

BIOGRAPHICAL SKETCH

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NAME Nikolai N. Modyanov, Ph.D.	POSITION TITLE Professor, Physiology and Pharmacology		
eRA COMMONS USER NAME Nmodyanov			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Lomonosov Moscow State University, USSR	M.S.	1967	Organic Chemistry
Shemyakin Institute of Bioorganic Chemistry, USSR	Ph.D.	1973	Bioorganic Chemistry
USSR Academy of Sciences, Moscow, Russia	D.Sc.	1987	Chemistry

A. PERSONAL STATEMENT

For over 30 years my research has focused on the molecular aspects of the ion-transporting X,K-ATPases (Na,K- and H,K-ATPases): receptors for cardiotonic and anti-ulcer drugs. Most important contributions in the field are determination of the complete primary structure of both subunits of Na,K-ATPase and discovery of family of closely related human genes encoding different X,K-ATPases. My major achievements also include discovery and characterization of the structure-function relationship of human non-gastric H,K-ATPase, a new type of human receptor for cardiotonic steroids. Major parts of these studies performed at UT-COM were continually supported by NIH grants.

I have pioneered the discovery of a new member of the Na,K-ATPase β -subunit gene family, termed ATP1B4. . It took my team more than 6 years of intense research to elucidate that ATP1B4 genes represent a rare instance of orthologous vertebrate gene co-option that created fundamental changes in the physiological role and functional properties of the encoded BetaM proteins. We demonstrated that BetaM proteins are β -subunits of Na,K-ATPase located in the cell membrane in lower vertebrates. In placental mammals, BetaM completely lost its ancestral role and became the only presently known skeletal and atrial cardiac muscle-specific protein of the inner nuclear membrane, where it functions as a regulator of gene expression and signal transduction during muscle development, growth and regeneration. Evolutionary mystery of the physiological importance of the radical change in BetaM functions through ATP1B4 gene co-option in placental mammals has led me in an absolutely new and exciting area of research. To understand the physiological role of the mammalian BetaM, we developed Atp1b4 knockout mouse model and determined that loss of BetaM resulted in growth retardation leading to high mortality of neonatal knockout mice. These findings point to the important role of BetaM in development of heart and skeletal muscles. In pilot experiments we have shown that knockout mice exhibit enhanced insulin sensitivity and improved glucose tolerance and are resistant to high-fat diet-induced obesity, thereby demonstrating a role for BetaM in metabolic control.

The overall goal of the current project is to provide new insights into the molecular basis of the development and metabolic regulation of placental mammals and may lead to a better understanding of mechanisms underlying human congenital heart and muscle abnormalities and metabolic diseases such as obesity and type 2 diabetes and their cardiovascular complications

B. POSITIONS AND HONORS

Positions and Employment

1970-1973	Staff Researcher, 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
1979-1986	Principal Investigator, Department of Protein Chemistry, Shemyakin Institute of Bioorganic Chemistry, Moscow, Russia

- 1986-1995 Professor, Head of Laboratory of Membrane Biochemistry, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia
- 1993 Visiting Professor, Department of Biochemistry of Swiss Federal Institute of Technology, one-year Fellowship from Swiss Federal Institute of Technology, Zurich, Switzerland
- 1994 Visiting Professor, Univ. of Lausanne, 6 month Fellowship, Zyma Foundation, Switzerland
- 1994-2005 Professor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
- 2006-present Professor, Department of Physiology and Pharmacology, The University of Toledo College of Medicine (formerly Medical College of Ohio), Toledo, OH

Honors

- 1975 Winner of the Annual USSR All-Union Prize for Young Scientists, USSR
- 1982 Winner of the Annual USSR State Prize for Outstanding Achievements in Science

C.SELECTED PEER-REVIEWED PUBLICATIONS (Selected from 152 peer-reviewed publications)

Most relevant to the current project

- 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.
- Pestov, N.B., Korneenko, T.V., Zhao, H., Adams, G., Shakhparonov, M.I., and **Modyanov, N.N.** (2000) Immunochemical demonstration of a novel β -subunit isoform of X,K-ATPase in human skeletal muscle. *Biochem. Biophys. Res. Commun.* 277:430-435.
- Pestov, N.B., Korneenko, T.V., Zhao, H., Adams, G., Kostina, M.B., Shakhparonov, M.I., and **Modyanov, N.N.** (2001) The β_m protein, a member of the X,K-ATPase β -subunits family, is located intracellularly in pig skeletal muscle. *Arch. Biochem. Biophys.* 396:80-88.
- Crambert, G., Beguin, P., Pestov, N.B., **Modyanov, N.N.**, and Geering, K. (2002) β_m , a structural member of the X,K-ATPase β subunit family, resides in the ER and does not associate with any known X,K-ATPase α subunit. *Biochemistry* 41:6723-6733.
- Zhao, H., Pestov, N.B., Korneenko, T.V., Shakhparonov, M.I., and **Modyanov, N.N.** (2004) Accumulation of beta(m), a structural member of X,K-ATPase beta-subunit family, in nuclear envelopes of perinatal myocytes. *Am. J. Physiol. Cell. Physiol.* 286:C757-C767.
- Pestov, N.B., Ahmad, N., Korneenko, T.V., Zhao, H., Radkov, R., Schaer, D., Roy S, Bibert S, Geering, K. and **Modyanov, N.N.** (2007) Evolution of Na,K-ATPase β_m -subunit into a co-regulator of transcription in placental mammals. *Proc. Natl. Acad. Sci. USA* 104:11215-11220.
- Pestov, N.B., Zhao, H., Basrur, V., **Modyanov N.N.** (2011) Isolation and characterization of BetaM protein encoded by ATP1B4--a unique member of the Na,K-ATPase β -subunit gene family. *Biochem. Biophys. Res. Commun.* 412:543-548.
- Korneenko, T.V., Pestov, N.B., Ahmad, N., Okkel'man, I.A., Dmitriev, R.I., Shakhparonov. M.I., **Modyanov, N.N.** (2016) Evolutionary diversification of the BetaM interactome acquired through co-option of the ATP1B4 gene
In placental mammals. *Scientific Reports.* 6:22395

Additional publications of importance to the field

- Ovchinnikov, Yu.A., **Modyanov, N.N.**, Broude NE, Petrukhin KE, Grishin AV, Arzamazova NM, Aldanova NA, Monastyrskaya GS, Sverdlov ED.. (1986) Pig kidney Na,K-ATPase. Primary structure and spatial organization. *FEBS Lett.* 201:237-245.
- 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.
- Ovchinnikov, Yu. A., Dzhandzhugazyan, K.N., Lusenko, S.V., Mustayev, A.A., and **Modyanov, N.N.** (1987) Affinity modification of E₁-form of Na,K-ATPase revealed Asp-710 in catalytic site. *FEBS Lett.* 217:111-116.
- Bernikov, L.P., Dzhandzhugazyan, K.N., Lutsenko, S.V., and **Modyanov, N.N.** (1990) Dialdehyde ATP derivative as affinity modifier of the Na,K-ATPase active site. *Eur. J. Biochem.* 194:413-421.
- Zvarich, E., James, P., Voherr, T., Falchetto, R., **Modyanov, N.**, and Carafoli, E. (1990) Mapping of functional domains in the plasma membrane Ca-pump using trypsin proteolysis. *Biochemistry* 29:8070-8076.

- 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.
- Arystarkhova, E., Gasparian, M., **Modyanov, N.N.**, and Sweadner, K.J. (1992) Na,K-ATPase extracellular surface probed with monoclonal antibody that enhances ouabain binding. J. Biol. Chem. 267:13694-13701.
- Grishin, A., Sverdlov, V., Kostina, M., and **Modyanov, N.** (1994) Cloning and characterization of the cDNA encoded by ATP1AL1 - a member of human Na,K/H, K-ATPase gene family. FEBS Lett. 349:144-150.
- 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.
- Modyanov, N.**, Mathews, P., Grishin, A., Beguin, P., Beggah, A., Rossier, B., Horisberger, J.-D., and Geering, K. (1995) The human ATP1AL1 gene encodes a ouabain-sensitive H,K-ATPase. Am. J. Physiol. 269: C992-C997.
- Sverdlov, V.E., 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.
- Yu, C., Xie, Z., Askari, A., and **Modyanov, N.N.** (1997) Enzymatic properties of human Na,K-ATPase $\alpha_1\beta_3$ isozyme. Arch. Biochem. Biophys. 345:143-149.
- Ivanov, A., Askari, A., and **Modyanov, N.N.** (1997) Structural analysis of the products of chymotryptic cleavage of the E1 form of Na,K-ATPase α -subunit: Identification of the N-terminal fragments containing transmembrane H1-H2 domain. FEBS Lett. 420:107-111.
- Pestov, N.B., Romanova, L.G., Korneenko, T.V., Egorov, M.V., Kostina, M.B., Sverdlov, V.E., Askari, A., Shakhparonov, M.I., and **Modyanov, N.N.** (1998) Ouabain-sensitive H,K-ATPase: tissue-specific expression of the mammalian genes encoding the catalytic α -subunit. FEBS Lett. 40:320-324.
- Crambert, G., Hasler, U., Beggah, A.T., Yu, C.L., **Modyanov, N.N.**, Horisberger, J.D., Lelievre, L., and Geering, K. (2000) Transport and pharmacological properties of nine different human Na,K-ATPase isozymes. J. Biol. Chem. 275:1976-1986.
- Ivanov, A., Zhao, H., and **Modyanov, N.N.** (2000) Packing of the transmembrane helices of Na,K-ATPase: Direct contact between beta-subunit and H8 segment of alpha-subunit revealed by oxidative cross-linking. Biochemistry 39:9778-9785.
- Geering, K., Crambert, G., Yu, C., Korneenko, T.V., Pestov, N.B., and **Modyanov, N.N.** (2000) Role of membrane domains M9 and M10 in the assembly process and association efficiency of human, non-gastric H,K-ATPase α subunits (ATP1AL1) with known β subunits. Biochemistry 39:12688-12698.
- 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.
- Pestov, N.B., Korneenko, T.V., Adams, G., Tillekeratne, M., Shakhparonov, M.I., and **Modyanov, N.N.** (2002) Nongastric H-K-ATPase in rodent prostate: lobe-specific expression and apical localization. Am. J. Physiol. Cell Physiol. 282 : C907-916..
- Ivanov, A., **Modyanov, N.N.**, and Askari, A. (2002) Role of the self-association of β subunits in the oligomeric structure of Na⁺/K⁺-ATPase. Biochem. J. 364:293-299.
- Crambert, G., Horisberger, J.-D., **Modyanov, N.N.**, and Geering, K. (2002) Human nongastric H⁺-K⁺-ATPase: transport properties of ATP1a1 assembled with different β -subunits. Am. J. Physiol. 283:C305-C314.
- Pestov, N.B., Korneenko, T.V., Radkov, R., Zhao, H., Shakhparonov, M.I., and **Modyanov, N.N.** (2004) Identification of the beta-subunit for nongastric H-K-ATPase in rat anterior prostate. Am. J. Physiol. Cell Physiol. 286:C1229-C1237.
- Dmitriev, R.I., Pestov, N.B., Korneenko, T.V., Gerasimova, A.V., Zhao, H., **Modyanov, N.N.**, Kostina, M.B., and Shakhparonov M.I. (2005) Tissue-specificity of alternative splicing of transcripts encoding hampin, a new protein homologous to msl1 Russian J. Bioorgan. Chem. 31:363-371
- Pestov, N.B., Korneenko, T.V., Shakhparonov, M.I., Shull, G.E., and **Modyanov, N.N.** (2006) Loss of acidification of anterior prostate fluids in Atp12a-null mutant mice indicates that nongastric H-K-ATPase functions as proton pump *in vivo*. Am. J. Physiol. Cell Physiol. 291:C366-C374.
- Dmitriev RI, Korneenko TV, Bessonov AA, Shakhparonov MI, **Modyanov NN**, Pestov NB. (2007) Characterization of hampin/MSL1 as a node in the nuclear interactome. Biochem Biophys Res Commun. 355:1051-1057
- Radkov R, Kharoubi-Hess S, Schaer D, **Modyanov NN**, Geering K, Horisberger JD. (2007) Role of homologous ASP334 and GLU319 in human non-gastric H,K- and Na,K-ATPases in cardiac glycoside binding. Biochem Biophys Res Commun. 356:142-146

Pestov NB, Dmitriev RI, Kostina MB, Korneenko TV, Shakhparonov MI, **Modyanov NN**. (2013) Structural evolution and tissue-specific expression of tetrapod-specific second isoform of secretory pathway Ca(2+)-ATPase. *Biochem Biophys Res Commun*. 417:1298-1303.

Salhi A., Christine Lamouroux, C., Pestov, N.B., **Modyanov, N.N.**, Doucet, A., and Crambert, G. (2012) A link between fertility and K⁺ homeostasis: Role of the renal H,K-ATPase type 2. *Pflügers Archiv – European Journal of Physiology* 465: 1149-1158

Pestov, N.B., M.B., Korneenko, T.V., Shakhparonov, M.I., and **Modyanov, N.N.** (2013) Postnatal regulation of X,K-ATPases in rat skin and conserved lateroapical polarization of Na,K-ATPase in vertebrate epidermis. *Experimental Dermatology*, 22: 423-425

Korneenko TV, Pestov NB, Okkel'man IA, **Modyanov NN**, Shakhparonov MI. (2015) P4-ATPase Atp8b1/FIC1: Structural Features and Physiological Functions in Health and Disease. *Russian Journal of Bioorganic Chemistry*, 41:1-9

D. RESEARCH SUPPORT

Ongoing Research Support

My research is currently supported by the Department of Physiology and Pharmacology and by Center for Diabetes and Endocrine Research University of Toledo College of Medicine

Completed Research Support

NHLBI, P01 HL36573-(16-20) Askari (PI) 03/01/03-02/28/09

Role: Leader of Project II "Structure and Function of X,K-ATPase Family Members"

The major goals of this project are to define specific features of reaction mechanism of human nongastric H,K-ATPase, to examine the roles of particular structural motifs and residues in ion specificity and inhibitor sensitivity of human nongastric H,K-ATPase, and to identify the protein counterpart(s) of the muscle-specific β_m protein, a new structural member of X,K-ATPase β -subunit family.

NHLBI, P01 HL36573-(11-15), Askari (PI) 03/01/98-02/28/03 Role: Leader of Project II "Structure-Function Relationships of Ouabain-Sensitive Ion-Pumps"

The major goals of this project are to identify the β -subunit of nongastric H,K-ATPase and to characterize functional properties of the entire human ouabain-sensitive H,K-ATPase.

NIH/NIGMS 1R55GM54997 Modyanov (PI) 09/30/97-09/29/01

Structure-Function Relationships in Na,K-/H,K-ATPases

The major goal of this project was to elucidate principal parameters of the intramembrane structure of X,K-ATPases using Na,K-ATPase as a model.

AHA NW-97-15-S Modyanov (PI) 07/01/97-06/30/99 Human Ouabain-Sensitive H,K-ATPase, Structure and Function Properties