SCIENCE CHINA
Life Sciences

THEMATIC ISSUE: Nanotechnology and nanomedicine
•REVIEW•

April 2018 Vol.61 No.4: 373–379
https://doi.org/10.1007/s11427-017-9257-1

Nanomedicine for obesity treatment

Yuqi Zhang[1,2], Jicheng Yu[1,2], Li Qiang[3*] & Zhen Gu[1,2,4*]

[1]*Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, Raleigh, NC 27695, USA;*
[2]*Center for Nanotechnology in Drug Delivery and Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA;*
[3]*Department of Pathology and Cell Biology, Naomi Berrie Diabetes Center, Columbia University, New York, NY 10032, USA;*
[4]*Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

Received October 10, 2017; accepted November 20, 2017; published online March 29, 2018

Obesity, as a chronic condition, has been a serious public health issue over the last decades both in the affluent Western world and developing countries. As reported, the risk of several serious diseases increases with weight gain, including type 2 diabetes, coronary heart disease, cancer, and respiratory diseases. In addition to lifestyle modifications, pharmacotherapy has become an important strategy to control weight gain. However, most of the anti-obesity drugs often show poor outcome for weight-loss and cause severe adverse effects. This review surveys recent advances in nanomedicine as an emerging strategy for obesity treatment with an emphasis on the enhanced therapeutic efficiency and minimized side effects. The insights for future development are also discussed.

drug delivery, nanomedicine, obesity, browning, fat absorption, energy expenditure

Citation: Zhang, Y., Yu, J., Qiang, L., and Gu, Z. (2018). Nanomedicine for obesity treatment. Sci China Life Sci 61, 373–379. https://doi.org/10.1007/s11427-017-9257-1

INTRODUCTION

Obesity has been classified as a chronic disease now (World Health Organization, 2014). Usually, people with a body mass index (BMI) above 30 kg m^{-2} are considered obese (Schneider and Mun, 2005). With the increasingly sedentary lifestyles and higher intake of calories in industrialized society, the obese population is rising dramatically in both developed and developing countries (Malik et al., 2013). Right now, obesity is one of the most prevalent health problems all over the world, affecting 15% of the population. The abnormal or excessive fat accumulation leads to a series of co-morbidities such as diabetes, cancer, and cardiovascular diseases (Friedman, 2009).

Obesity is caused by a positive energy balance, while certain factors are involved in this imbalance, including behavioral, environmental, and genetic interactions (Jackson et al., 2015). Careful management of diets and adjustment of lifestyle are important for obesity treatment since pre- and perinatal periods, and it should be lifelong lifestyle changes (Friedman, 2009; Kushner and Ryan, 2014; Wadden et al., 2007). In some severe cases, surgery such as gastric by-pass can restore body weight (Heymsfield and Wadden, 2017). Besides, pharmacotherapy is the focus for obesity treatment over the last decade through either suppression of appetite or inhibition of fat absorption (Mun et al., 2001; Yanovski et al., 1996). However, the commercialization of these anti-obesity drugs is hampered by their serious side effects such as intestinal bleeding or even suicide (George et al., 2014; Kakkar and Dahiya, 2015).

*Corresponding authors (Li Qiang, email: lq2123@cumc.columbia.edu; Zhen Gu, email: zgu@email.unc.edu)

With the development of nanotechnology (Mura and Couvreur, 2012; Parveen et al., 2012; Sun et al., 2017), the integration of anti-obesity drugs into nanomedicine has exhibited tremendous therapeutic potency for obesity treatment (des Rieux et al., 2013; Hossen et al., 2013). Nanoparticlization provides unique advantages based on different synthetic strategies. For example, nanoparticles with targeting moiety are able to achieve targeted drug delivery to minimize side effects (Yameen et al., 2014; Zhang et al., 2013). The poor water-solubility of anti-obesity drugs can be addressed via nano-encapsulation (Musthaba et al., 2009). In this review, we will summarize the recent advances in the development of nanomedicine for obesity treatment with different mechanisms, including suppression of digestibility and enhancement of energy expenditure (Figure 1). In the end, the challenges and future opportunities will also be discussed.

SUPPRESSION OF ENERGY ABSORPTION

As the imbalance of food intake exceeding energy expenditure is the major cause of obesity (Jackson et al., 2015), appetite suppression and fat absorption inhibition are considered as the most straightforward methods to control body weight. A lot of pharmacological agents have been developed and clinically approved for obesity treatment, such as desoxyephedrine and orlistat (Haslam, 2016; Kang and Park, 2012; Rodgers et al., 2012). However, these drugs are often associated with unacceptable adverse effects including gastric function disorder, steatorrhea, strokes, and kidney injury (Ballinger and Peikin, 2002; Kushner, 2008; Rucker et al., 2007).

Orlistat can inhibit lipase in the intestine to reduce the hydrolysis and subsequent absorption of dietary fat (Ballinger and Peikin, 2002). However, due to the poor water-solubility of orlistat, its bioavailability is very low by oral administration (Ballinger and Peikin, 2002). Nanoemulsion of orlistat has been demonstrated to overcome the high lipophilicity and improve its dissolution and pancreatic lipase inhibition *in vivo* (Sangwai et al., 2014). Another issue for orlistat is its adverse effects in the digestive system (Kolonin et al., 2004). Chen et al. designed a conjugated polymer nanocarrier with the negative-feedback loop to reduce the side effects of orlistat (Chen et al., 2016). In this system, they encapsulated orlistat in nanocarriers using a kind of amphiphilic copolymers with hydrophobic side chains of poly (ε-caprolactone) (PCL). Since PCL is also the substrate of lipase, the copolymer side chains gradually degraded in the intestine, leading to the disassembly of nanocarriers and subsequent release of orlistat. The released drug was able to bind to lipase and suppress its enzymatic activity, which in turn slowed down the degradation rate of nanocarriers. An on-demand drug delivery was thus achieved via this negative-feedback loop, which improved the bioavailability of orlistat and minimized its side effects. Instead of small-molecule drug, Kupferschmidt et al. investigated the ability of mesoporous silica particles to reduce body weight (Kupferschmidt et al., 2014). They found the silica particles embedded in food could sequestrate lipase in the small pores through a lipase-specific interaction, leading to a lower fat absorption. Additionally, some other mechanisms such as bile acid sequestration and a faster passage through the intestine might also contribute to the resulting low energy intake. They further demonstrated that the silica particles with the large pore of 11 nm showed a better effect on weight loss compared to those with small pore size (2 nm).

Appetite suppression is an alternative method to decrease food intake and impact energy homeostasis (Mun et al.,

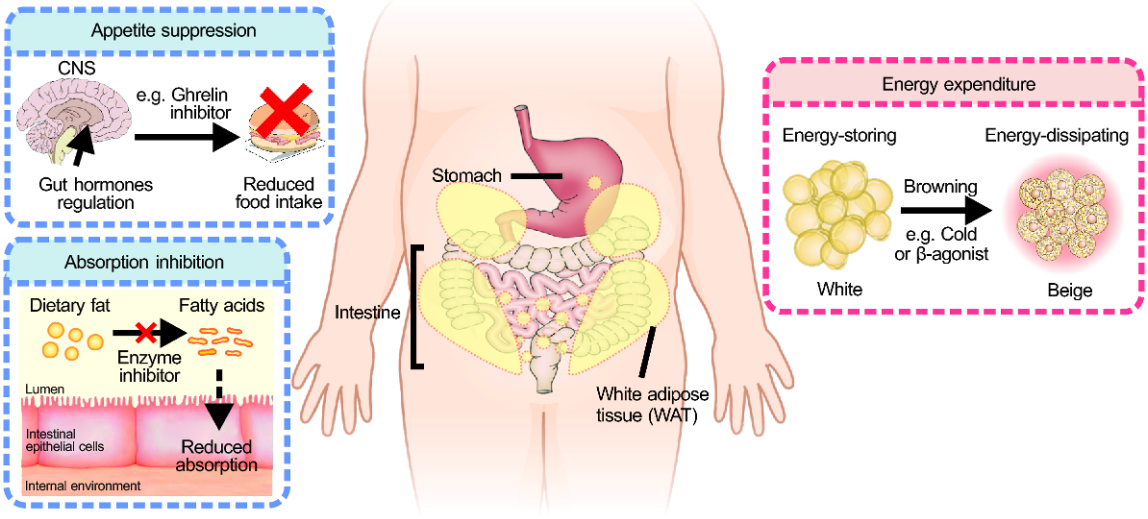

Figure 1 (Color online) Schematic of nanomedicine for obesity treatment with different mechanisms, including suppression of digestibility and enhancement of energy expenditure.

2001). For example, Andrade et al. reported an anti-ghrelin vaccine using virus-like particles for obesity treatment (Andrade et al., 2013). Ghrelin is a gastro-intestinal hormone that stimulates food intake and decreases energy expenditure (Wiedmer et al., 2007). However, the passive delivery of anti-ghrelin antibodies cannot lead to the long-term inhibition of food intake. To address this issue, they immunoconjugated ghrelin with virus proteins to create a vaccine, which was able to trigger an immune response to generate specific anti-ghrelin antibodies. This anti-ghrelin vaccine displayed a significant impact on energy homeostasis in a diet-induced obese (DIO) mouse model.

White adipose tissue (WAT) is used for lipid storage, and white adipocytes contain unilocular lipid droplets (Trayhurn and Beattie, 2001). Inhibition of fat uptake and accumulation in white adipocytes can achieve obesity control. Recently, Kim and coworkers developed an oligopeptide complex for targeted gene delivery to adipocytes (Won et al., 2014). They designed a short-hairpin RNA to silence fatty-acid-binding protein 4 (shFABP4), which coats lipid droplets in adipocytes (Figure 2). They further constructed shFABP4 with D-form 9-arginine (ATS-9R) to obtain an adipocyte-targeted gene carrier. The selective delivery of shFABP4 to WATs was demonstrated to reduce fat accumulation in adipocytes and consequently inhibit weight gain.

Adipocyte needs a suitable microenvironment to grow (Cao, 2007; Ledoux et al., 2008). Besides lipid deposition, the expansion of WATs requires vascularization (Cao, 2007; Carmeliet and Jain, 2000; Voros et al., 2005). Therefore, antiangiogenic therapy that induced the apoptosis of endothelial cells is able to inhibit the progression of adipocyte hyperplasia and reduce weight gain. A cell death-inducing

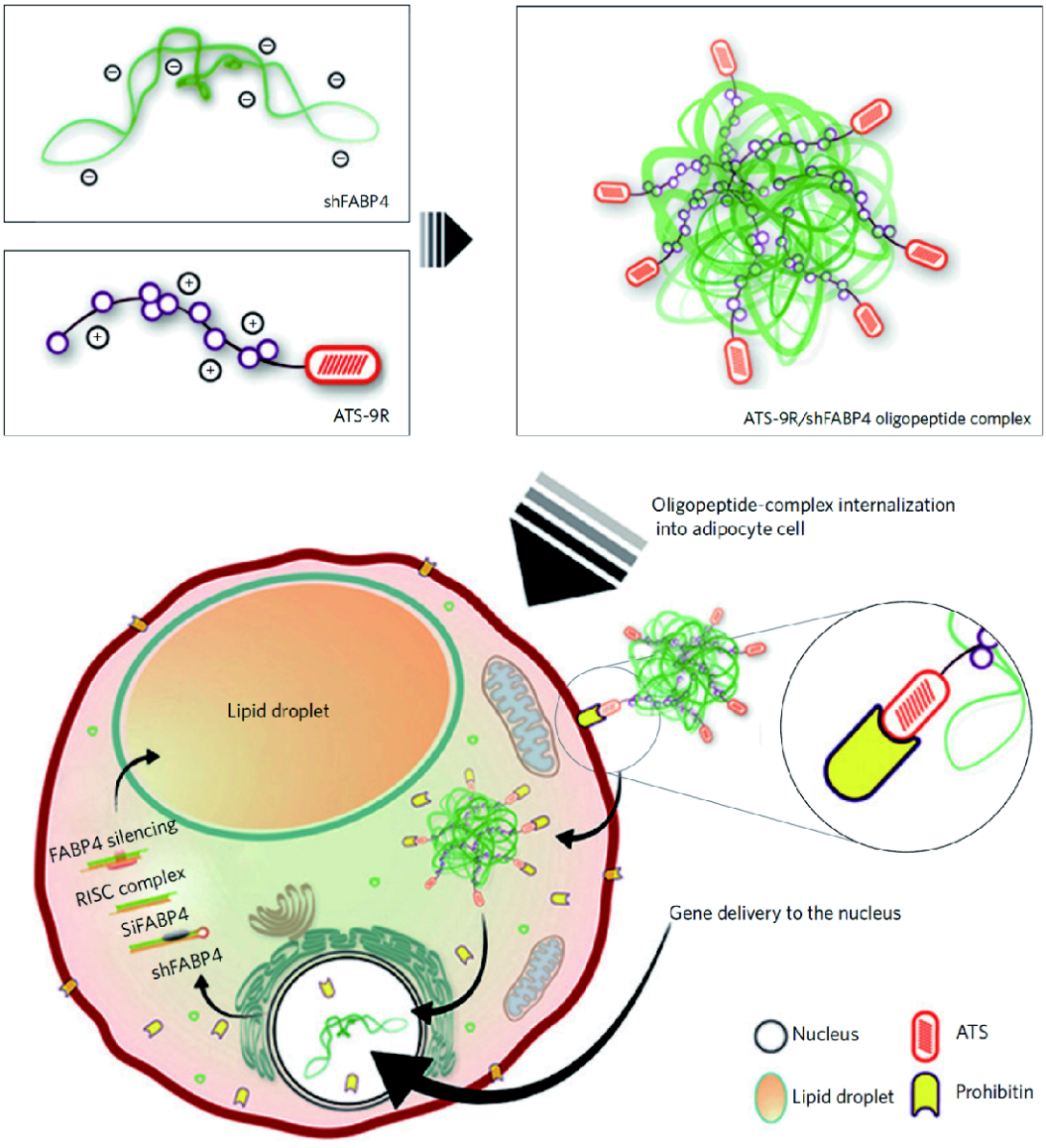

Figure 2 (Color online) Mechanism of the targeted gene delivery to adipocytes by ATS-9R (Figure adapted and modified from Won et al., 2014).

peptide [$_{D}$(KLAKLAK)$_2$] has been evidenced to promote the death of endothelial cells in adipocyte tissue in obese animals (Barnhart et al., 2011; Kolonin et al., 2004). In order to enhance the accumulation of the antiangiogenic drug in WATs, Harashima and coworkers developed a targeting nanoparticle to deliver their cargo to vascular endothelial cells (Kajimura et al., 2015). A prohibitin-targeting peptide, which can specifically bind to the prohibitin protein on the surface of endothelial cell was modified on the PEG-lipid nanoparticles (Hossen et al., 2010; Hossen et al., 2012). They demonstrated that these nanoparticles were specifically taken up by the adipose vascular endothelial cells through prohibitin-mediated endocytosis and then led to the cell apoptosis. However, the metabolic consequences of this method should be carefully evaluated since the shortage of oxygen supply indeed causes hypoxic stress in adipose tissue, resulting in chronic inflammation and insulin resistance in WATs (Cao, 2013; Harms and Seale, 2013; Voros et al., 2005).

ENHANCEMENT OF ENERGY EXPENDITURE

Unlike WATs, brown adipose tissues (BATs) are formed by a type of adipocytes with enriched mitochondria and vascular structure, which can transform chemical energy to heat through nonshivering thermogenesis (Harms and Seale, 2013). The "browning" of WATs or activation of BATs to increase energy expenditure capacity has been considered as a promising strategy to combat obesity (Almeida et al., 2014; Jiang et al., 2015). Many thermogenic inducers and the related pathways have been identified recently (Bartelt and Heeren, 2014; Harms and Seale, 2013; Kajimura et al., 2015; Wu et al., 2013). Based on these better understandings, numerous browning agents have been investigated in obesity treatment, while undesired side effects on other organs such as heart and liver are still urgent issues during clinical translation (Harms and Seale, 2013). To address this issue, Langer, Farokhzad and coworkers developed two peptide-functionalized nanoparticle platforms to specifically deliver browning agents to adipose tissue vasculature (Xue et al., 2016). In this system, an endothelial-targeted peptide was modified on the surface of biodegradable poly (lactic-co-glycolic acid)-*b*-poly (ethylene glycol) (PLGA-*b*-PEG) nanoparticles, which promoted their homing capability to adipose blood vessels (Figure 3). They demonstrated that these nanoparticles were able to transport rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-gamma) activator, into WATs to stimulate angiogenesis and

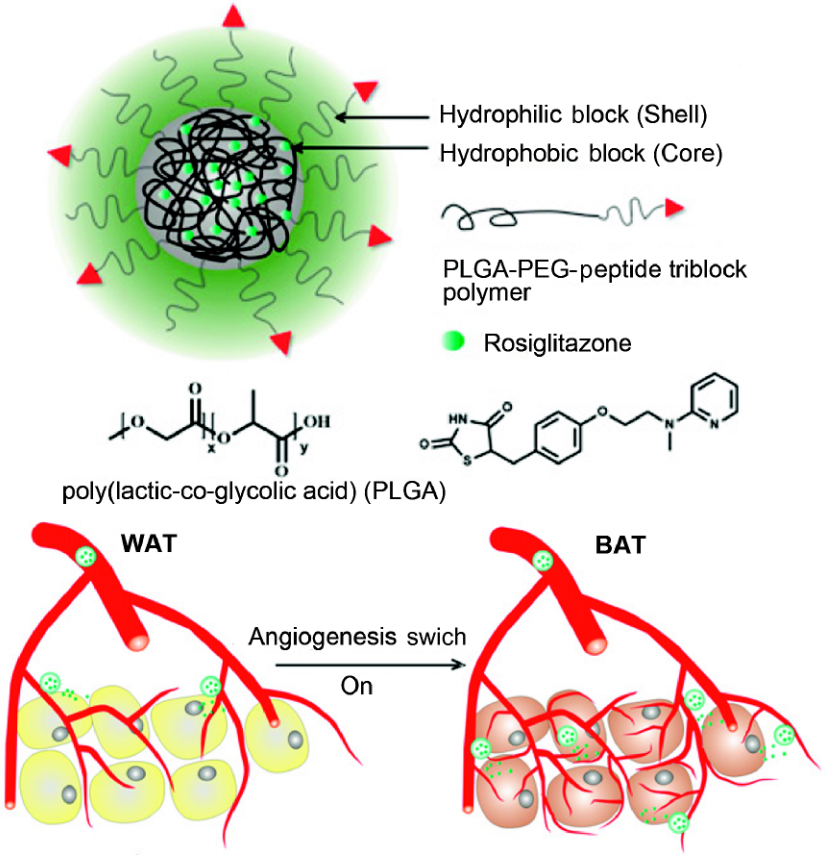

Figure 3 (Color online) Chemical structure of browning agent-loaded nanoparticles and schematic of the WAT browning process through a positive feedback drug delivery system (Figure adapted and modified from Xue et al., 2016).

induce browning via intravenous injection in a DIO mouse model, which further inhibited weight gain.

Marrache and Dhar reported a mitochondria-targeted nanoparticle to deliver anti-obesity drug (Marrache and Dhar, 2012). These nanoparticles were composed of PLGA-*b*-PEG-triphenylphosphonium (TPP) polymer. The PEG shell extends the circulation time of nanoparticles, and TPP could facilitate the internalization into the mitochondrial matrix space to achieve targeted drug delivery. By loading with the mitochondrial decoupler 2,4-dinitrophenol (2,4-DNP), the polymeric nanoparticles were able to reduce lipid accumulation in the adipocytes to manage obesity. However, the over-activation of mitochondria may lead to the excessive generation of reactive oxygen species (ROS), and its possible impairment in non-adipose tissues, such as heart and muscle, should be carefully examined.

Instead of targeted delivery, a localized and sustained release of the browning agent is a promising alternative to facilitate the browning of WATs with minimized side effect. Deng and coworkers locally injected drug-loaded nanoparticles into the inguinal WAT, which allowed localized retention of browning agents and subsequent browning of this fat depot (Jiang et al., 2017). The local browning improved glucose homeostasis and attenuated weight gain in a DIO mouse model.

Recently, Zhang et al. took the advantage of painless microneedle array patches to directly deliver drugs to the adipose tissue underneath the skin (Figure 4) (Yu et al., 2015; Yu et al., 2017; Zhang et al., 2017a; Zhang et al., 2017b). To achieve a sustained release, they encapsulated browning agents into a glucose-responsive nanoparticle (Bakh et al., 2017; Gu et al., 2013a; Gu et al., 2013b; Lu et al., 2016). Under the physiological glucose condition, a localized acidic environment was generated due to the glucose oxidase-mediate glucose oxidation and then the pH-sensitive nanoparticles gradually degraded to release the drugs within 3 days. *In vivo* studies indicated that the tips of microneedles were exposed to the inguinal adipose tissue after application and *in situ* fluorescent section revealed the model drug was successfully delivered into the adipose tissue. They achieved a ~15% inhibition of weight gain after a four-week treatment. Of note, the inguinal fat pad treated with browning microneedles was significantly smaller compared to the untreated side, confirming the localized release of browning

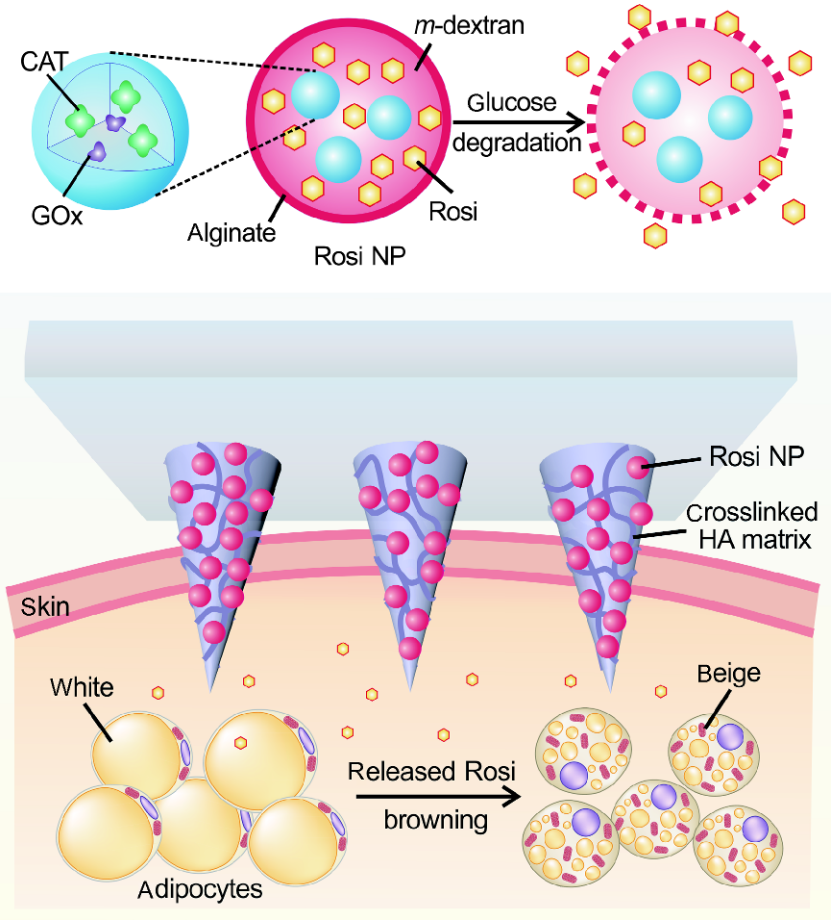

Figure 4 (Color online) Schematic illustration of the browning reagents-loaded transcutaneous MN patch for the brown remodeling of the white fat (Figure adapted and modified from Zhang et al., 2017a).

agents.

CONCLUSION

As summarized above, a large amount of nanomedicine-based strategies have shown promising preclinical activity for weight control via suppression of digestibility or enhancement of energy expenditure. Through different approaches such as oral administration and transdermal delivery, nanocarriers exhibit an efficient and convenient method for body weight control. Despite these advances, the successful clinical trials and further marketization remain challenging by several aspects. First of all, a clear understanding of different critical pathway involved in the regulation of energy homeostasis is required for the design of transformative delivery platforms. For example, the leptin and melanocortin systems have been well investigated in the recent years (Ahima et al., 1996; Sohn et al., 2013), and several agonists are reported to reduce weight gain (Atasoy et al., 2014; Clemmensen et al., 2014; Ghamari-Langroudi et al., 2015). Therefore, it is possible to exploit nanocarriers for these drugs to achieve more effective weight control. Meanwhile, different drug delivery carriers/materials and administration routes may also affect the therapy efficiency. Second, how to reduce the side effects of these nanomedicines remains a barrier for translation. Adipose tissue-targeting groups may be incorporated into nanoparticle-based drug delivery systems to achieve precise therapy (Ma et al., 2016; Thovhogi et al., 2015) but the defects of certain designs must be taken into consideration, such as targeting efficiency and potential immune response. Last but not least, since the weight control requires long-term treatment, a thorough evaluation of the biocompatibility should be carefully performed (Lu et al., 2016).

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

Acknowledgements *This work was supported by the grant from Sloan Research Fellowship.*

Ahima, R.S., Prabakaran, D., Mantzoros, C., Qu, D., Lowell, B., Maratos-Flier, E., and Flier, J.S. (1996). Role of leptin in the neuroendocrine response to fasting. Nature 382, 250–252.

Almeida, M.A., Nadal, J.M., Grassiolli, S., Paludo, K.S., Zawadzki, S.F., Cruz, L., Paula, J.P., and Farago, P.V. (2014). Enhanced gastric tolerability and improved anti-obesity effect of capsaicinoids-loaded PCL microparticles. Mater Sci Eng-C 40, 345–356.

Andrade, S., Pinho, F., Ribeiro, A., Carreira, M., Casanueva, F., Roy, P., and Monteiro, M. (2013). Immunization against active ghrelin using virus-like particles for obesity treatment. Curr Pharm Des 19, 6551–6558.

Atasoy, D., Betley, J.N., Li, W.P., Su, H.H., Sertel, S.M., Scheffer, L.K., Simpson, J.H., Fetter, R.D., and Sternson, S.M. (2014). A genetically specified connectomics approach applied to long-range feeding regulatory circuits. Nat Neurosci 17, 1830–1839.

Bakh, N.A., Cortinas, A.B., Weiss, M.A., Langer, R.S., Anderson, D.G., Gu, Z., Dutta, S., and Strano, M.S. (2017). Glucose-responsive insulin by molecular and physical design. Nat Chem 9, 937–943.

Ballinger, A., and Peikin, S.R. (2002). Orlistat: its current status as an anti-obesity drug. Eur J Pharmacol 440, 109–117.

Barnhart, K.F., Christianson, D.R., Hanley, P.W., Driessen, W.H.P., Bernacky, B.J., Baze, W.B., Wen, S., Tian, M., Ma, J., Kolonin, M.G., et al. (2011). A peptidomimetic targeting white fat causes weight loss and improved insulin resistance in obese monkeys. Sci Transl Med 3, 10-8ra112.

Bartelt, A., and Heeren, J. (2014). Adipose tissue browning and metabolic health. Nat Rev Endocrinol 10, 24–36.

Cao, Y. (2007). Angiogenesis modulates adipogenesis and obesity. J Clin Invest 117, 2362–2368.

Cao, Y. (2013). Angiogenesis and vascular functions in modulation of obesity, adipose metabolism, and insulin sensitivity. Cell Metab 18, 478–489.

Carmeliet, P., and Jain, R.K. (2000). Angiogenesis in cancer and other diseases. Nature 407, 249–257.

Chen, Y.L., Zhu, S., Zhang, L., Feng, P.J., Yao, X.K., Qian, C.G., Zhang, C., Jiang, X.Q., and Shen, Q.D. (2016). Smart conjugated polymer nanocarrier for healthy weight loss by negative feedback regulation of lipase activity. Nanoscale 8, 3368–3375.

Clemmensen, C., Chabenne, J., Finan, B., Sullivan, L., Fischer, K., Küchler, D., Sehrer, L., Ograjsek, T., Hofmann, S.M., Schriever, S.C., et al. (2014). GLP-1/glucagon coagonism restores leptin responsiveness in obese mice chronically maintained on an obesogenic diet. Diabetes 63, 1422–1427.

des Rieux, A., Pourcelle, V., Cani, P.D., Marchand-Brynaert, J., and Préat, V. (2013). Targeted nanoparticles with novel non-peptidic ligands for oral delivery. Adv Drug Deliver Rev 65, 833–844.

Friedman, J.M. (2009). Causes and control of excess body fat. Nature 459, 340–342.

George, M., Rajaram, M., and Shanmugam, E. (2014). New and emerging drug molecules against obesity. J Cardiovasc Pharmacol Ther 19, 65–76.

Ghamari-Langroudi, M., Digby, G.J., Sebag, J.A., Millhauser, G.L., Palomino, R., Matthews, R., Gillyard, T., Panaro, B.L., Tough, I.R., Cox, H.M., et al. (2015). G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons. Nature 520, 94–98.

Gu, Z., Aimetti, A.A., Wang, Q., Dang, T.T., Zhang, Y., Veiseh, O., Cheng, H., Langer, R.S., and Anderson, D.G. (2013a). Injectable nano-network for glucose-mediated insulin delivery. ACS Nano 7, 4194–4201.

Gu, Z., Dang, T.T., Ma, M., Tang, B.C., Cheng, H., Jiang, S., Dong, Y., Zhang, Y., and Anderson, D.G. (2013b). Glucose-responsive microgels integrated with enzyme nanocapsules for closed-loop insulin delivery. ACS Nano 7, 6758–6766.

Harms, M., and Seale, P. (2013). Brown and beige fat: development, function and therapeutic potential. Nat Med 19, 1252–1263.

Haslam, D. (2016). Weight management in obesity—past and present. Int J Clin Pract 70, 206–217.

Heymsfield, S.B., and Wadden, T.A. (2017). Mechanisms, pathophysiology, and management of obesity. N Engl J Med 376, 254–266.

Hossen, M.N., Kajimoto, K., Akita, H., Hyodo, M., Ishitsuka, T., and Harashima, H. (2010). Ligand-based targeted delivery of a peptide modified nanocarrier to endothelial cells in adipose tissue. J Control Release 147, 261–268.

Hossen, M.N., Kajimoto, K., Akita, H., Hyodo, M., and Harashima, H. (2012). Vascular-targeted nanotherapy for obesity: unexpected passive targeting mechanism to obese fat for the enhancement of active drug delivery. J Control Release 163, 101–110.

Hossen, M.N., Kajimoto, K., Akita, H., Hyodo, M., and Harashima, H. (2013). A comparative study between nanoparticle-targeted therapeutics and bioconjugates as obesity medication. J Control Release 171, 104–112.

Jackson, V.M., Breen, D.M., Fortin, J.P., Liou, A., Kuzmiski, J.B., Loomis, A.K., Rives, M.L., Shah, B., and Carpino, P.A. (2015). Latest approa-

ches for the treatment of obesity. Expert Opin Drug Discov 10, 825–839.
Jiang, C., Kuang, L., Merkel, M.P., Yue, F., Cano-Vega, M.A., Narayanan, N., Kuang, S., and Deng, M. (2015). Biodegradable polymeric microsphere-based drug delivery for inductive browning of fat. Front Endocrinol 6, 169.
Jiang, C., Cano-Vega, M.A., Yue, F., Kuang, L., Narayanan, N., Uzunalli, G., Merkel, M.P., Kuang, S., and Deng, M. (2017). Dibenzazepine-loaded nanoparticles induce local browning of white adipose tissue to counteract obesity. Mol Ther 25, 1718–1729.
Kajimura, S., Spiegelman, B.M., and Seale, P. (2015). Brown and beige fat: physiological roles beyond heat generation. Cell Metab 22, 546–559.
Kakkar, A.K., and Dahiya, N. (2015). Drug treatment of obesity: current status and future prospects. Eur J Intern Med 26, 89–94.
Kang, J.G., and Park, C.Y. (2012). Anti-obesity drugs: a review about their effects and safety. Diabetes Metab J 36, 13–25.
Kolonin, M.G., Saha, P.K., Chan, L., Pasqualini, R., and Arap, W. (2004). Reversal of obesity by targeted ablation of adipose tissue. Nat Med 10, 625–632.
Kupferschmidt, N., Csikasz, R.I., Ballell, L., Bengtsson, T., and Garcia-Bennett, A.E. (2014). Large pore mesoporous silica induced weight loss in obese mice. Nanomedicine 9, 1353–1362.
Kushner, R.F. (2008). Anti-obesity drugs. Expert Opin Pharmacother 9, 1339–1350.
Kushner, R.F., and Ryan, D.H. (2014). Assessment and lifestyle management of patients with obesity. JAMA 312, 943–952.
Ledoux, S., Queguiner, I., Msika, S., Calderari, S., Rufat, P., Gasc, J.M., Corvol, P., and Larger, E. (2008). Angiogenesis associated with visceral and subcutaneous adipose tissue in severe human obesity. Diabetes 57, 3247–3257.
Lu, Y., Aimetti, A.A., Langer, R., and Gu, Z. (2016). Bioresponsive materials. Nat Rev Mater 2, 16075.
Ma, L., Liu, T.W., Wallig, M.A., Dobrucki, I.T., Dobrucki, L.W., Nelson, E. R., Swanson, K.S., and Smith, A.M. (2016). Efficient targeting of adipose tissue macrophages in obesity with polysaccharide nanocarriers. ACS Nano 10, 6952–6962.
Malik, V.S., Willett, W.C., and Hu, F.B. (2013). Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 9, 13–27.
Marrache, S., and Dhar, S. (2012). Engineering of blended nanoparticle platform for delivery of mitochondria-acting therapeutics. Proc Natl Acad Sci USA 109, 16288–16293.
Mun, E.C., Blackburn, G.L., and Matthews, J.B. (2001). Current status of medical and surgical therapy for obesity. Gastroenterology 120, 669–681.
Mura, S., and Couvreur, P. (2012). Nanotheranostics for personalized medicine. Adv Drug Deliver Rev 64, 1394–1416.
Musthaba, S., Ahmad, S., Ahuja, A., Ali, J., and Baboota, S. (2009). Nano approaches to enhance pharmacokinetic and pharmacodynamic activity of plant origin drugs. Curr Nanosci 5, 344–352.
World Health Organization. (2014). Obesity and overweight. J Physiother 60, 114.
Parveen, S., Misra, R., and Sahoo, S.K. (2012). Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine 8, 147–166.
Rodgers, R.J., Tschöp, M.H., and Wilding, J.P.H. (2012). Anti-obesity drugs: past, present and future. Dis Model Mech 5, 621–626.
Rucker, D., Padwal, R., Li, S.K., Curioni, C., and Lau, D.C.W. (2007). Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 335, 1194–1199.
Sangwai, M., Sardar, S., and Vavia, P. (2014). Nanoemulsified orlistat-embedded multi-unit pellet system (MUPS) with improved dissolution and pancreatic lipase inhibition. Pharmaceut Dev Tech 19, 31–41.
Schneider, B.E., and Mun, E.C. (2005). Surgical management of morbid obesity. Diabetes Care 28, 475–480.
Sohn, J.W., Harris, L.E., Berglund, E.D., Liu, T., Vong, L., Lowell, B.B., Balthasar, N., Williams, K.W., and Elmquist, J.K. (2013). Melanocortin 4 receptors reciprocally regulate sympathetic and parasympathetic preganglionic neurons. Cell 152, 612–619.
Sun, W., Hu, Q., Ji, W., Wright, G., and Gu, Z. (2017). Leveraging physiology for precision drug delivery. Physiol Rev 97, 189–225.
Thovhogi, N., Sibuyi, N., Meyer, M., Onani, M., and Madiehe, A. (2015). Targeted delivery using peptide-functionalised gold nanoparticles to white adipose tissues of obese rats. J Nanopart Res 17, 112.
Trayhurn, P., and Beattie, J.H. (2001). Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 60, 329–339.
Voros, G., Maquoi, E., Demeulemeester, D., Clerx, N., Collen, D., and Lijnen, H.R. (2005). Modulation of angiogenesis during adipose tissue development in murine models of obesity. Endocrinology 146, 4545–4554.
Wadden, T.A., Butryn, M.L., and Wilson, C. (2007). Lifestyle modification for the management of obesity. Gastroenterology 132, 2226–2238.
Wiedmer, P., Nogueiras, R., Broglio, F., D'Alessio, D., and Tschöp, M.H. (2007). Ghrelin, obesity and diabetes. Nat Rev Endocrinol 3, 705–712.
Won, Y.W., Adhikary, P.P., Lim, K.S., Kim, H.J., Kim, J.K., and Kim, Y.H. (2014). Oligopeptide complex for targeted non-viral gene delivery to adipocytes. Nat Mater 13, 1157–1164.
Wu, J., Cohen, P., and Spiegelman, B.M. (2013). Adaptive thermogenesis in adipocytes: is beige the new brown? Genes Dev 27, 234–250.
Xue, Y., Xu, X., Zhang, X.Q., Farokhzad, O.C., and Langer, R. (2016). Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. Proc Natl Acad Sci USA 113, 5552–5557.
Yameen, B., Choi, W.I., Vilos, C., Swami, A., Shi, J., and Farokhzad, O.C. (2014). Insight into nanoparticle cellular uptake and intracellular targeting. J Control Release 190, 485–499.
Yanovski, S., Dietz, W., Goodwin, N., Hill, J., PiSunyer, F., Rolls, B., Stern, J., Weinsier, R., Wilson, G., and Wing, R. (1996). Long-term pharmacotherapy in the management of obesity. JAMA 276, 1907–1915.
Yu, J., Zhang, Y., Ye, Y., DiSanto, R., Sun, W., Ranson, D., Ligler, F.S., Buse, J.B., and Gu, Z. (2015). Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proc Natl Acad Sci USA 112, 8260–8265.
Yu, J., Zhang, Y., Kahkoska, A.R., and Gu, Z. (2017). Bioresponsive transcutaneous patches. Curr Opin Biotech 48, 28–32.
Zhang, Y., Chan, H.F., and Leong, K.W. (2013). Advanced materials and processing for drug delivery: the past and the future. Adv Drug Deliver Rev 65, 104–120.
Zhang, Y., Liu, Q., Yu, J., Yu, S., Wang, J., Qiang, L., and Gu, Z. (2017a). Locally induced adipose tissue browning by microneedle patch for obesity treatment. ACS Nano 11, 9223–9230.
Zhang, Y., Yu, J., Wang, J., Hanne, N.J., Cui, Z., Qian, C., Wang, C., Xin, H., Cole, J.H., Gallippi, C.M., Zhu, Y., and Gu, Z. (2017b). Thrombin-responsive transcutaneous patch for auto-anticoagulant regulation. Adv Mater 29, 1604043.