DEPARTMENT OF LIPIDOMICS

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Major position/appointments and professional training

- Member of the Romanian Academy
- Scientific Secretary of ICBP-NS
- PhD Advisor in Biology, Advisor for graduate and master programs
- President of the Biology and Biochemistry Commission of the Romanian Council for Attestation of University Titles, Diplomas and Certificates
- Executive Director of the Advanced Study Course of Cellular and Molecular Medicine
- Expert evaluator of national and international grants
- Member of the Editorial Board of Scientific Reports (Nature group)

MAJOR RESEARCH INTERESTS

● **Lipid metabolism in health and disease**: dysregulation of lipid metabolism in atherosclerosis, diabetes, metabolic syndrome and obesity, cellular and molecular biology of lipoproteins (Lp), transport of Lp across the vascular endothelium, interaction of Lp with the cells of the arterial wall, in vivo and in vitro modification of low density Lp (LDL), dysfunctional high density Lp (HDL), entero-hepatic metabolism of Lp, molecular biology of proteins involved in cellular cholesterol efflux, implication in atheroma formation.

● **Cellular biology and biochemistry of blood vessels**: heart and cardiac valves in pathological conditions, biochemical and biophysical modifications in atherogenesis, diabetes and obesity, experimental animal models of atherosclerosis and/or diabetes.

● **Novel biomarkers for cardiovasculardisease**: dysfunctional Lp, oxidized lipids, Lp-associated enzymes, inflammatory mediators.

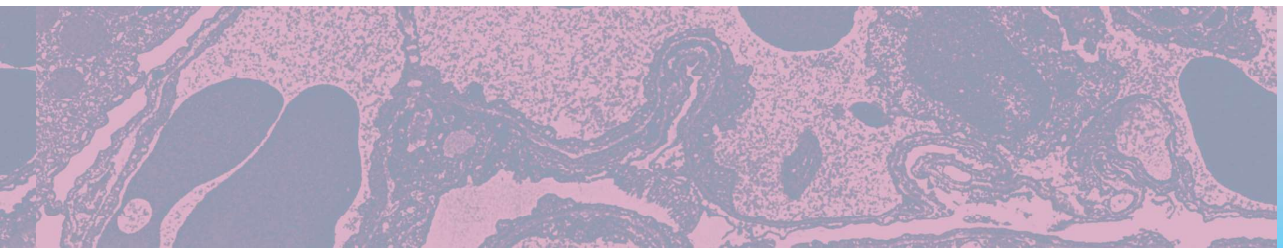
● **Genetic and epigenetic mechanisms of atherosclerosis and/or diabetes**: gene polymorphisms, functional analysis of RNA-related epigenetic markers (microRNAs, lncRNAs), identification and validation of specific microRNAs target genes, gene editing of lipid-related proteins to improve cardiovascular diseases.

● **Pharmacologic attempts to arrest or reverse cardiovascular diseases**: pleiotropic properties of anti-atherosclerotic drugs (statins, calcium channel blockers - amlodipine), biologically active natural compounds (probiotics, caffeic acid, ginger extract).

PUBLICATIONS

Over 90 original articles (>2,000 citations) were published in Web of Sciences Core Collection journals and 11 book chapters between 1979-2019 by researchers of the Lipidomics Department.

- 2 articles with over 200 citations, 5 articles with over 100 citations
- H index of team members: 7– 20



SELECTED NEW FINDINGS OF THE DEPARTMENT

• HDL from acute coronary syndrome (ACS) patients become pro-inflammatory and correlate with a panel of plasma parameters (apoC-III, MPO, oxidized-apoA-I, ceruloplasmin, and PON1), and together can discriminate between this group and stable angina CAD patients.

• A new mechanism by which hyperlipidemia induces dysfunctional HDL production in the small intestine and liver of hyperlipidemic hamsters: high fat diet induces endoplasmic reticulum stress and decreased expression of LXRβ and PPARγ (regulators of HDL apolipoproteins and enzymes production).

• A panel of circulating miRNAs was identified in sera from hyperlipidemic and/or hyperglycemic subjects, correlated with increased lipids and inflammatory markers.

• Two circulating miRNAs, miR-486 and miR-92a, together with dysfunctional HDL can be used as an additional statistical tool to designate vulnerable CAD patients.

• A preferential distribution of miR-486 and miR-92a in the HDL subpopulations (HDL2, HDL3) can discriminate between ACS and stable CAD patients.

• Hyperglycemia determines increased specific microRNAs levels in sera and HDL of ACS patients and stimulates microRNAs production in human macrophages.

• Inhibition of miR-486 and miR-92a decreases liver and plasma cholesterol levels by modulating lipid-related genes in hyperlipidemic hamsters.

• Probiotics exert lipid-lowering effects based on the entero-hepatic regulation of cholesterol metabolism, increased HDL apolipoproteins and enzymes synthesis, decreased oxidative stress and lipid deposits in aortic valves, all mediated by upregulation of nuclear receptors PPARγ/RXR and LXRs.

• Probiotics administration decrease serum and hepatic expression of miR-223, miR-122a, miR-92a and miR-486, the miRNAs production proteins (Dicer, DGCR8) in the HL livers, and decrease lipid deposits in the aortic valves.

• Ginger extract exerts anti-inflammatory action by decreasing ninjurin 1 (Ninj-1), TNFα receptor 1 and NADPH oxidase subunits expression and increasing sRAGE levels in the culture media of TNFα-exposed human endothelial cells.

• The simultaneous administration of ginger extract with the high-fat diet induces in hamsters' livers the inhibition of ERS and the increase of LXRα/β and PPARγ protein expression, leading to increased synthesis of ABCG5/G8 and CYP7A1 proteins and the decrease of accumulated cholesterol.

• Ginger extract reduces the oxidized-apoAI levels (induced by the high-fat diet) by diminishing the MPO/PON1 ratio; these effects are associated with the retrieval of SIRT1-LXRα/β-PPARγ pathway, that further adjust the levels of MPO, PON1 and ABC transporters in hamster's small intestine.

• Simvastatin inhibits transcytosis of LDL in hyperlipemia reducing plaque progression.

• Simvastatin and Amlodipin increase the sera antioxidant potential in patients with stable angina.

• Atorvastatin downregulates NADPH oxidase activity, and decreases NOX1 and p22phox gene expression in human aortic smooth muscle cells exposed to glycated LDL.

• PPAR agonists decrease plaque vulnerability through modulation of MMP-2 activity.

• Anti-oxidant potential of felodipine is higher than that of amlodipine.

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PREVIOUS PROJECTS

1. TRANSCYTOSIS OF LDL THROUGH THE VASCULAR ENDOTHELIUM

All plasma macromolecules cross the vascular endothelium to reach the interstitial fluid and subendothelial cells. Results obtained by Nicolae Simionescu, Maya Simionescu and George E. Palade revealed that in endothelial cells (EC) the transport of macromolecules is accomplished via vesicles, channels, and fenestrae and depends both on the chemistry of plasma macromolecules and on the biochemical makeup of the EC plasmalemma. Based on accumulated data, Professor Nicolae Simionescu introduced the concept and coined the name "transcytosis" (transport across the cell) as a basic cellular process and identified its mechanisms - fluid-phase-, adsorptive- and receptor-mediated transcytosis of plasma proteins (*Simionescu* N., 1989).

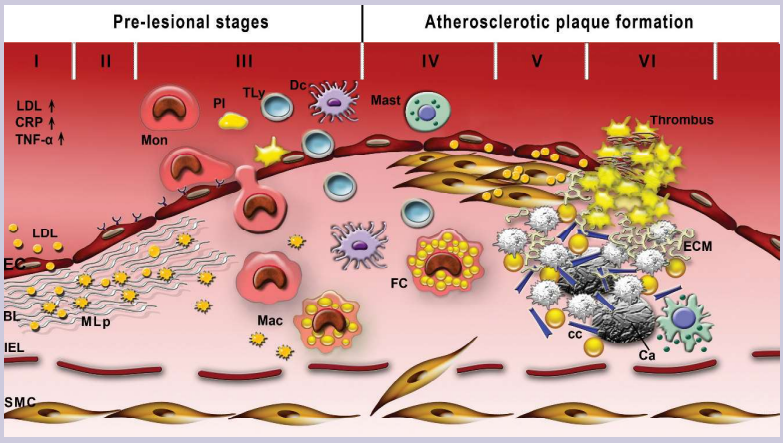
The new findings were published in:

• Transcytosis and endocytosis of LDL through endothelium in arteries and lung capillaries *(Vasile E. et al., J.Cell.Biol. 1983;Nistor-Sima A. and M. Simionescu, Am. J. Resp. Diseases 1986*).

2.PATHOBIOCHEMICAL EVENTS OF ATHEROSCLEROSIS - AN ORIGINAL MODEL, THE HYPERLIPEMIC HAMSTER

• pathobiochemical events occurring at the inception of atherosclerosis
• lesional stages of atherosclerosis

Atherosclerosis is the main cause of morbidity and mortality both in industrialized countries and in Romania. An important step in the study of a disease is finding a suitable animal model. We introduced as experimental model to study atherogenesis the Golden Syrian hamster fed a fat-rich diet, which develops hyperlipidemia and atherosclerotic plaques similar in many respects to human atheroma *(Nistor-SimaA. et al., Atherosclerosis 1987; SimaA. et al.,J.Submicrosc.Cytol.Pathol. 1990)*.
Understanding of the prelesional stage is crucial because it is the critical point at which therapeutic interventions to retard or regress the evolution of the atherosclerotic plaque can be most efficient. Based on a large number of experiments on hyperlipemic rabbits and hamsters, prelesional and lesional stages of atherosclerosis were identified and the sequence of events occurring in each stage were documented *(Simionescu N. et al., Am. J. Pathol. 1986; Mora R. et al., J. Lipid Res. 1986; Nistor-Sima A. et al., Atherosclerosis 1987; Filip D. et al., Atherosclerosis 1987).*



Diagrammatic representation of the atheroma formation and the arbitrarily delineated consecutive stages