R. A. DeFronzo, E. Ferrannini, L. Groop, R. R. Henry, W. H. Herman, J. J. Holst, F. B. Hu, C. R. Kahn, I. Raz, G. I. Shulman, D. C. Simonson, M. A. Testa, R. Weiss, *Nat. Rev. Dis. Primers* **2015**, *1*, 15019.
[58] B. W. Bode, H. T. Sabbah, T. M. Gross, L. P. Fredrickson, P. C. Davidson, *Diabetes/Metabol. Res. Rev.* **2002**, *18*, S14.
[59] P. R. Schauer, D. L. Bhatt, J. P. Kirwan, K. Wolski, S. A. Brethauer, S. D. Navaneethan, A. Aminian, C. E. Pothier, E. S. Kim, S. E. Nissen, *N. Engl. J. Med.* **2014**, *370*, 2002.
[60] a) P. Zeitler, K. Hirst, L. Pyle, B. Linder, K. Copeland, S. Arslanian, L. Cuttler, D. M. Nathan, S. Tollefsen, D. Wilfley, F. Kaufman, T. S. Grp, *N. Engl. J. Med.* **2012**, *366*, 2247; b) M. Foretz, B. Guigas, L. Bertrand, M. Pollak, B. Viollet, *Cell Metab.* **2014**, *20*, 953; c) F. Ismail-Beigi, *N. Engl. J. Med.* **2012**, *367*, 183.
[61] F.-Z. Wang, Z.-S. Xie, L. Xing, B.-F. Zhang, J.-L. Zhang, P.-F. Cui, J.-B. Qiao, K. Shi, C.-S. Cho, M.-H. Cho, X. Xu, P. Li, H.-L. Jiang, *Biomaterials* **2015**, *73*, 149.
[62] a) H. S. Han, K. Y. Choi, H. Lee, M. Lee, J. Y. An, S. Shin, S. Kwon, D. S. Lee, J. H. Park, *ACS Nano* **2016**, *10*, 10858; b) N. V. Rao, H. Y. Yoon, H. S. Han, H. Ko, S. Son, M. Lee, H. Lee, D.-G. Jo, Y. M. Kang, J. H. Park, *Expert Opin. Drug Delivery* **2016**, *13*, 239; c) H. S. Han, K. Y. Choi, H. Ko, J. Jeon, G. Saravanakumar, Y. D. Suh, D. S. Lee, J. H. Park, *J. Controlled Release* **2015**, *200*, 158.
[63] J. G. Rho, H. S. Han, J. H. Han, H. Lee, W. H. Lee, S. Kwon, S. Heo, J. Yoon, H. H. Shin, E.-y. Lee, *J. Controlled Release* **2018**, *279*, 89.
[64] Y.-H. Tsou, J. Khoneisser, P.-C. Huang, X. Xu, *Bioact. Mater.* **2016**, *1*, 39.
[65] Y. Lu, K. Hajifathalian, M. Ezzati, M. Woodward, E. B. Rimm, G. Danaei, *Lancet* **2014**, *383*, 970.
[66] C. M. Kusminski, P. E. Scherer, *Circ. Res.* **2015**, *116*, 1293.
[67] S. Karimian, J. Stein, B. Bauer, C. Teupe, *J. Obes.* **2016**, *2016*, 1.
[68] N. J. Stone, J. G. Robinson, A. H. Lichtenstein, C. N. B. Merz, C. B. Blum, R. H. Eckel, A. C. Goldberg, D. Gordon, D. Levy, D. M. Lloyd-Jones, *J. Am. Coll. Cardiol.* **2014**, *63*, 2889.
[69] J. F. Lassen, N. R. Holm, A. Banning, F. Burzotta, T. Lefevre, A. Chieffo, D. Hildick-Smith, Y. Louvard, G. Stankovic, *EuroIntervention* **2016**, *12*, 38.
[70] G. W. Stone, A. Maehara, J. E. Muller, D. G. Rizik, K. A. Shunk, O. Ben-Yehuda, P. Genereux, O. Dressler, R. Parvataneni, S. Madden, P. Shah, E. S. Brilakis, A. S. Kini, C. Investigators, *JACC: Cardiovasc. Interventions* **2015**, *8*, 927.
[71] J. H. Alexander, P. K. Smith, *N. Engl. J. Med.* **2016**, *374*, 1954.
[72] J. Warren, R. Mehran, U. Baber, K. Xu, D. Giacoppo, B. J. Gersh, G. Guagliumi, B. Witzenbichler, E. M. Ohman, S. J. Pocock, G. W. Stone, *Am. Heart J.* **2016**, *171*, 40.
[73] H. S. Kruth, *Front. Biosci.* **2001**, *6*, d429.
[74] S. Marrache, S. Dhar, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 9445.
[75] S. M. Gordon, J. Y. Deng, L. J. Lu, W. S. Davidson, *J. Proteome Res.* **2010**, *9*, 5239.
[76] B. L. Sanchez-Gaytan, F. Fay, M. E. Lobatto, J. Tang, M. Ouimet, Y. Kim, S. E. M. van der Staay, S. M. van Rijs, B. Priem, L. F. Zhang, E. A. Fisher, K. J. Moore, R. Langer, Z. A. Fayad, W. J. M. Mulder, *Bioconjugate Chem.* **2015**, *26*, 443.
[77] C.-M. J. Hu, R. H. Fang, K.-C. Wang, B. T. Luk, S. Thamphiwatana, D. Dehaini, P. Nguyen, P. Angsantikul, C. H. Wen, A. V. Kroll, *Nature* **2015**, *526*, 118.
[78] X. L. Wei, M. Ying, D. Dehaini, Y. Y. Su, A. V. Kroll, J. R. Zhou, W. W. Gao, R. H. Fang, S. Chien, L. F. Zhang, *ACS Nano* **2018**, *12*, 109.
[79] C. D. Felismino, E. Helal-Neto, F. L. Portilho, S. R. Pinto, F. Sancenon, R. Martinez-Manez, A. D. Ferreira, S. V. da Silva, T. C. Barja-Fidalgo, R. Santos-Oliveira, *J. Controlled Release* **2018**, *281*, 11.
[80] A. A. Manzoor, L. H. Lindner, C. D. Landon, J. Y. Park, A. J. Simnick, M. R. Dreher, S. Das, G. Hanna, W. Park, A. Chilkoti, G. A. Koning,

T. L. ten Hagen, D. Needham, M. W. Dewhirst, *Cancer Res.* **2012**, *72*, 5566.
[81] Y. Zhang, J. Yu, L. Qiang, Z. Gu, *Sci. China: Life Sci.* **2018**, *61*, 373.
[82] a) A. C. Anselmo, S. Mitragotri, *Bioeng. Transl. Med.* **2016**, *1*, 10; b) P. Kumari, B. Ghosh, S. Biswas, *J. Drug Targeting* **2016**, *24*, 179; c) J. Shi, P. W. Kantoff, R. Wooster, O. C. Farokhzad, *Nat. Rev. Cancer* **2017**, *17*, 20.
[83] D. Rosenblum, N. Joshi, W. Tao, J. M. Karp, D. Peer, *Nat. Commun.* **2018**, *9*, 1410.
[84] Y. Hayashi, E. Suemitsu, K. Kajimoto, Y. Sato, A. Akhter, Y. Sakurai, H. Hatakeyama, M. Hyodo, N. Kaji, Y. Baba, *Mol. Ther.–Nucleic Acids* **2014**, *3*, e154.
[85] D. Di Mascolo, C. J. Lyon, S. Aryal, M. R. Ramirez, J. Wang, P. Candeloro, M. Guindani, W. A. Hsueh, P. Decuzzi, *J. Controlled Release* **2013**, *170*, 460.
[86] M. N. Hossen, K. Kajimoto, H. Akita, M. Hyodo, H. Harashima, *J. Controlled Release* **2012**, *163*, 101.
[87] S.-B. Yong, Y. Song, Y.-H. Kim, *Biomaterials* **2017**, *148*, 81.
[88] M. N. Hossen, K. Kajimoto, H. Akita, M. Hyodo, H. Harashima, *J. Controlled Release* **2013**, *171*, 104.
[89] M. N. Hossen, K. Kajimoto, H. Akita, M. Hyodo, T. Ishitsuka, H. Harashima, *Mol. Ther.* **2013**, *21*, 533.
[90] M. Sahuri-Arisoylu, L. Brody, J. Parkinson, H. Parkes, N. Navaratnam, A. D. Miller, E. Thomas, G. Frost, J. Bell, *Int. J. Obes.* **2016**, *40*, 955.
[91] R. M. El-Gharbawy, A. M. Emara, S. E.-S. Abu-Risha, *Biomed. Pharmacother.* **2016**, *84*, 810.
[92] M. P. Ferreira, S. Ranjan, S. Kinnunen, A. Correia, V. Talman, E. Mäkilä, B. Barrios-Lopez, M. Kemell, V. Balasubramanian, J. Salonen, *Small* **2017**, *13*, 1701276.
[93] 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, *Adv. Mater.* **2015**, *27*, 5547.
[94] A. Ishikita, T. Matoba, G. Ikeda, J. i. Koga, Y. Mao, K. Nakano, O. Takeuchi, J. Sadoshima, K. Egashira, *J. Am. Heart Assoc.* **2016**, *5*, e003872.
[95] V. Segura-Ibarra, F. E. Cara, S. Wu, D. A. Iruegas-Nunez, S. Wang, M. Ferrari, A. Ziemys, M. Valderrabano, E. Blanco, *J. Controlled Release* **2017**, *262*, 18.
[96] H.-S. Chou, M. Larsson, M.-H. Hsiao, Y.-C. Chen, M. Röding, M. Nydén, D.-M. Liu, *J. Controlled Release* **2016**, *224*, 33.
[97] M. Nurunnabi, S.-A. Lee, V. Revuri, Y. H. Hwang, S. H. Kang, M. Lee, S. Cho, K. J. Cho, Y. Byun, Y. H. Bae, *J. Controlled Release* **2017**, *268*, 305.
[98] F.-Y. Su, K.-J. Lin, K. Sonaje, S.-P. Wey, T.-C. Yen, Y.-C. Ho, N. Panda, E.-Y. Chuang, B. Maiti, H.-W. Sung, *Biomaterials* **2012**, *33*, 2801.
[99] S. Lau, J. Fei, H. Liu, W. Chen, R. Liu, *J. Controlled Release* **2017**, *265*, 113.
[100] S. Yang, F. Wu, J. Liu, G. Fan, W. Welsh, H. Zhu, T. Jin, *Adv. Funct. Mater.* **2015**, *25*, 4633.
[101] Y. Zhang, J. Yu, J. Wang, N. J. Hanne, Z. Cui, C. Qian, C. Wang, H. Xin, J. H. Cole, C. M. Gallippi, *Adv. Mater.* **2017**, *29*, 1604043.
[102] A. Than, K. Liang, S. Xu, L. Sun, H. Duan, F. Xi, C. Xu, P. Chen, *Small Methods* **2017**, *1*, 1700269.
[103] M. Dangol, S. Kim, C. G. Li, S. F. Lahiji, M. Jang, Y. Ma, I. Huh, H. Jung, *J. Controlled Release* **2017**, *265*, 41.
[104] Z. Tong, J. Zhou, J. Zhong, Q. Tang, Z. Lei, H. Luo, P. Ma, X. Liu, *ACS Appl. Mater. Interfaces* **2018**, *10*, 20014.
[105] W. Chen, R. Tian, C. Xu, B. C. Yung, G. Wang, Y. Liu, Q. Ni, F. Zhang, Z. Zhou, J. Wang, *Nat. Commun.* **2017**, *8*, 1777.