Editorial

Mechanisms of Atherogenesis and Development of Anti-Atherosclerotic Therapy

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Atherosclerosis and atherosclerotic diseases is the problem number one of modern medicine and health care, being the leading cause of myocardial infarction, stroke, sudden death, etc. [1-4]. Atherosclerotic diseases account for more than 50% of total mortality in industrialized societies [5-7]. For a long time, atherosclerotic lesion develops asymptomatically. Because of this, clinical manifestation of atherosclerosis takes place when atherosclerotic plaque becomes a pronounced lesion significantly narrowing the vascular lumen. Treatment of clinical manifestations of atherosclerosis is mainly symptomatic and does not affect atherosclerotic lesion *per se* [8-14]. Symptomatic therapy, along with the improvement of patient's state, frequently provokes further development of atherosclerosis [9]. Lipid-lowering therapeutic approaches, especially statin-based therapies, demonstrated atherosclerosis regression [15-20]. However, non-lipid direct anti-atherosclerotic therapy aimed at regression of atherosclerotic plaque practically does not exist so far [8, 9, 20]. Taking into account medical and social significance of the problem of atherosclerosis, direct anti-atherosclerotic therapy should be developed.

Lack of knowledge of the mechanisms of atherogenesis and the absence of modern concepts of atherosclerosis prevent the development of effective direct anti-atherosclerotic therapy. Comprehensive and thorough studies of molecular and cellular mechanisms of atherosclerosis should be conceptual, i.e. be aimed to understanding the causes of atherosclerotic lesion and its development. Certainly, such studies should be focused on lipid metabolism, innate immunity, chronic inflammation, cell differentiation, etc. In addition to conventional methods of morphology and biochemistry, the most advanced techniques of cell biology, molecular biology and approaches used in different fields of science should be used. New concepts based on conceptual researches will be created. These new concepts of atherogenesis should generate the ideas about pharmacological targets for direct anti-atherosclerotic therapy. In recent years, we can see that in addition to lipid concept of atherogenesis, new targets for anti-atherosclerotic therapy including the approaches associated with innate immunity and inflammation are considered [21-27].

Thematic issue "Mechanisms of atherogenesis and development of anti-atherosclerotic therapy" is a platform to discuss the results of investigations related to molecular and cellular mechanisms of atherogenesis and novel concepts that will become the scientific basis for the development of direct anti-atherosclerotic therapy.

A team of international experts provides a series of reviews outlining the various aspects of atherosclerosis and atherosclerotic disease with a special focus on the translation of the available data to development of anti-atherosclerotic therapy.

The review of Sasaki *et al*. (Kobe, Japan) entitled "Regulatory T Cells and Tolerogenic Dendritic Cells as Critical Immune Modulators in Atherogenesis" [28] discusses possible roles of Tregs and tolerogenic DCs in the prevention of atherosclerosis and the promising strategies to prevent or cure atherosclerotic disease by modulating regulatory immune responses mediated by these suppressor cells. Authors have made a significant contribution to our understanding of roles of Tregs and tolerogenic dendritic cells in atherogenesis. In contrast to earlier published reviews on dendritic cells in atherosclerosis, the present review highlights, in particular, the importance of intestinal immune system as a possible therapeutic target to treat atherosclerosis. No doubts, this review would represent great value for specialists working in the field of dendritic cell research, as well as for researches searching new therapeutic targets against atherosclerosis.

An international team (Australia and Russia) chaired by Chistiakov [29] highlights the different roles that dendritic cells play in the progression or recession of the inflammatory reactions in atherosclerosis. The review specifically discusses the balance between anti-atherogenic and pro-atherogenic roles played by immature and mature dendritic cells in different stages of atherosclerosis development. This review significantly benefits from the figure that shows delicate balance between anti-atherogenic and pro-atherogenic roles of dendritic cells. Taking into account the growing interest in dendritic cells as a diagnostic marker and therapeutic target in atherosclerosis, further research in this direction will certainly lead to important practical developments.

Association of atherosclerotic plaque formation with accumulation of fibrillar collagens in the arterial wall is a well-known fact. Collagen structures are considered to be the elements that determine mechanoelastic properties of the wall in parallel with elastin responsible for elasticity and resilience. The team lead by Domogatskaya (Stockholm, Sweden) [30] try to clear up how the changes in collagen scaffold composition might correlate with development of atherosclerosis. Their review covers different aspects of collagen scaffold remodeling, synthesis, fibril formation, formation of the meshwork and incorporation of fibril-associated collagens into fibrils. Importantly, the authors emphasize that in vivo collagen synthesis and controlled degradation in arterial wall occurs under strong pulsatile tension. They discuss the impact of mechanical tensile forces on cells ability to synthesize collagens, and of matrix metalloproteinases to decompose both collagen molecules and collagen fibrils. Authors provide the evidence that an inverse effect may also take place: alterations of vessel elasticity in atherosclerosis may cause alterations in local tensile forces and, therefore, affect the rate of collagen biosynthesis and rate of local collagen-type specific digestion by matrix metalloproteinases.

The authors lead by Jenkins (Leicester, UK) [31] discuss the pathogenic roles of different resources of reactive oxygen species (ROS) in atherosclerosis. ROS in large amounts clearly have detrimental effects on cell physiology, whereas low concentrations of ROS are permanently produced in cells and play a role as signalling molecules. An imbalance in ROS production and defence mechanisms can lead to pathological vascular remodeling, atherosclerosis being among them. The scope of the review is to examine several possible sources of ROS as risk factors for atherosclerosis, including mitochondria, NADPH-oxidases, xanthine oxidase, peroxidases, NO-synthases, cytochrome P450, cyclooxygenases, lipoxygenases, and hemoglobin of red blood cells. A great challenge for future research is establishing interrelations, feedback and feed-forward regulation mechanisms of various sources of ROS in development of atherosclerosis and other vascular pathologies.

Bobryshev (Sydney, Australia) *et al*. [32] validate the rationale for interleukin-35 (IL-35) pathway as targets in atherosclerosis. Accumulating evidences suggest that IL-35 can represent an attractive target for future anti-atherosclerotic therapy due to several atheroprotective properties, including immunosuppressive and anti-inflammatory activity, suppressing a variety of T cells specifically pro-inflammatory Th1 and Th17 cells and probably dendritic cells, supporting proliferation of regulatory T cells, promoting production of anti-inflammatory cytokines such as IL-10 and down-regulates expression of pro-inflammatory cytokines such as IL-17. Very clear explanation of IL-35 pathway and this regulation is of particular interest. Recently 2 teams have shown the protective effect of IL-35 via regulatory B cells [33, 34].

The article "Tissue factor and atherothrombosis" by Saha (Kolkata, India) *et al*. [35] is very topical as tissue factor (TF) plays significant role in coronary artery thrombosis. The authors analyse various experimental works and clinical trials focused on biologic activity of TF. TF has

been demonstrated to bind with different cellular receptors affecting production and release of inflammatory mediators. TF is known to be the key element in the initiation of the extrinsic pathway of the coagulation cascade and appears to be a critical determinant of atherosclerotic plaque. TF pathway is a potential target for new therapeutic agents that can decrease TF activity.

The review entitled "Mutations of Mitochondrial DNA in Atherosclerosis and Atherosclerosis-Related Diseases" by Sobenin *et al*. (Moscow, Russia) [36] describes association of mitochondrial mutations with such multifactorial pathology as atherosclerosis. There is a growing body of evidence in support of the role of mitochondrial factors in the pathogenesis of atherosclerosis. It is known that DNA damage is present in both genomic and mitochondrial DNA in atherosclerosis. However, whether DNA damage itself promotes atherosclerosis, or is simply a by-product of the risk factors that promote atherosclerosis, is still unknown. The impact of certain mtDNA mutations to atherogenesis is widely unknown, and more studies focused on the assessment of the role of mtDNA mutations in the development of atherosclerosis-related pathologies are definitely required. The further areas of research should obviously include the studies evaluating the mechanistic role of mtDNA mutations in cellular and molecular mechanisms of atherogenesis, This understanding is of direct clinical relevance because increased mtDNA damage can be an important pathogenic factor, an additional prognostic predictor, and a potential target of therapeutic strategies in atherosclerosis.

The review by Ravani *et al*. (Milan, Italy) [37] provides an important overview on the relevance of the method of carotid intima-media thickness (CIMT) evaluation. The authors have a unique experience in this field. CIMT measurement is used in cardiovascular research over two decades. There is an abundance of evidence that CIMT can be measured reproducibly and CIMT is increased with high levels of atherosclerosis risk factor and with the risk of vascular events. Change over time CIMT can be easily evaluated, and it was shown that the rate of change is modified by the treatment. The review outlines the rationale for the potential use of CIMT in the stratification of cardio- and cerebrovascular risk and discusses several topics related to the measurement of this variable, which are still controversial among experts of the field.

An international team of authors from Germany, USA, and Russia describes a test system designed for complex analysis of monocyte activity in individuals to diagnose atherosclerosis-associated immunopathology and monitor treatment efficacy [38]. This cell-based test system may also be useful for screening compounds with immune-correcting effects. Both diagnostic and screening systems are based on primary culture of human monocyte-derived macrophages. This is the first step in creating a method for assessment of macrophage activity, which is required for further development of immune-correcting drugs. The existing preliminary data provide the basis for realization of this idea. The article will be of great interest to a wide range of biomedical scientists, and specifically to those working on cardio-vascular diseases.

Češka and Štulc (Prague, Czech Republic) [39] demonstrate that the emphasis on systematic application of principles of cardiovascular prevention results in improved control of cardiovascular risk factors. Implementation of clinical guidelines into primary care is one of the most difficult challenges in modern internal medicine, especially in low income countries. Review paper "Implementation of cardiovascular disease prevention guidelines into clinical practice: an unmet challenge" addresses very important question, how to shorten barriers between evidence-based cardiovascular guidelines and situation in real clinical practice. Authors try to express their attitude towards implementation of knowledge into clinical activities of health care professionals to improve prognosis of patients with different pathologies, in particular with cardiovascular diseases. Češka and Štulc proved their viewpoint on treatment strategies by providing data from experience in their country.

In the review entitled "Therapies Targeting Innate Immunity for Fighting Inflammation in Atherosclerosis" Mendel *et al*. (Or Yehuda, Israel) [40] provide information about pre-clinical studies and clinical trials with antagonists and agonists that have been designed to counteract inflammation in atherosclerosis and associated diseases, specifically highlighting targets expressed predominantly in monocytes. Recent investigation reveals that it is not all about cholesterol, and that another mechanism, namely inflammation, is central in the development of atherosclerosis. The authors show that there is still much anticipation for results from existing trials and room for innovative new compounds originating from basic research that could impair inflammation and be effective in treating atherosclerotic patients who are not benefiting from existing remedies.

The review by Maranhão and Leite, Jr. (São Paulo, Brazil) [41] describes the current knowledge on the possibilities of anti-inflammatory drug therapies in atherosclerosis treatment. Atherosclerotic diseases would have to be treated chronically with either primary or secondary prevention purposes. This would raise additional problems regarding not only long-term safety but also the treatment costs. Alternatively, short-term treatment with potent anti-inflammatory drugs could revert stages of disease aggravation demanding prompt intervention. In addition, effective systemic anti-inflammatory drug treatments would be of interest as adjuvants. Several aspects are elucidated, such as the key steps of atherogenesis, cells involved in the process, pro- and anti-inflammatory secreted factors, the concept of unstable and stable plaque, as well as the intertwining between inflammation, lipid arterial deposition, thrombus formation, and therapeutically targetable mechanisms. The perspectives of using monoclonal antibodies, enzymatic inhibitors, phyto-therapeutic compounds and anti-proliferative agents used in cancer chemotherapy are well described.

Cardioprotective properties of olive oil result from a positive influence of its components, such as phenolic compounds, on the cardiovascular system. One of the most abundant phenolic compounds of extra virgin olive oil is the dialdehydic form of elenolic acid 15 conjugated with 3,4-(dihydroxyphenyl)ethanol (3,4-DHPEA-EDA), also known as oleacein. The review entitled "Oleacein. Translation from Mediterranean diet to potential anti-atherosclerotic drug" by Naruszewicz *et al*. (Warsaw, Poland) [42] summarizes numerous findings about this phenolic compound. The authors show a broad knowledge on the pharmacological mechanisms of this substance, which may explain the traditional use of olive tree components against atherosclerosis. Authors believe that oleacein is a substance with high pharmacological potential and may become a new drug used in prevention of atherosclerosis.

International team of experts from Italy and Japan gives critical overview on the effect of green tea on the bioavailability or activity of cardiovascular drugs [43]. The review deals with a rather neglected issue, and also provides some interesting original data from two independent Italian and Japanese pharmacokinetic studies designed to assess the effect of different green tea preparations on simvastatin pharmacokinetics in healthy male subjects. Green tea is one of the most popular beverages worldwide, and many preventive or therapeutic effects on common diseases are being attributed to its consumption and strongly publicized. This may encourage patients treated with several cardiovascular drugs to consume these products as a "natural" and presumably innocuous adjunctive way to increase their overall health. However, green tea or green tea products may interfere by various mechanisms with the absorption, oral bioavailability, or activity of cardiovascular drugs, potentially leading to reduced drug efficacy or increased risk of drug toxicity.

Šimić and Reiner (Zagreb, Croatia) [44] review the possible side effects of statins. Statins are widely used in prevention and treatment of atherosclerotic diseases. Moreover, as mentioned above, statins cause regression of atherosclerotic lesion in arterial wall. According to

authors, the most important well-documented side effects of statins are rare or extremely rare. Increased activity of liver enzymes occurs occasionally and is reversible. Concerns that statins might increase cancer have not been proven. On the contrary, several studies have indicated a potentially benefit of statins in patients with different types of cancer. Also, early concerns about cognitive dysfunction and memory loss associated with statins use could not be substantiated and most recent data even suggest a possible beneficial effect of statins in the prevention of dementia. Authors state that although many different possible adverse effects were attributed to statins in the past, today they are considered to be drugs with a very good safety profile.

The article "Modular nanotransporters for targeted intracellular delivery of drugs: folate receptors as potential targets" is a review paper written by a group of experts in the field from Russia and USA [45]. This review describes the main approaches, which allow choosing internalizable receptors permitting both recognition of target cells and penetration into them. It is focused on the subcellular drug delivery system, modular nanotransporters (MNT) that can deliver a therapeutic into subcellular compartments. Authors believe that the MNT may be considered as an artificial transporting platform for different bioactive agents. Of particular interest are folate receptors, which are overexpressed and readily accessible to blood-borne agents after malignant transformation and in several pathologies like atherosclerosis in contrast to their negligible exposure to the blood pool in normal tissues. Authors consider a combination of MNT concept with folate receptor targeting as a new possible approach for treatment diseases characterized by folate receptor overexpression.

Thus, in this issue, a team of international experts discuss the most novel topics on therapeutic targets for atherosclerosis. I would like to thank the contributors to this special issue for their participation. We hope that this issue will be helpful for the development of novel therapeutic drugs against atherosclerosis and novel approaches for prevention, diagnosis and treatment of atherosclerotic diseases.

REFERENCES

[1] Smith SC Jr, Grundy SM. 2013 ACC/AHA Guideline Recommends Fixed-Dose Strategies Instead of Targeted Goals to Lower Blood Cholesterol. J Am Coll Cardiol 2014; 64: 601-12.

[2] Gitsioudis G, Katus HA, Korosoglou G. Assessment of coronary artery disease using coronary computed tomography angiography and biochemical markers. World J Cardiol 2014; 6: 663-70.

[3] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014; 114: 1852-66.

[4] Chyu KY, Shah PK. Advances in immune-modulating therapies to treat atherosclerotic cardiovascular diseases. Ther Adv Vaccines 2014; 2: 56-66.

[5] Salter AM. Dietary fatty acids and cardiovascular disease. Animal 2013; 7: 163-71.

[6] Arsenault BJ, Kritikou EA, Tardif JC. Regression of atherosclerosis. Curr Cardiol Rep 2012; 14: 443-9.

[7] Girotra S, Murarka S, Migrino RQ. Plaque regression and improved clinical outcomes following statin treatment in atherosclerosis. Panminerva Med 2012; 54: 71-81.

[8] Sobenin IA, Chistiakov DA, Bobryshev YV, Orekhov AN. Blood atherogenicity as a target for anti-atherosclerotic therapy. Curr Pharm Des 2013; 19: 5954-62.

[9] Orekhov AN. Direct anti-atherosclerotic therapy; development of natural anti-atherosclerotic drugs preventing cellular cholesterol retention. Curr Pharm Des 2013; 19: 5909-28.

[10] Montecucco F, Quercioli A, Mirabelli-Badenier M, Viviani GL, Mach F. Statins in the treatment of acute ischemic stroke. Curr Pharm Biotechnol 2012; 13: 68-76.

[11] Montecucco F, Quercioli A, Dallegri F, Viviani GL, Mach F. New evidence for nicotinic acid treatment to reduce atherosclerosis. Expert Rev Cardiovasc Ther 2010; 8: 1457-67.

[12] Riboldi P, Gerosa M, Meroni PL. Statins and autoimmune diseases. Lupus 2005; 14:765-8.

[13] Comparato C, Altana C, Bellosta S, Baetta R, Paoletti R, Corsini A. Clinically relevant pleiotropic effects of statins: drug properties or effects of profound cholesterol reduction? Nutr Metab Cardiovasc Dis 2001; 11: 328-43.

[14] Besler C, Heinrich K, Riwanto M, Lüscher TF, Landmesser U. High-density lipoprotein-mediated anti-atherosclerotic and endothelial-protective effects: a potential novel therapeutic target in cardiovascular disease. Curr Pharm Des 2010; 16: 1480-93.

[15] Babelova A, Sedding DG, Brandes RP. Anti-atherosclerotic mechanisms of statin therapy. Curr Opin Pharmacol 2013; 13: 260-4.

[16] Montecucco F, Quercioli A, Dallegri F, Viviani GL, Mach F. New evidence for nicotinic acid treatment to reduce atherosclerosis. Expert Rev Cardiovasc Ther 2010; 8: 1457-67.

[17] Smith SC Jr, Grundy SM. 2013 ACC/AHA Guideline Recommends Fixed-Dose Strategies Instead of Targeted Goals to Lower Blood Cholesterol. J Am Coll Cardiol 2014; 64: 601-612.

[18] Blum A. HMG-CoA reductase inhibitors (statins), inflammation, and endothelial progenitor cells-New mechanistic insights of atherosclerosis. Biofactors 2014; 40: 295-302.

[19] Noyes AM, Thompson PD. A systematic review of the time course of atherosclerotic plaque regression. Atherosclerosis 2014; 234: 75-84.

[20] Sipahi I, Tuzcu EM. Candidate mechanisms for regression of coronary atherosclerosis with high-dose statins: insight from intravascular ultrasonography trials. Am J Cardiovasc Drugs 2008; 8: 365-71.

[21] Wang L, Yang Y, Hong B. Advances in the role of microRNAs in lipid metabolism-related anti-atherosclerotic drug discovery. Expert Opin Drug Discov 2013; 8: 977-90.

[22] Puri R, Nissen SE. The complementary roles of imaging and 'omics' for future anti-atherosclerotic drug development. Curr Pharm Des 2013; 19: 5963-71.

[23] Nagarajan S. Mechanisms of anti-atherosclerotic functions of soy-based diets. J Nutr Biochem 2010; 21: 255-60.

[24] von der Thüsen JH, Kuiper J, van Berkel TJ, Biessen EA. Interleukins in atherosclerosis: molecular pathways and therapeutic potential. Pharmacol Rev 2003; 55: 133-66.

[25] Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniades C, Stefanadis C. Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. J Am Coll Cardiol 2014; 63: 2491-502.

[26] Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 2011; 17: 1410-22.

[27] Gómez-Guerrero C, Mallavia B, Egido J. Targeting inflammation in cardiovascular diseases. still a neglected field? Cardiovasc Ther 2012; 30: e189-97.

[28] Sasaki N, Yamashita T, Kasahara K, Takeda M, Hirata K. Regulatory T cells and tolerogenic dendritic cells as critical immune modulators in atherogenesis. Curr Pharm Des 2015; 21(9): 1107-17.

[29] Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV. Dendritic cells: a double-edge sword in atherosclerotic inflammation. Curr Pharm Des 2015; 21(9): 1118-23.

[30] Osidak MS, Osidak EO, Akhmanova MA, Domogatsky SP, Domogatskaya AS. Fibrillar, fibril-associated and basement membrane collagens of the arterial wall: architecture, elasticity and remodeling under stress. Curr Pharm Des 2015; 21(9): 1124-33.

[31] Goncharov NV, Avdonin PV, Nadeev AD, Zharkikh IL, Jenkins RO. Reactive oxygen species in pathogenesis of atherosclerosis. Curr Pharm Des 2015; 21(9): 1134-46.

[32] Bobryshev YV, Sobenin IA, Orekhov AN, Chistiakov DA. Novel anti-inflammatory interleukin-35 as an emerging target for anti-atherosclerotic therapy. Curr Pharm Des 2015; 21(9): 1147-51.
[33] Shen P, Roch T, Lampropoulou V, O'Connor RA, Stervbo U, Hilgenberg E, Ries S, Dang VD, Jaimes Y, Daridon C, Li R, Jouneau L, Boudinot P, Wilantri S, Sakwa I, Miyazaki Y, Leech MD, McPherson RC, Wirtz S, Neurath M, Hoehlig K, Meinl E, Grützkau A, Grün JR, Horn K, Kühl AA, Dörner T, Bar-Or A, Kaufmann SH, Anderton SM, Fillatreau S. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 2014; 507: 366-70.
[34] Wang RX, Yu CR, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev YV, Wingfield PT, Kim SH, Egwuagu CE. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nat Med 2014; 20: 633-41.
[35] Saha D, Saha S, Sergeeva EG, Ionova ZI, Gorbach AV. Tissue factor and atherothrombosis. Curr Pharm Des 2015; 21(9): 1152-7.
[36] Sobenin IA, Zhelankin AV, Mitrofanov KY, Sinyov VV, Sazonova MA, Postnov AY, Orekhov AN. Mutations of Mitochondrial DNA in Atherosclerosis and Atherosclerosis-Related Diseases. Curr Pharm Des 2015; 21(9): 1158-63.
[37] Ravani A, Werba JP, Frigerio B, Sansaro D, Amato M, Tremoli E, Baldassarre D. Assessment and relevance of carotid intima-media thickness (C-IMT) in primary and secondary cardiovascular prevention. Curr Pharm Des 2015; 21(9): 1164-71.
[38] Orekhov AN, Sobenin IA, Gavrilin MA, Gratchev A, Kotyashova SY, Nikiforov NG, Kzhyshkowska J. Macrophages in immunopathology of atherosclerosis: a target for diagnostics and therapy. Curr Pharm Des 2015; 21(9): 1172-9.
[39] Richard Češka, Tomáš Štulc. Implementation of cardiovascular disease prevention guidelines into clinical practice: an unmet challenge? Curr Pharm Des 2015; 21(9): 1180-84.
[40] Mendel I, Yacov N, Harats D, Breitbart E. Therapies targeting innate immunity for fighting inflammation in atherosclerosis. Curr Pharm Des 2015; 21(9): 1185-95.
[41] Maranhão RC, Leite ACA, Jr. Development of anti-atherosclerosis therapy based on the inflammatory and proliferative aspects of the disease. Curr Pharm Des 2015; 21(9): 1196-1204.
[42] Naruszewicz M, Czerwińska ME, Kiss AK. Oleacein. Translation from Mediterranean diet to potential antiatherosclerotic drug. Curr Pharm Des 2015; 21(9): 1205-12.
[43] Werba JP, Misakab S, Girolia MG, Yamadac S, Cavalcaa V, Kawabec K, Squellerioa I, Laguzzia F, Onouec S, Vegliaa F, Myasoedova V, Takeuchie K, Adachie E, Inuie N, Tremolia E, Watanabe H. Overview of green tea interaction with cardiovascular drugs. Curr Pharm Des 2015; 21(9): 1213-9.
[44] Šimić I, Reiner Ž. Adverse effects of statins – myths and reality. Curr Pharm Des 2015; 21(9): 1220-6.
[45] Slastnikova TA, Rosenkranz AA, Zalutsky MR, Sobolev AS. Modular nanotransporters for targeted intracellular delivery of drugs: folate receptors as potential targets. Curr Pharm Des 2015; 21(9): 1227-38.

Alexander N. Orekhov

Laboratory of Angiopathology
Institute of General Pathology and Pathophysiology
Russian Academy of Medical Sciences
8 Baltiyskaya Street
125315 Moscow
Russia
Tel: +7 903 169 08 66
Fax: +7 495 415 95 94
E-mail: a.h.opexob@gmail.com