Vladimir R. Muzykantov

Professor of Pharmacology

Member, Institute of Medical Engineering, University of Pennsylvania School of Medicine
Member, Center for Cancer Pharmacology, University of Pennsylvania School of Medicine
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Description of Research Expertise

Research Interests:
Drug/gene targeting and vascular biology

Particular areas of interest/expertise include the recognition of surface antigens on normal or pathologically altered endothelial cells; vascular inflammation and leukocytes adhesion; mechanisms of oxidative stress and antioxidant protection of the endothelium; evaluation of specific markers of endothelial injury; immunotargeting of antioxidant enzymes, fibrinolytics and genes to the pulmonary endothelium; pulmonary pathophysiology; lung ischemia/reperfusion; prolongation of enzymes life-time in the bloodstream; controlled elimination of radiolabeled antibodies or pathogens from the bloodstream; exploration of red blood cells as carriers for prolonged circulation and site-specific delivery of drugs (fibrinolytics and anticoagulants); regulation of fibrinolysis and complement; mechanisms and regulation of intracellular targeting/trafficking of drugs.

Research Summary
The laboratory is focused on several projects. First is the targeting of drugs (enzymes either degrading or generating oxidants, fibrinolytics, interferon,

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Department: Pharmacology

Graduate Group Affiliations

- Bioengineering
- Pharmacology

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Pharmacological Sciences Graduate Group Faculty

Primary Work Website

Education:

M.D. (Internal Medicine)

antisense oligos and genes) to the pulmonary vascular endothelium. The purpose is to develop strategies for controlled site-specific delivery of a drug to the defined subcellular compartments of the pulmonary endothelium. For example, genetic material must be delivered into the nucleus, antioxidants must accumulate in the cytoplasm, and fibrinolytics must avoid internalization. We therefore study how carrier antibodies and their derivatives recognize endothelium, and characterize cellular trafficking and local effects of the targeted agents in cell cultures, perfused animal lungs and in intact animals. Our research includes identification of the molecules localized on the surface of endothelium useful as targets for drug delivery to either normal or pathologically challenged endothelium. Endothelium-specific antigens may serve as such targets. Affinity carriers that are currently explored in our laboratory include monoclonal antibodies (and their fragments) to: angiotensin-converting enzyme (ACE), thrombomodulin and surface adhesion molecules, ICAM, PECAM, P- and E-selectins. We have characterized carriers and their modifications providing: i) a drug with an affinity to endothelium (recognition and targeting) and, ii) drug delivery in a proper cellular compartment (sub-cellular addressing). Targeting to either surface (by non-internalizable carriers) or intracellularly has been documented in cell culture, perfused lungs and in rodents in vivo.

Secondly, we explore red blood cells (RBC) as natural carriers for drugs. We have developed an original methodology for effective conjugation of large amounts of a drug (e.g., fibrinoytic enzymes or

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Ph.D. (Biochemistry)
National Cardiology Research Center, Moscow, Russia, 1985.
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University of Pennsylvania, 2004.

Post-Graduate Training
Senior Research Assistant, Immunomorphology Laboratory, Institute of Experimental Cardiology, Russian Cardiology Research Center, Moscow, 1982-1984.
Senior Research Fellow, Institute for Environmental Medicine, University of Pennsylvania School of Medicine, 1993-1994.
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Permanent link

receptors for plasminogen activators) on RBC, without loss of biocompatibility of the complex. Conjugation provides prolongation of half-life of plasminogen activators in vivo by orders of magnitude and offers specific transfer of the conjugated protein (tPA, uPA-receptor) to the pulmonary endothelium. Both mechanism of the transfer (tentatively via exchange of GPI-anchored membrane proteins between RBC and endothelium) and potential therapeutic applications of RBC-conjugated fibrinolytics (treatment/prevention of pulmonary embolism/deep vein thrombosis) are in the focus of the research. We also explore RBC as carriers for intracellular drug delivery in phagocyte cells in the reticuloendothelial tissue (liver and spleen) and endothelial cells.

Description of Itmat Expertise

Dr. Muzykantov is interested in targeted drug delivery.

Selected Publications

Glassman PM, Villa CH, Marcos-Contreras OA, Hood ED, Walsh LR, Greineder CF, Myerson JW, Shuvaeva T, Puentes L, Brenner JS, Siegel DL, Muzykantov VR.: *Targeted In Vivo Loading of Red Blood Cells Markedly Prolongs Nanocarrier Circulation.* Bioconjug Chem. June 2022.

Parhiz H, Brenner JS, Patel PN, Papp TE, Shahnawaz H, Li Q, Shi R, Zamora ME, Yadegari A, Marcos-Contreras OA, Natesan A, Pardi N, Shuvaev VV, Kiseleva R, Myerson JW, Uhler T, Riley RS, Han X, Mitchell MJ, Lam K, Heyes J, Weissman D, Muzykantov VR.: *Added to pre-existing inflammation, mRNA-lipid nanoparticles induce*

inflammation exacerbation (IE). J Control Release(344), 50-61, Apr 2022.

Ferguson LT, Hood ED, Shuvaeva T, Shuvaev VV, Basil MC, Wang Z, Nong J, Ma X, Wu J, Myerson JW, Marcos-Contreras OA, Katzen J, Carl JM, Morrisey EE, Cantu E, Villa CH, Mitragotri S, Muzykantov VR, Brenner JS.: *Dual Affinity to RBCs and Target Cells (DART) Enhances Both Organ- and Cell Type-Targeting of Intravascular Nanocarriers.* ACS Nano. (16), 4666-4683, Mar 2022.

Wang Z, Hood ED, Nong J, Ding J, Marcos-Contreras OA, Glassman PM, Rubey KM, Zaleski M, Espy CL, Gullipali D, Miwa T, Muzykantov VR, Song WC, Myerson JW, Brenner JS. : *Combating complement's deleterious effects on nanomedicine by conjugating complement regulatory proteins to nanoparticles.* Adv Mater. Feb 2022.

Myerson JW, Patel PN, Rubey KM, Zamora ME, Zaleski MH, Habibi N, Walsh LR, Lee YW, Luther DC, Ferguson LT, Marcos-Contreras OA, Glassman PM, Mazaleuskaya LL, Johnston I, Hood ED, Shuvaeva T, Wu J, Zhang HY, Gregory JV, Kiseleva RY, Nong J, Grosser T, Greineder CF, Mitragotri S, Worthen GS, Rotello VM, Lahann J, Muzykantov VR, Brenner JS. : *Supramolecular arrangement of protein in nanoparticle structures predicts nanoparticle tropism for neutrophils in acute lung inflammation.* Nanotechnol 17(1): 86-97, Jan 2022.

Parhiz H, Brenner JS, Patel P, Papp TE, Shahnawaz H, Li Q, Shi R, Zamora M, Yadegari A, Marcos-Contreras OA, Natesan A, Pardi N, Shuvaev VV, Kiseleva R, Myerson J, Uhler T, Riley RS, Han X,

Mitchell MJ, Lam K, Heyes J, Weissman D, Muzykantov V.: *Added to pre-existing inflammation, mRNA-lipid nanoparticles induce inflammation exacerbation(IE).* J Control Release Dec 2021.

Tutwiler V, Litvinov RI, Protopopova A, Nagaswami C, Villa C, Woods E, Abdulmalik O, Siegel DL, Russell JE, Muzykantov VR, Lam WA, Myers DR, Weisel JW.: *Pathologically stiff erythrocytes impede contraction of blood clots: Reply to comment.* J Thromb Haemost. 19(11): 2894-2895, Nov 2021.

Nikfar M, Razizadeh M, Paul R, Muzykantov V, Liu Y.: *A numerical study on drug delivery via multiscale synergy of cellular hitchhiking onto red blood cells.* Nanoscale Sep 2021 Notes: doi: 10.1039/d1nr04057j. Epub ahead of print.

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Tombácz I, Laczkó D, Shahnawaz H, Muramatsu H, Natesan A, Yadegari A, Papp TE, Alameh MG, Shuvaev V, Mui BL, Tam YK, Muzykantov V, Pardi N, Weissman D, Parhiz H: *Highly efficient CD4+ T cell targeting and genetic recombination using engineered CD4+ cell-homing mRNA-LNP.* Mol Ther. Jun 2021.