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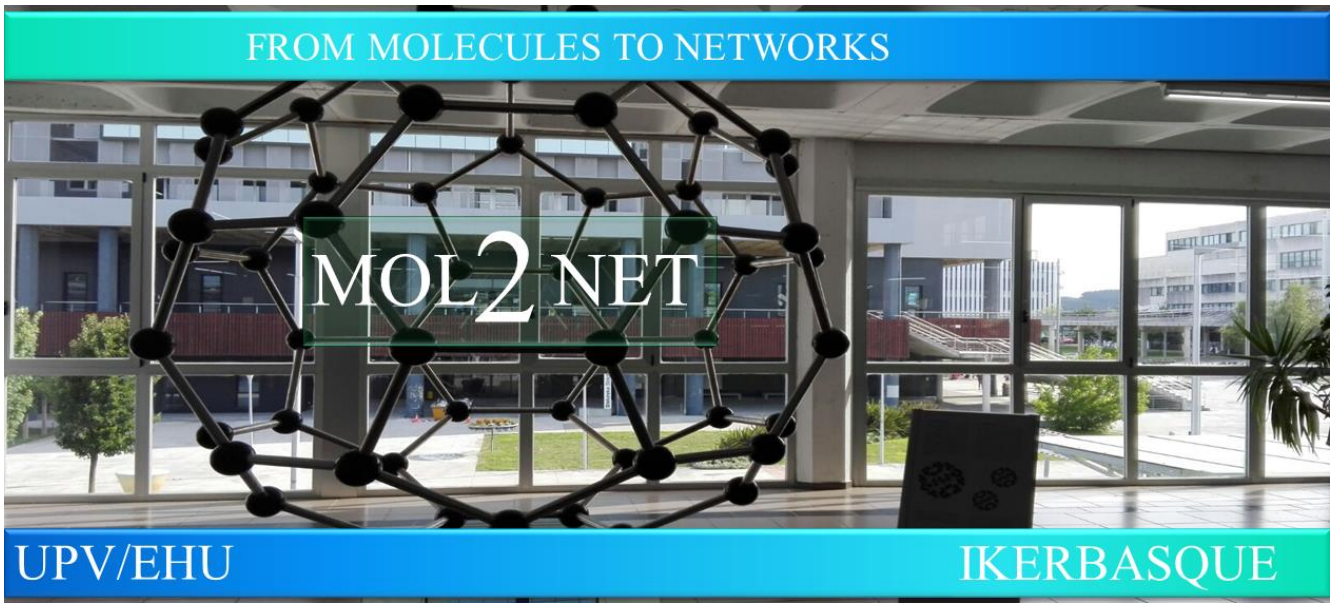
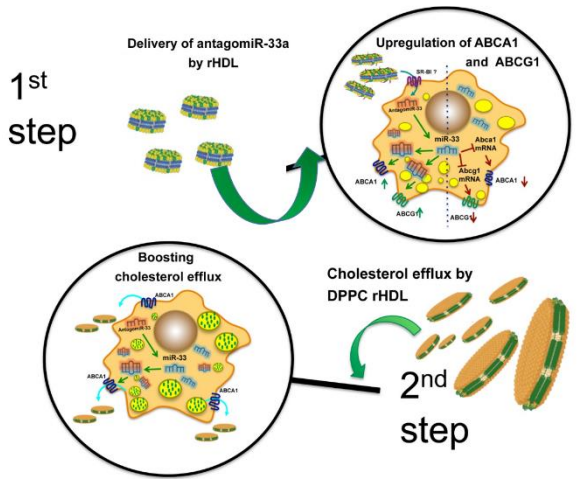


Boosting Cholesterol Efflux from Foam Cells by Sequential Administration of rHDL to Deliver MicroRNA and to Remove Cholesterol in a Triple-Cell Two-Dimensional Atherosclerosis Model

S. Jebari Benslaiman[a,b], K. B. Uribe[a], A. Benito Vicente[a], U. Galicia García[a], A. Larrea Seba[b], A. San José[a], C. Martin [a,b]

[a]University of Basque Country, Department of Bioquemistry and Molecular Biology, Leioa, Spain,
[b]Biofisika Institute (CSIC/UPV), Leioa, Spain

Graphical Abstract	Abstract.
	Cardiovascular disease, the leading cause of mortality worldwide, is primarily caused by atherosclerosis, which is characterized by lipid and inflammatory cell accumulation in blood vessels and carotid intima thickening, among others. Although disease management has improved significantly, new therapeutic strategies focused on accelerating atherosclerosis regression must be developed. Atherosclerosis models mimicking in vivolike conditions provide essential information for research and new advances towards clinical application. Here a therapeutic strategy to improve cholesterol efflux



has been developed based on a twostep administration of rHDL consisting on a first dose of antagomiR33aloaded rHDLs to induce ABCA1 transporter overexpression, followed by a second dose of DPPC rHDLs, which remove efficiently cholesterol from foam cells. A triplecell 2D atheroma plaque model reflecting the cellular complexity of atherosclerosis has been used to overcome the translational gap providing a suitable model to improve the efficiency of the nanoparticles in promoting cholesterol efflux. The results show that sequential administration of rHDL potentiates cholesterol efflux indicating that this approach might be used in vivo to target more efficiently atherosclerotic lesions and improve prognosis of the disease. Sequential targeting of foam cells with nanoparticles including a first antagomiR33a delivery by DPPC:CE:LPC rHDL followed by a second infusion of DPPC rHDL induces a potent cholesterol efflux from foam cells, which may overcome current technique barriers to promote clinical applications.

Introduction *(optional)*

Cardiovascular disease, the leading cause of mortality worldwide, is primarily caused by atherosclerosis, which is characterized by lipid and inflammatory cell accumulation in blood vessels and carotid intima thickening, among others[1]. Although disease management has improved significantly, new therapeutic strategies focused on accelerating atherosclerosis regression must be developed. Atherosclerosis models mimicking *in vivo*-like conditions provide essential information for research and new advances towards clinical application[2,3].

Materials and Methods *(optional)*

Here a therapeutic strategy to improve cholesterol efflux has been developed based on a two-step administration of rHDL consisting on a first dose of antagomiR-33a-loaded rHDLs to induce ABCA1 transporter overexpression, followed by a second dose of DPPC rHDLs, which remove efficiently cholesterol from foam cells[4]. A triple-cell 2D atheroma plaque model reflecting the cellular complexity of atherosclerosis has been used to overcome the translational gap providing a suitable model to improve the efficiency of the nanoparticles in promoting cholesterol efflux.

Results and Discussion *(optional)*

The results show that sequential administration of rHDL potentiates cholesterol efflux indicating that this approach might be used in vivo to target more efficiently atherosclerotic lesions and improve prognosis of the disease.

Conclusions *(optional)*

Sequential targeting of foam cells with nanoparticles including a first antagomiR-33a delivery by DPPC:CE:LPC rHDL followed by a second infusion of DPPC rHDL induces a potent cholesterol efflux from foam cells, which may overcome current technique barriers to promote clinical applications.

References *(mandatory)*

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