Reconstituted High-Density Lipoprotein Nanoparticles

Subjects: Nanoscience & Nanotechnology

Contributor: Jiansheng Huang

Epidemiological results revealed that there is an inverse correlation between high-density lipoprotein (HDL) cholesterol levels and risks of atherosclerotic cardiovascular disease (ASCVD). Mounting evidence supports that HDLs are atheroprotective, therefore, many therapeutic approaches have been developed to increase HDL cholesterol (HDL-C) levels. Nevertheless, HDL-raising therapies, such as cholesteryl ester transfer protein (CETP) inhibitors, failed to ameliorate cardiovascular outcomes in clinical trials, thereby casting doubt on the treatment of cardiovascular disease (CVD) by increasing HDL-C levels. Therefore, HDL-targeted interventional studies were shifted to increasing the number of HDL particles capable of promoting ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux. One such approach was the development of reconstituted HDL (rHDL) particles that promote ABCA1-mediated cholesterol efflux from lipid-enriched macrophages. Here, we explore the manipulation of rHDL nanoparticles as a strategy for the treatment of CVD. In addition, we discuss technological capabilities and the challenge of relating preclinical in vivo mice research to clinical studies. Finally, by drawing lessons from developing rHDL nanoparticles, we also incorporate the viabilities and advantages of the development of a molecular imaging probe with HDL nanoparticles when applied to ASCVD, as well as gaps in technology and knowledge required for putting the HDL-targeted therapeutics into full gear.

Keywords: ABCA1 ; reconstituted high-density lipoprotein ; cardiovascular disease ; molecular imaging

1. Introduction

Epidemiological studies identified several independent risk factors for cardiovascular disease (CVD), including hypertension, age, smoking, insulin resistance, elevated low-density lipoprotein cholesterol (LDL-C) levels, and triglyceride levels [1]. The majority of people establish plaques during young adulthood, making plaque regression the optimal therapeutic strategy [2][3][4][5]. The most effective LDL lowering agent, PCSK9 inhibitor evolocumab, only regressed coronary atheroma volume as assessed by serial coronary intravascular ultrasound by 0.95%, although 78 weeks of treatment reduced the LDL-C to 36.6 mg/dL in humans [6][7]. Clinical studies confirm that apolipoprotein AI (apoAI) can largely promote the regression of atherosclerosis by increasing functional high-density lipoprotein (HDL) particles [8][9][10][11][12].

2. rHDL Nanoparticles as a Drug Delivery Vehicle

The application of rHDL nanoparticles for delivering therapeutic compounds for the treatment of cancer has been studied extensively [13][14][15]. Recent studies show that rHDL nanoparticle serve as a drug delivery system to deliver compounds efficiently into macrophages and atherosclerotic plaques [16]. To investigate the immunomodulatory drugs for atherosclerosis, several nanoparticles were developed to increase the specificity of the drug delivery. rHDLs were efficiently used to deliver a liver X receptors (LXR) agonist GW3965 to atherosclerotic plaques of Apoe$^{-/-}$ mice [17]. Importantly, rHDLs loaded with GW3965 completely abolished the liver toxicity of GW3965 in a one-week intensive treatment regimen in atherosclerotic mice. The long-term treatment with rHDLs significantly reduced atherosclerotic plaques in Apoe$^{-/-}$ mice [18].

Statins have potent anti-inflammatory functions, but these cannot be fully exploited with oral statin therapy owing to a low systemic bioavailability. Interestingly, an injectable rHDL nanoparticle was synthesized to deliver simvastatin, and the effect of simvastatin-rHDL on atherosclerotic plaques was examined in mice. This study demonstrates that statin-loaded reconstituted HDL nanoparticles improved inflammation in atherosclerotic plaque [19]. More interestingly, nanoparticle-based delivery of simvastatin inhibited plaque macrophage proliferation in Apoe$^{-/-}$ mice with advanced atherosclerotic plaques [20]. rHDL nanoparticles increased the plasma half-life of statins to 20 h. In addition, a recent study showed that rHDL-mediated targeted delivery of the LXR agonist promoted atherosclerosis regression [21].

Arachidonic acid (AA) was engineered into the rHDL complex to increase the efficacy of statins. AA-LT-rHDL (arachidonic acid-lovastatin-rHDL) exhibited lower reactivity with LCAT and more potent inhibition effects on foam cell formation in the presence of LCAT because of less undesired LT leakage during the remodeling of rHDLs induced by LCAT and more cellular drug uptake [22]. In addition, increasing AA concentration in AA-LT-rHDL particles reduced intracellular lipid deposition, decreased intracellular cholesterol esters content, and DiI-oxLDL uptake, and inhibited the expressions of pro-inflammatory cytokines TNF-α and IL-6 [22]. Together, these results proved that AA modification prevented the reactivity of LT-rHDL with LCAT, thereby inhibiting the undesired drug leakage during rHDL remodeling induced by LCAT. To better fulfill the targeted-delivery of rHDL, it might be interesting to determine whether the efficacy of the incorporation of AA into LT-rHDL is better than LT-rHDL for the treatment of atherosclerosis in mice. It would also be intriguing to investigate whether the polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have better efficacy than AA in preventing LCAT-induced degradation of rHDL.

3. Delivery of Oligonucleotides Using rHDL Nanoparticles

HDLs are highly heterogeneous and transport a large variety of lipids, proteins, and microRNAs [23]. Anti-sense nucleotides and siRNA(s) are widely used to modulate gene expression and are being considered for therapeutics of atherosclerosis [24][25][26]. One of the major issues is that the half-life of anti-sense nucleotides is usually low in the presence of serum nucleases [27]. In addition, the therapeutic efficiency of nucleic acids is relatively low owing to the non-specific bio-distribution and subsequent off-target effects of nucleotides. Recent studies demonstrate that HDLs are natural at carrying nucleotides and transporting nucleotides specifically to recipient cells [28]. Moreover, HDL-miRNA cargoes from atherosclerotic patients induced remarkable gene expression, with substantial loss of conserved mRNA targets in hepatocytes. Collectively, these results show that HDL is involved in a mechanism of intercellular communication by transporting and specific delivery of miRNAs to cells. Therefore, rHDLs are believed to be an efficient vehicle for the specific delivery of siRNA and other anti-sense nucleotides for therapeutic applications [13],[29].

4. Molecular Imaging of rHDL-Based Nanoparticles in Atherosclerosis

Mounting evidence shows that early stages of the lesion development is dominant by monocyte recruitment followed by monocyte differentiation into macrophages in mice, whereas macrophage proliferation is more predominant in advanced atherosclerotic plaques [30],[31][32]. Molecular imaging approaches are developed to detect macrophage inflammation and lipid accumulation [33][34]. Immune cells such as neutrophils and monocytes are major sources of peroxidases because these enzymes are stored in granules, such as myeloperoxidase (MPO). MPO plays important roles in the inflammatory response and perpetuation of chronic inflammation in atherosclerosis [35]. Inactivation of MPO reduced reactive oxygen species (ROS)-mediated vascular inflammation and atherosclerosis [36][37][38]. Several imaging agents targeting myeloperoxidase were developed to monitor the inflammatory response and macrophage accumulation [35],[39][40][41]. rHDLs were recently developed as imaging agents due to their ability of specific delivery to macrophages [42],[43]. Interestingly, superparamagnetic rHDL nanoparticles were developed for magnetically-guided drug delivery and lipoprotein drug delivery through magnetic targeting which have shown to be effective chemotherapeutic approaches for prostate cancer [44]. Recent studies demonstrate that this nanomedicine-based delivery strategy based on rHDL nanoparticles also allows for the delivery of compounds to atherosclerotic plaque. Statin-rHDL ameliorates plaque inflammation and opens a new field for atherosclerosis nanotherapy [19]. S-rHDL labeled with Cy5.5 (lipid monolayer) and DiR (hydrophobic core) show that Cy5.5 and DiR were accumulated and detected in the atherosclerotic lesions [19]. Similarly, HDL mimetic CER-001 was radiolabeled with 89Zr to allow for imaging macrophage accumulation and positron emission tomography–computed tomography (PET/CT) imaging [45].

LXRs, oxysterol-activated nuclear receptors, play an important role in RCT through promoting ABCA1 and/or ABCG1-mediated cholesterol efflux. In vivo PET imaging probes radiolabeled with zirconium-89 (89Zr) on discoidal HDL nanoparticles were made by the reconstituting apoAI and the phospholipid 1,2-dimyristoyl-sn-glycero-3-phosphocholine, the chelator deferoxamine B, and 89Zr [46]. It was demonstrated that the radioactivity in atherosclerotic aortas of rabbits was more than three-fold higher than the control animals after the injection with 89Zr-HDL nanoparticles. There was increased accumulation of radioactivity in lesions measured by the in vivo PET imaging [46]. Therefore, rHDLs demonstrated to be a reliable imaging probe and this allows us to study its in vivo properties to visualize the macrophage accumulation in advanced atherosclerotic lesions by using noninvasive PET imaging [46].

5. Concluding Remarks

HDL-targeted drug CETP inhibitors except anacetrapib did not decrease cardiovascular events in clinical trials. Convincing results demonstrate that increased HDL cholesterol levels do not always correlate with enhanced protective HDL properties [47][48][49], thus questioning its potential as a biomarker of HDL functionality. In addition, the association between low levels of HDL-C and CVD may be confounded by other factors, such as insulin resistance, inflammation, and/or metabolic derangements leading to altered plasma lipids. Importantly, current research is focused on both developing robust HDL functional assays and determining specific proteins or lipid molecules within the HDL complex to promote cholesterol efflux capacity for future translational and pre-clinical studies.

Although several rHDL nanoparticles failed to regress the atherosclerotic plaques in humans, it should be noted that these clinical trials are relatively short-term studies; the duration of these trials was only 4–6 weeks. There is solid evidence that HDL beneficial effects have to do more with the achievement of a continuous flux and steady export of cholesterol, rather than absolute levels of HDL cholesterol [50]. Whether rHDL nanoparticles would be more effective for the treatment of coronary artery disease over a longer period of time remains to be investigated. Furthermore, the field of rHDL nanoparticles has developed considerably and is poised for a big leap with the application of drug delivery systems and technologies that enable the specific delivery of new compounds to the biological system [51]. In conclusion, recent advances on rHDL nanoparticles have opened up a new avenue by which to ameliorate the inflammatory response for the treatment of CVD. Better understanding of the functional roles of HDL will likely lead to new approaches to battle and monitor the expanding burden of CVD.

References

1. Linton, M.R.F.; Yancey, P.G.; Davies, S.S.; Jerome, W.G.; Linton, E.F.; Song, W.L.; Doran, A.C.; Vickers, K.C. The Role of Lipids and Lipoproteins in Atherosclerosis. In Endotext; Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., Dungan, K., Grossman, A., Hershman, J.M., Kaltsas, G., Koch, C., Kopp, P., et al., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2000.
2. J. J. McNamara; Coronary artery disease in combat casualties in Vietnam. *JAMA* **1971**, *216*, 1185-1187, 10.1001/jama.216.7.1185.
3. H C Stary; Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults.. *Arteriosclerosis: An Official Journal of the American Heart Association, Inc.* **1989**, *9*, 119-132, .
4. Gerald S. Berenson; Sathanur R. Srinivasan; Weihang Bao; William P. Newman; Richard E. Tracy; Wendy A. Wattigney; Association between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young Adults. *New England Journal of Medicine* **1998**, *338*, 1650-1656, 10.1056/NEJM199806043382302.
5. E. Murat Tuzcu; S R Kapadia; E Tutar; K M Ziada; R E Hobbs; P M McCarthy; J B Young; S E Nissen; High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound.. *Circulation* **2001**, *103*, 2705–2710, .
6. Nicholls, S.J.; Puri, R.; Anderson, T.; Ballantyne, C.M.; Cho, L.; Kastelein, J.J.; Koenig, W.; Somaratne, R.; Kassahun, H.; Yang, J.; et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA 2016, 316, 2373–2384.
7. Puri, R.; Nissen, S.E.; Somaratne, R.; Cho, L.; Kastelein, J.J.; Ballantyne, C.M.; Koenig, W.; Anderson, T.J.; Yang, J.; Kassahun, H.; et al. Impact of PCSK9 inhibition on coronary atheroma progression: Rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV). Am Heart J. 2016, 176, 83–92.
8. Sylvain Galvani; Timothy Hla; Quality Versus Quantity: Making HDL Great Again.. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2017**, *37*, 1018-1019, 10.1161/ATVBAHA.117.309441.
9. Nicholas Brownell; Anand Rohatgi; Modulating cholesterol efflux capacity to improve cardiovascular disease. *Current Opinion in Lipidology* **2016**, *27*, 398-407, 10.1097/mol.0000000000000317.
10. William Sean Davidson; HDL-C vs HDL-P: How Changing One Letter Could Make a Difference in Understanding the Role of High-Density Lipoprotein in Disease. *Clinical Chemistry* **2014**, *60*, e1-e3, 10.1373/clinchem.2014.232769.
11. J C Fruchart; P Duriez; [Anti-cholesterol agents, new therapeutic approaches].. *Annales Pharmaceutiques Françaises* **2004**, *62*, 405–412, .
12. Jonathan E. Feig; Bernd Hewing; Jonathan D. Smith; Stanley L. Hazen; Edward A Fisher; High-density lipoprotein and atherosclerosis regression: evidence from preclinical and clinical studies.. *Circulation Research* **2014**, *114*, 205-13, 10.

1161/CIRCRESAHA.114.300760.

13. Andras G Lacko; Nirupama A. Sabnis; Bhavani Nagarajan; Walter J. McConathy; HDL as a drug and nucleic acid delive ry vehicle. *Frontiers in Pharmacology* **2015**, *6*, 437, 10.3389/fphar.2015.00247.

14. Sangram Raut; Linda Mooberry; Nirupama Sabnis; Ashwini Garud; Akpedje Dossou; Andras G Lacko; Reconstituted H DL: Drug Delivery Platform for Overcoming Biological Barriers to Cancer Therapy. *Frontiers in Pharmacology* **2018**, *9*, 1154, 10.3389/fphar.2018.01154.

15. Jaideep Chaudhary; Joseph Bower; Ian Corbin; Lipoprotein Drug Delivery Vehicles for Cancer: Rationale and Reason. *International Journal of Molecular Sciences* **2019**, *20*, 6327, 10.3390/ijms20246327.

16. Mengyuan Zhang; Jianhua He; Cuiping Jiang; Wenli Zhang; Yun Yang; Zhiyu Wang; Jianping Liu; Plaque-hyaluronidas e-responsive high-density-lipoprotein-mimetic nanoparticles for multistage intimal-macrophage-targeted drug delivery a nd enhanced anti-atherosclerotic therapy. *International Journal of Nanomedicine* **2017**, *12*, 533-558, 10.2147/IJN.S124 252.

17. Yu, M.; Amengual, J.; Menon, A.; Kamaly, N.; Zhou, F.; Xu, X.; Saw, P.E.; Lee, S.J.; Si, K.; Ortega, C.A.; et al. Targeted Nanotherapeutics Encapsulating Liver X Receptor Agonist GW3965 Enhance Antiatherogenic Effects without Adverse Effects on Hepatic Lipid Metabolism in Ldlr(−/−) Mice. *Adv. Healthc. Mater.* **2017**, *6*, no, .

18. Jun Tang; Samantha Baxter; Arjun Menon; Amr Alaarg; Brenda Sanchez-Gaytan; Francois Fay; Yiming Zhao; Mireille O uimet; Mounia S. Braza; Valerie A. Longo; et al. Immune cell screening of a nanoparticle library improves atherosclerosi s therapy.. *Proceedings of the National Academy of Sciences* **2016**, *113*, E6731-E6740, 10.1073/pnas.1609629113.

19. Duivenvoorden, R.; Tang, J.; Cormode, D.P.; Mieszawska, A.J.; Izquierdo-Garcia, D.; Ozcan, C.; Otten, M.J.; Zaidi, N.; Lobatto, M.E.; van Rijs, S.M.; et al. A statin-loaded reconstituted high-density lipoprotein nanoparticle inhibits atherosclerotic plaque inflammation. . *Nat. Commun.* **2014**, *5*, 3065, .

20. Jun Tang; Mark E. Lobatto; Laurien Hassing; Susanne Van Der Staay; Sarian M. Van Rijs; Claudia Calcagno; Mounia S. Braza; Samantha Baxter; Francois Fay; Brenda L. Sanchez-Gaytan; et al. Inhibiting macrophage proliferation suppresses atherosclerotic plaque inflammation. *Science Advances* **2015**, *1*, e1400223, 10.1126/sciadv.1400223.

21. Yanhong Guo; Wenmin Yuan; Bilian Yu; Rui Kuai; Wenting Hu; Emily E. Morin; Minerva T. Garcia-Barrio; Jifeng Zhang; James J. Moon; Anna Schwendeman; et al. Synthetic High-Density Lipoprotein-Mediated Targeted Delivery of Liver X Receptors Agonist Promotes Atherosclerosis Regression.. *EBioMedicine* **2017**, *28*, 225-233, 10.1016/j.ebiom.2017.12. 021.

22. Hongliang He; Lisha Liu; Hui Bai; Ji Wang; Yan Zhang; Wenli Zhang; Mengyuan Zhang; Zimei Wu; Jianping Liu; Arachi donic Acid-Modified Lovastatin Discoidal Reconstituted High Density Lipoprotein Markedly Decreases the Drug Leakag e during the Remodeling Behaviors Induced by Lecithin Cholesterol Acyltransferase. *Pharmaceutical Research* **2014**, *3 1*, 1689-1709, 10.1007/s11095-013-1273-3.

23. Danielle L. Michell; Kasey C. Vickers; HDL and microRNA therapeutics in cardiovascular disease.. *Pharmacology & Th erapeutics* **2016**, *168*, 43-52, 10.1016/j.pharmthera.2016.09.001.

24. Mark J. Graham; Teresa A. Brandt; Li-Jung Tai; Wuxia Fu; Raechel Peralta; Rosie Yu; Erika Paz; Bradley W. McEvoy; B renda F. Baker; Nguyen Pham; et al. Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. *N ew England Journal of Medicine* **2017**, *377*, 222-232, 10.1056/NEJMoa1701329.

25. Lim, G.B. Dyslipidaemia: ANGPTL3: A therapeutic target for atherosclerosis. Nat. Rev. Cardiol. 2017, 14, 381.

26. Dongdong Wang; Atanas G. Atanasov; The microRNAs Regulating Vascular Smooth Muscle Cell Proliferation: A Minire view. *International Journal of Molecular Sciences* **2019**, *20*, 324, 10.3390/ijms20020324.

27. Alberto Davalos; Angeliki Chroni; Antisense Oligonucleotides, microRNAs, and Antibodies. *Bile Acids and Their Recept ors* **2014**, *224*, 649-689, 10.1007/978-3-319-09665-0_22.

28. Fatiha Tabet; Kasey C. Vickers; Luisa F. Cuesta Torres; Carrie Wiese; Bassem M. Shoucri; Gilles Lambert; Claire Cath erinet; Leonel Prado-Lourenço; Michael Levin; Seth Thacker; et al. HDL-transferred microRNA-223 regulates ICAM-1 e xpression in endothelial cells. *Nature Communications* **2014**, *5*, 3292-3292, 10.1038/ncomms4292.

29. Sangram Raut; Jean-Louis Dasseux; Nirupama A Sabnis; Linda Mooberry; Andras G Lacko; Lipoproteins for therapeuti c delivery: recent advances and future opportunities. *Therapeutic Delivery* **2018**, *9*, 257-268, 10.4155/tde-2017-0122.

30. MacRae F. Linton; Vladimir R. Babaev; Jiansheng Huang; Edward F. Linton; Huan Tao; Patricia G. Yancey; Macrophag e Apoptosis and Efferocytosis in the Pathogenesis of Atherosclerosis.. *Circulation Journal* **2016**, *80*, 2259-2268, 10.125 3/circj.CJ-16-0924.

31. Jenny E. Kanter; Monocyte Recruitment Versus Macrophage Proliferation in Atherosclerosis.. *Circulation Research* **201 7**, *121*, 1109-1110, 10.1161/CIRCRESAHA.117.311973.

32. Vladimir R. Babaev; Jiansheng Huang; Lei Ding; Youmin Zhang; James M. May; Edward F. Linton; Loss of Rictor in Monocyte/Macrophages Suppresses Their Proliferation and Viability Reducing Atherosclerosis in LDLR Null Mice. *Frontiers in Immunology* **2018**, *9*, , 10.3389/fimmu.2018.00215.

33. Claire E. DelBove; Claire E. Strothman; Roman M. Lazarenko; Hui Huang; Charles R. Sanders; Qi Zhang; Reciprocal modulation between amyloid precursor protein and synaptic membrane cholesterol revealed by live cell imaging. *Neurobiology of Disease* **2019**, *127*, 449-461, 10.1016/j.nbd.2019.03.009.

34. Moritz Wildgruber; Filip K. Swirski; Alma Zernecke; Molecular Imaging of Inflammation in Atherosclerosis. *Theranostics* **2013**, *3*, 865-884, 10.7150/thno.5771.

35. Jiansheng Huang; Amber Milton; Robert Arnold; Hui Huang; Forrest Smith; Jennifer R. Panizzi; Peter Panizzi; Methods for measuring myeloperoxidase activity toward assessing inhibitor efficacy in living systems. *Journal of Leukocyte Biology* **2016**, *99*, 541-548, 10.1189/jlb.3RU0615-256R.

36. Jiansheng Huang; Forrest Smith; Jennifer R. Panizzi; Douglas C. Goodwin; Peter Panizzi; Inactivation of myeloperoxidase by benzoic acid hydrazide.. *Archives of Biochemistry and Biophysics* **2015**, *570*, 14-22, 10.1016/j.abb.2015.01.028.

37. Jiansheng Huang; Forrest Smith; Peter Panizzi; Ordered cleavage of myeloperoxidase ester bonds releases active site heme leading to inactivation of myeloperoxidase by benzoic acid hydrazide analogs.. *Archives of Biochemistry and Biophysics* **2014**, *548*, 74-85, 10.1016/j.abb.2014.02.014.

38. David Cheng; Jihan Talib; Christopher P. Stanley; Imran Rashid; Erik Michaëlsson; Eva-Lotte Lindstedt; Kevin Croft; Anthony J. Kettle; Ghassan J. Maghzal; Roland Stocker; et al. Inhibition of MPO (Myeloperoxidase) Attenuates Endothelial Dysfunction in Mouse Models of Vascular Inflammation and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2019**, *39*, 1448-1457, 10.1161/atvbaha.119.312725.

39. John A Ronald; John W. Chen; Yuanxin Chen; Amanda M. Hamilton; Elisenda Rodríguez; Fred Reynolds; Robert A. Hegele; Kem A. Rogers; Manel Querol; Alexei A. Bogdanov; et al. Enzyme-sensitive magnetic resonance imaging targeting myeloperoxidase identifies active inflammation in experimental rabbit atherosclerotic plaques.. *Circulation* **2009**, *120*, 592-9, 10.1161/CIRCULATIONAHA.108.813998.

40. Michael O. Breckwoldt; John W. Chen; Lars Stangenberg; Elena Aikawa; Elisenda Rodriguez; Shumei Qiu; Michael A. Moskowitz; Ralph Weissleder; Tracking the inflammatory response in stroke in vivo by sensing the enzyme myeloperoxidase. *Proceedings of the National Academy of Sciences* **2008**, *105*, 18584-18589, 10.1073/pnas.0803945105.

41. John W. Chen; Michael O. Breckwoldt; Elena Aikawa; Gloria Chiang; Ralph Weissleder; Myeloperoxidase-targeted imaging of active inflammatory lesions in murine experimental autoimmune encephalomyelitis.. *Brain* **2008**, *131*, 1123-33, 10.1093/brain/awn004.

42. Sunil Shah; Rahul Chib; Sangram Raut; Jaclyn Bermudez; Nirupama Sabnis; Divya Duggal; Joseph D. Kimball; Andras G. Lacko; Zygmunt Gryczynski; Ignacy Gryczynski; et al. Photophysical characterization of anticancer drug valrubicin in rHDL nanoparticles and its use as an imaging agent.. *Journal of Photochemistry and Photobiology B: Biology* **2015**, *155*, 60-65, 10.1016/j.jphotobiol.2015.12.007.

43. Brenda L. Sanchez-Gaytan; Francois Fay; Mark E. Lobatto; Jun Tang; Mireille Ouimet; Yongtae Kim; Susanne E. M. Van Der Staay; Sarian M. Van Rijs; Bram Priem; Liangfang Zhang; et al. HDL-Mimetic PLGA Nanoparticle To Target Atherosclerosis Plaque Macrophages. *Bioconjugate Chemistry* **2015**, *26*, 443-451, 10.1021/bc500517k.

44. Sarika Sabnis; Nirupama A Sabnis; Sangram Raut; Andras G Lacko; Superparamagnetic reconstituted high-density lipoprotein nanocarriers for magnetically guided drug delivery. *International Journal of Nanomedicine* **2017**, *12*, 1453-1464, 10.2147/IJN.S122036.

45. Kang He Zheng; Fleur M. Van Der Valk; Loek P. Smits; Mara Sandberg; Jean-Louis Dasseux; Rudi Baron; Ronald Barbaras; Constance Keyserling; Bram F. Coolen; A.J. Nederveen; et al. HDL mimetic CER-001 targets atherosclerotic plaques in patients. *Atherosclerosis* **2016**, *251*, 381-388, 10.1016/j.atherosclerosis.2016.05.038.

46. Carlos Perez-Medina; Jun Tang; Dalya Abdel-Atti; Brandon Hogstad; Miriam Merad; Edward A Fisher; Zahi A. Fayad; Jason S. Lewis; Willem J. M. Mulder; Thomas Reiner; et al. PET Imaging of Tumor-Associated Macrophages with 89Zr-Labeled High-Density Lipoprotein Nanoparticles. *Journal of Nuclear Medicine* **2015**, *56*, 1272-1277, 10.2967/jnumed.115.158956.

47. Paolo Zanoni; Sumeet A. Khetarpal; Daniel Larach; William Hancock-Cerutti; John S. Millar; Marina Cuchel; Stephanie DerOhannessian; Anatol Kontush; Praveen Surendran; Danish Saleheen; et al. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science* **2016**, *351*, 1166-1171, 10.1126/science.aad3517.

48. Jesús Timón-Zapata; Emilio J. Laserna-Mendieta; Daniel Pineda-Tenor; Mercedes Agudo-Macazaga; Carmen Narros-Cecilia; María Jesús Rocha-Bogas; Guadalupe Ruiz-Martín; Manuel Gómez-Serranillos; Extreme concentrations of hig

h density lipoprotein cholesterol affect the calculation of low density lipoprotein cholesterol in the Friedewald formula and other proposed formulas. *Clinical Biochemistry* **2011**, *44*, 1451-1456, 10.1016/j.clinbiochem.2011.09.009.

49. Christian M Madsen; Anette Varbo; Anne Tybjærg-Hansen; Ruth Frikke-Schmidt; Børge Grønne Nordestgaard; U-shaped relationship of HDL and risk of infectious disease: two prospective population-based cohort studies. *European Heart Journal* **2017**, *39*, 1181-1190, 10.1093/eurheartj/ehx665.
50. Marsche, G.; It's Time to Reassess the High-Density Lipoprotein (HDL) Hypothesis: CSL112, a Novel Promising Reconstituted HDL Formulation. *J. Am. Heart Assoc.* **2015**, *4*, e002371, .
51. Alyssa M. Flores; Jianqin Ye; Kai-Uwe Jarr; Niloufar Hosseini-Nassab; Bryan R. Smith; Nicholas J. Leeper; Nanoparticle Therapy for Vascular Diseases.. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2019**, *39*, 635-646, 10.1161/ATVBAHA.118.311569.