BIOGRAPHICAL SKETCH

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NAME: Nikolai N Modyanov

eRA COMMONS USER NAME (credential, e.g., agency login): NMODYANOV

POSITION TITLE: Professor of Physiology and Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Lomonosov Moscow State University, USSR	M.S	05/1967	Organic chemistry
Shemyakin Institute of Bioorganic Chemistry, Moscow, USSR	Ph.D.	03/1973	Bioorganic chemistry
USSR Academy of Sciences, Moscow, Russia	D.Sc.	05/1987	Chemistry

A. Personal Statement

For over 40 years my research has focused on the molecular aspects of the ion-transporting X,K-ATPases (X=Na or H): receptors for cardiotonic and anti-ulcer drugs. Most important contributions in the field are determination of the complete primary structure and transmembrane spatial organization of Na,K-ATPase and discovery of family of closely related human genes encoding different X,K-ATPases. My laboratory pioneered in discovery of the hitherto unknown human ion pump encoded by ATP12A gene (alias ATP1AL1), which I later named non-gastric H,K-ATPase, a new type of human receptor for cardiotonic steroids. Major parts of these studies performed at UT-COMLS were continually supported by NIH grants R55 and as Project II of a Program Project Grant.

In the framework of these Grants my Lab discovered f a new member of the X,K-ATPase gene family, termed ATP1B4. It took us years of intense research to elucidate that orthologous ATP1B4 genes encoding the Na,K-ATPase BetaM subunit in lower vertebrates, were co-opted for new functions in placental mammals. Eutherian BetaM completely lost its ancestral role and became the only currently known atrial cardiac and skeletal muscle-specific protein of the inner nuclear membrane that possesses the ability to regulate gene expression and signal transduction.

The evolutionary mystery of the radical change in BetaM functions has led me in an absolutely new and exciting area of research directed to understanding the physiologically important necessity that trigger ATP1B4 gene co-option and elucidation of the evolutionarily acquired functions of BetaM in placental mammals.

Through ablation of X-chromosome *Atp1b4* gene in mice, we have determined that eutherian-specific functons of BetaM are physiologically essential, even might be necessary for survival of placental mammals in natural conditions, and that they provide an evolutionary advantage. On the other hand, our experimental data revealed an essential role of BetaM in development of pathways regulating metabolism of adult placental mammals including their predisposition to obesity.

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a. **Modyanov, N.**, Petrukhin, K., Sverdlov, V., Grishin, A., Orlova, M., Kostina, Makarevich, O., Broude, N., Monastyrskaya, G., and Sverdlov, E. (1991) Family of human Na,K-ATPase genes. ATP1AL1 gene is transcriptionally competent and probably encodes related ion transport ATPase. FEBS Lett. 278:91-94.

b. **Modyanov, N.N.**, Mathews, P.M., Grishin, A.V., Beguin, P., Beggah, A.T., Rossier, B.C., Horisberger, J.-D., and Geering, K. (1995) The human *ATP1AL1* gene encodes a ouabain-sensitive H,K-ATPase. Am. J. Physiol. 269:C992-C997.

c. Pestov NB, Korneenko TV, Shakhparonov MI, Shull GE, **Modyanov NN** (2006) Loss of acidification of anterior prostate fluids in ATP12A null mutant mice indicates that the nongastric H,K-ATPase functions as a proton pump *in vivo* Am J Physiol Cell Physiol 291:C366-C374

d. Pestov, N.B., Ahmad, N., Korneenko, T.V., Zhao, H., Radkov, R., Schaer, D., Roy S, Bibert S, Geering, K., **Modyanov, N.N.** (2007) **Evolution of Na,K-ATPase βm-subunit into a co-regulator of transcription in placental mammals. Proc. Natl. Acad. Sci. USA 104: 11215-11220**

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2006-present	Professor, Department of Physiology and Pharmacology, The University of Toledo College of Medicine (formerly Medical College of Ohio), Toledo, OH
2010-present	Investigator, Center for Diabetes and Endocrine Research (CeDER), The University of Toledo College of Medicine, Toledo, OH
1994-2005	Professor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
1994	Visiting Professor, Department of Pharmacology and Toxicology, University of Lausanne, Lausanne ,Switzerland, (1/1/1994 -6/30/1994)
1993	Visiting Professor, Department of Biochemistry of Swiss Federal Institute of Technology, Zurich, Switzerland (1/1/1993 -12/31/1993)
1986-1995	Russian (USSR) Academy of Sciences, Scientific Council "Research on Biological Membranes", Member of Executive Board
1986-1994	International Cell Research Organization (ICRO) at the United Nations Educational, Scientific and Cultural Organization,(UNESCO). Member of the Council "Molecular Structure and Function"
1986-1995	Professor, Head of Laboratory of Membrane Biochemistry, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia
1979-1986	Principal Investigator, Department of Protein Chemistry, Shemyakin Institute of Bioorganic Chemistry, Moscow, Russia
1973-1979	Senior Scientist, Department of Protein Chemistry, Shemyakin Institute of Bioorganic Chemistry, Moscow, Russia
1970-1973	Staff Researcher, Department of Protein Chemistry, Shemyakin Institute of Bioorganic Chemistry, Moscow, Russia

Honors

1982	USSR National State Prize for Outstanding Achievements in Science
1975	USSR National Prize for Young Scientists

C. Contributions to Science

1. My early investigations in the area of ion-transporting X,K-ATPases were focused on structure of Na,K-ATPase using a combination of protein chemistry and molecular biology methods. Our group pioneered in determination of the complete primary structure of both subunits of pig Na,K-ATPase and discovery of family of closely related human genes encoding different X,K-ATPases.

a. Ovchinnikov, Yu.A., **Modyanov, N.N.**, Broude, N.E., Petrukhin, K.E., Grishin, A.V., Kiyatkin, N.I., Arzamazova, N.M., Aldanova, N.A., Monastyrskaya, G.S., and Sverdlov, E.D. (1986) Pig kidney Na,K-ATPase. Primary structure and spatial organization. (1986) FEBS Lett. 201:237-245.

b. Sverdlov, E.D., Monastyrskaya, G.S., Broude, N.E., Ushkaryov, Yu. A., Allikmets, R.L., Melkov, A.M., Smirnov, Yu. V., Malyshev, I.V., Dulubova, I.E., Petrukhin, K.E., Grishin, A.V., Kiyatkin, N.I., Kostina, M.B., **Modyanov, N.N.**, and Ovchinnikov, Yu.A. (1987) Family of human Na,K-ATPase genes: no less than five genes and/or pseudogenes related to the alpha subunit. FEBS Lett. 217:275-278.
C .Sverdlov, E.D., Akopanz, N.S., Petrukhin, K.E., Broude, N.E., Monastyrskaya, G.S., and **Modyanov, N.N.** (1988) Na,K-ATPase. Tissue-specific expression of genes coding for α-subunit in diverse human tissues. FEBS Lett. 239:65-68.
d. Ovchinnikov, Yu.A., Monastyrskaya, G.S., Broude, N.E., Ushkaryov, Yu.A., Melkov, A.M., Smirnov, Yu.V., Malyshev, I.V., Allikmets, R.L., Kostina, M.B., Dulubova, I.E., Kiyatkin, N.I., Grishin, A.V., **Modyanov, N.N.**, and Sverdlov, E.D. (1988) Family of human Na,K-ATPase genes. Structure of the gene for the catalytic subunit (alpha III-form) and its relationship with structural features of the protein. FEBS Lett. 233:87-94.

2. Determination of the Na,K-ATPase primary structure initiated more detailed studies of the enzyme molecule. Several original experimental approaches were developed in my laboratory to directly probe the Na,K-ATPase structure. These include a unique procedure of stepwise limited proteolysis of the native Na,K-ATPase, the differential analysis of the secondary structure of hydrophilic and hydrophobic domains, the hydrophobic photolabeling of the intramembrane domains and vectorial lactoperoxidase iodination of the alpha-subunit C-terminus. Several components of the active site were identified by affinity modification with substrate analogs. These experimental data were used to build the first model of the Na,K-ATPase transmembrane spatial organization.

a. Ovchinnikov, Yu.A., Arzamazova, N.M., Arystarkhova, E.A., Gevondyan, N.M., Aldanova, N.A., and **Modyanov, N.N.** (1987) Detailed structural analysis of exposed domains of membrane-bound Na,K-ATPase. FEBS Lett. 217:269-274.
b. Ovchinnikov, Yu. A., Dzhandzhugazyan, K.N., Lusenko, S.V., Mustayev, A.A., and **Modyanov, N.N.** (1987) Affinity modification of E_1form of Na,K-ATPase revealed Asp710 in the catalytic site. FEBS Lett. 217:111-116.
c. Chertova, E.N., Lutsenko, S.V., Levina, N.B., **Modyanov, N.N.** (1989) Probing the topography of the intramembrane part of Na,K-ATPase by photolabeling with 3-(trifluoromethyl)-3-(iodophenyl)diazerine. Analysis of the hydrophobic domain of the beta subunit. FEBS Lett. 254:13-16.
d. Vladimirova, N.M., Potapenko, N.A., Sachs, G., and **Modyanov, N.N.** (1995) Determination of the sidedness of the carboxy-terminus of the Na^+/K^+-ATPase α-subunit using lactoperoxidase iodination. Biochim. Biophys. Acta 1233:175-184.

3. Further clarification of the functional status of the ATP12a encoded human protein and its animal homologs form the third distinct group of X,K-ATPases,that I designated as non-gastric H,K-ATPases. The ability of the alpha subunit of non-H,K-ATPase to assemble with different known beta-subunits was analyzed using expression in *Xenopus* oocytes. For the first time, my laboratory was able to analyze directly the enzymatic properties of a human non-H,K-ATPase using the baculovirus expression system. Our studies revealed the important role of the non-gastric H,K-ATPase in regulation of potassium balance during pregnancy. Most importantly, our recent experimental data argue that non-gastric H,K-ATPase is a potential therapeutic target for proton pump inhibitors and potassium-competitive acid blockers

a. Sverdlov, V.E., Grishin, A.V., Kostina, M.B., and **Modyanov, N.N.** (1996) Genomic organization of the human ATP1AL1 gene encoding a ouabain-sensitive H,K-ATPase. Genomics 32:317-327.
b. Adams,G., Tillekeratne, M., Yu, C., Pestov, N.B., and **Modyanov, N.N.** (2001) Catalytic Function of Nongastric H,K-ATPase Expressed in Sf-21 Insect Cells. Biochemistry 40; 5765-5776
c. Crambert, G., Horisberger, J.D**., Modyanov**, N.N. and Geering, K., (2002) Human non-gastric H,K-ATPase: Structural properties and transport functions of ATP1al1 assembled with different beta subunits Am. J. Physiol., Cell Physiol. 283: C305-C314
d. Min JY, Ocampo CJ, Stevens WW, Price CPE, Thompson CF, Homma T, Huang JH,Norton JE, Suh LA, Pothoven KL, Conley DB, Welch KC, Shintani-Smith S, Peters AT, Grammer LC 3rd, Harris KE, Hulse KE, Kato A**, Modyanov NN**, Kern RC, Schleimer RP, Tan BK. (2017) Proton pump inhibitors decrease eotaxin-3/CCL26 expression in patients with chronic rhinosinusitis with nasal polyps: Possible role of the non-gastric H,K-ATPase.Journal of Allergy and Clinical Immunology,139: 130-141

e. Abdelgied M UK, Chen OG, Schultz C, Tripp K, Peraino AM, Paithankar S,Chen C, Tamae Kakazu M, Castillo Bahena A, Jager TE, Lawson C, Chesla DW, Pestov N, **Modyanov NN**, Prokop J,Neubig RR, Uhal BD, Girgis RE, Xiaopeng Li.(2023) Targeting ATP12A, a non-gastric proton pump alpha subunit, for idiopathic pulmonary fibrosis treatment. . *Am J Respir Cell Mol Biol*. 68:638-650..

4. I have pioneered in the discovery of a hitherto unknown member of the X,K-ATPase gene family, termed ATP1B4. Vertebrate ATP1B4 genes represent a rare instance of orthologous gene co-option that transformed Na,K-ATPase BetaM subunit of lower vertebrates into skeletal and atrial cardiac muscle-specific regulator of transcription in placental mammals. To understand the physiological role of the eutherian BetaM and to elucidate impact of ATP1B4 co-option on mammalian evolution, we developed knockout mouse model.

Up to now we have determined that loss of BetaM results in lower body weight and growth retardation leading to high mortality of knockout neonates. Strong down-regulation of genes implicated in lipid metabolism and thermoregulation in skeletal muscle of neonatal knockout mice indicates the importance of BetaM in critical period of perinatal development. On the other hand, *Atp1b4* disruption has caused profound beneficial effect on metabolic parameters of adult knockout males, which have lower body fat, exhibit enhanced metabolic rate and are resistant to high-fat diet-induced obesity. Thus, evolutionary acquired functions of BetaM also play a role in development of pathways regulating metabolism of adult placental mammals including their predisposition to obesity. Currently, my research in this direction is focused on elucidation of BetaM's functional role in regulatory networks controlling myocardial gene expression in normal and pathophysiological conditions using knockout mouse model.

a. Pestov, N.B., Adams, G., Shakhparonov, M.I., and **Modyanov, N.N.** (1999) Identification of a novel gene of the X,K-ATPase β-subunit family that is predominantly expressed in skeletal and heart muscles. FEBS Lett.456:243-248.

b. Pestov, N.B., Ahmad, N., Korneenko, T.V., Zhao, H., Radkov, R., Schaer, D., Roy S, Bibert S, Geering, K., **Modyanov, N.N.** (2007) Evolution of Na,K-ATPase βm-subunit into a co-regulator of transcription in placental mammals. Proc. Natl. Acad. Sci. USA 104: 11215-11220

c. Kornienko TV, Pestov NB, Ahmad N, Okkelman IA, Dmitriev RI, Shakhparonov MI, **Modyanov NN.** (2016) Evolutionary diversification of the BetaM interactome acquired through co-option of the ATP1B4 gene in placental mammals. Scientific reports. 6:22395.

d. Ahmad N, de la Serna IL, Marathe HG, Fan X, Dube P, Zhang S, Haller ST, Kennedy DJ, Pestov NB, **Modyanov NN.** (2023) Eutherian-Specific Functions of BetaM Acquired through *Atp1b4* Gene Co-Option in the Regulation of MyoD Expression. Life 13 :414.

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https://www.ncbi.nlm.nih.gov/myncbi/1X3trnn1ptckz/bibliography/public/