Laboratory of proteins and peptides

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Laboratory of proteins and peptides was founded on the basis of Zoophytotoxins Department founded in 1973 as a part of the Bioorganic Chemistry Department, Uzbekistan Academy of Sciences. The Department dealt with the structures and functions of biologically active compounds of natural origin, toxins, enzymes and other biologically active components. For the first time, more than 50 physiologically active proteins and peptides with toxic effects were isolated from the Central Asian animals' venoms, for 15 of them chemical primary structures were identified. A neurotoxin of protein origin with a complex quaternary structure formed by four subunits with molecular mass of 75,000 Da (Tashmukhamedov M.S., Kasymov A.A., Adylbekov M.T., Salikhov Sh.I.). Research on highly specific toxins isolated from the venoms of various arthropods allowed studying mechanisms of their actions to use them as tools for neurophysiological investigations (Salikhov Sh.I., Kasymov A.A.).

The use of some highly specific neurotoxins made possible understanding of mechanisms of vitally significant processes taking place in the live cells associated with peculiarities of the structural and molecular organization of biological membranes. Generation of antisera for the venoms of cobra, scorpion and black widow spider with the isolated neurotoxins used as the antibodies was the practical completion of the research (Salikhov Sh.I., Kasymov A.A., Inogamov U.K.). The structures of some low molecular toxins formed upon various pathologies, to name the kidney disease, traumas and various viral diseases, were studied. The rapid tests were developed for quantitative assessment of concentrations of low molecular toxins to facilitate programming of the hemodialysis processes (Mukhamadieva Sh.G., Kadyrova A.F., Sultanova E.M.). The immunoadsorbents based on the conjugates of toxins and sorbents were generated (Kasymov A.A., Salikhov Sh.I.). Joint works were conducted with the medical professionals of Uzbekistan for the doctoral and candidate dissertations were defended in the medical sphere.

In 1984, the laboratory's activity was refocused on the study on proteins and peptides isolated from the plant and animal organisms, as well as on processes taking place in the cotton growth and development. The structures and functions of the cotton hormone-binding proteins were studied. The receptors of the cotton phytohormones were isolated to prove their regulatory role in the cotton leaf fall. The molecular mechanisms underlying processes taking place in the cotton defoliation were studied serving as the basis for development of criteria for screening compounds with the defoliating and growth-stimulating activity (Veshkurova O.N., Salikhov SH.I.).

Seven doctoral dissertations were defended; Dolimbek Bekhzod Ziyotbek, Texas University professor, and Abulimiti Yili, director deputy of Xianjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences are among the persons with the doctorate.

In a time of the laboratory's existence, it was headed by Academician Salikhov Sh.I., Doctor of Biological Sciences, (1973-2017) and Oschepkova Yu.I., Doctor of Chemical Sciences (2018-up to present).

In 2018, as the result of the Institute reorganization, there was a merge with the laboratory of bioregulators headed by Prof. Leont'ev V.B. (1973-1999), Prof. Sadykov A.A. (1999-2005) and Sagdiev N.J., Candidate of Chemical Sciences (2005-2017). Professor Leont'ev V.B. supervised the generation of the reconstructednucleoprotein complexes, studies on the role of the nuclear proteins of histones, non-histone proteins, HMG-proteins in the regulation of *in vitro* transcription and in the native chromatin. Significant role of conformational transformations of allosteric and cooperative character in the changes of chemical structures both of the nuclear proteins and of functionally significant genome regionswas identified (Mangutova Yu.S., Fainboim A.M., Leont'ev V.B.). Some studies were devoted to elucidation of role of the cell nuclei in the protein biosynthesis (Saitmuratova O.Kh., Leont'ev V.B.), as well as to endonuclear mechanism of biosynthesis and functional role of neutral and nuclear proteins of the nerve tissue. The experiments on synthesis of polyacrylamide gels in the gravity-free environment were proposed and conducted. The interrelation between properties of net structures and gravity action was found (Sadykov A.A., Leont'ev V.B., Grechko G.M.).

At the laboratory, the monoclonal antibody biotechnology as a high technology was applied (Khashimova Z.S., Mangutova Yu.S., Suslo M.E., Leont'ev V.B.). The finite cell lines, to name mouse skin cancer, mouse small intestine cancer (Akat) and sarcoma (S-180) were generated; test-systems for screening of

biologically active agents, including the anti-tumor ones, were produced on their basis (Kuznetsova N.N., Mardanova Z.I., Leont'ev V.B., Khashimova Z.S., Sadykov A.A.); a metastazing model was obtained using the mouse skin cancer cell line.
In the last years, at the laboratory of proteins and peptides, studies on structural-functional characterization of bioregulators of plant and animal origins were conducted; some preparations on their basis successfully used in medicine and agriculture were generated.

Principle research direction

Structural-functional characterization and study on mechanisms of actions of bioregulators and antimicrobial peptides of plant and animal origins; development of production procedure for protein-peptide bioregulators and generation of preparations for medicine and agriculture on their basis; constructing of macromolecular therapeutic systems having stability, prolonged effect and improved bioavailability.



Directions of research include

- Study on the Central Asian protein-peptide physiologically active agents of plan and animal origins
- Generation and production of novel medications based on the protein-

peptide bioregulators from the plant and animal raw materials

- Construction of macromolecular therapeutic systems with stability, prolonged action and improved bioavailability.

Main achievements include

- isolation of the cotton receptor proteins to phytohormones, to name ethylene, cytokinins and auxins. Their structural-functional parameters were studied; a competitive-receptor technology for analyzing pesticides was developed
- study on molecular mechanism of action of defoliants, derivatives of phenyl heteryl urea
- study on structural-functional characteristics of toxins isolated from the Central Asian animals' venoms, to name black widow spider (*Latrodectus tridicimgutattus)*, basement spider (*Segestria florentina),* hornet (*Vespa orientalis*), green toad (*Bufo viridis*), red Californian earthworm (*Eisenia foetida*), scorpion (*Mesobuthus caucasicus*)
- calculation of energetic characteristics of intermolecular complexes of herbicides and heliocides with active centers of enzymes by means of a quantum-chemical method
- study on role of antimicrobial peptides an PR-proteins in the plant resistance to fungal pathogens. Some cysteine-rich peptides were isolated, their partial-terminal amino acid sequence was determined
- completion of study on molecular mechanisms of toxic actions of gossypol and some terpenoids for the cotton insect pests of *Heliothis* family
- organization of test facility for the pharmaco-kinetic evaluation of biosafety and bioequivalence of medications
- production of recombinant forms of defensin Ns-D2 and insectotoxin *BucaIT*
- generation of "Aflan" medication for treatment of inflammatory diseases and "Kardin" medication for prevention and management of thrombogenesis bases on the regulatory peptides from organs of the mammalians
- generation of "Sedanil" pharmaceutical composition for treatment of mechanically induced wounds and thermal burns upon purulent-septic

complications

- generation of “Biokor”, an immunomodulator recommended for combined treatment of the breast cancer, melanoma, rectal cancer and endometrial cancer
- generation of “Soyaflan”, a medication of immune-rehabilitating type for treatment of the osteoporosis, cardiovascular diseases, breast cancer, endometrial cancer, ovarian cancer and menopause symptoms
- generation of efficient set-up for biodiesel from vegetable oils by the fermentation method
- generation of methods for synthesis of ion-exchange, hydrophobic and affine sorbents for isolation of biologically active agents from the natural objects on the local raw materials
- generation of novel passaged cell culture from the mouse small intestine cancer
- generation of a test system based on the AKAT-cell line for screening of protein-peptide compounds
- generation of the cell culture bank for those cultured at the laboratory, to name Melanoma B-16 (skin cancer), Hela (ovarian cancer), X-63 (myeloma), AKAT (small intestine cancer), C_{127} (breast cancer), U_{937} (human leukemic monocytic lymphoma)

Practicalvalueoftheresults includes

- pharmacokinetic study on bioequivalence of the brand-name medications and generics produced at the pharmaceutical enterprises of Uzbekistan
- production of “Tymoptin”, a highly efficient immune stimulating medication in the form of the lyophilized powder for injections No.5 in the 100μg- medicine bottles(produced at the Institute of Bioorganic Chemistry since 2000 to be put up for sale in the drug stores of Uzbekistan)
- introduction into medical practice of “Apikapsalvin”, a medication for management of inflammations of locomotor system disorders
- introduction into medical practice of “Erytim 0.001% solution” as a stimulant of erythropoiesis for treatment of mild, intermediate and severe anemia (produced at the Institute of Bioorganic Chemistry since 2016 to be put up for sale in the drug stores of Uzbekistan)

Research results

Temporal pharmacopoeil monograph 42 Uz-1470-2014 Capsaicinoids
Temporal pharmacopoeil monograph 42 Uz-1471-2014 “Apikasalvin” liniment
Pharmacopoeil monograph 42 Uz-286-2012 “Tymoptin” substance
Pharmacopoeil monograph 42 Uz-287-2012 “Tymoptin for injections”
Temporal pharmacopoeil monograph 42 Uz-2759-2015 “Erytim” substance
Temporal pharmacopoeil monograph 42 Uz-2760-2015 “Erytim 0.001% solution”
Marketing authorization for “Erytim” substance DV/M 00276/09/15
Marketing authorization for “Erytim 0.001% solution”DV/M 00277/09/15
Marketing authorization for “Biokor” substance No. 0166/06/17

Prospects include

- generation of novel macromolecular therapeutic systems with stability, prolonged effect and improved bioavailability
- production of novel passaged cell cultures and generation of test systems on their bases for wide screening of biologically active agents and study on mechanisms of their actions
- clinical trials of “Aflan” medication and organization of its production at the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences
- clinical trials of “Kardin” medication and organization of its production at the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences
- clinical trials of “Sedanil” medication and organization of its production at the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences
- clinical trials of “Biokor” medication and organization of its production at the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences

Scientific ties

M.I. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences
A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences

Cotton Pathology Department, College Station, USA
Ames Laboratory, Iowa State University, USA
Xynjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences
Shanghai Institute of Materia Medica, Chinese Academy of Sciences
Institut national de la recherche agronomique (French National Institute for Agricultural Research)
Stuttgart University (Germany)
Institute of Technical Biochemistry National Technical University of Athens, School of chemical engineering, Athens, Greece;
Food Materials Science Division, Institute of Food Research, Norwich Research Park, Norwich, Norfolk, Great Britain

International grants

STCU Uz 001 "Investigation of Functionality of Significant Proteins of Cotton Seeds and Development of Highly Effective Technologies of the Production of Provender on the Basis of Cotton Seed Oil Cake" 1999-2000
STCU Uz 75 "Development of biosensors for pesticides determination in environmental in cotton-cultivated countries" 2002-2003
STCU P 115 "Characterization of Phytoalexins from the Malvaceae in Uzbekistan" 2003-2006
M-11"Study on bioactive peptides from some the Central Asian wild species of plants and venomous animals"Russian-Uzbekproject 2005-2006
STCU 3024"Biologically valuable tetrapyrroles of propionibacteria isolated in Uzbekistan" 2005-2007
CRDFUZB2-31009-TA-08"Production of bentonite-based animal feed additives to prevent gossypol's toxicity in the poultry enterprises" 2008-2011
MP-38-2008"Searchfor novel biologically active compounds from the endemics of Uzbekistan" Russian-Uzbek project 2008-2009
INTAS-2000-00681 "Evaluation of the Role of Plant Cell Wall Degrading Enzymes on Yield and Quality of Oil Produced By Cold pressing from oil-producing crops" 2001-2003.
STCU P-119 "Development of Baculovirus-Based Bio-Insecticide Technology in Uzbekistan" 2003-2005.
INTAS Ref. № 05-1000005-7662 "Specific lipase catalyzed production

of biodiesel" 2006 – 2008

M–K–20"Study on effect of polysaccharidase enzymes on the yield and quality of biologically valuable oils from seeds of low oil-yielding plants and isolation of native gossypol rom the cotton seeds" 2008-2009 Uzbek-Korean project

M–K–20-1 "Study on polysaccharidase enzymes from local strains of *Aspergillus terreus* fungus". 2010-2011

Services include

- Determination of amino acid composition (free and bonded amino acids) in biological objects
- Carrying out of the proteomic analysis
- Determination of overall energy value
- Determination of total gossypol and its enantiomers
- Screening of wide range of low molecular weight agents, extracts, compounds of protein-peptide origins based on cell lines cultured at the laboratory
- Development of methods for qualitative and quantitative analysis of substances and pharmaceutical forms to be added to the standard technical documentation
- Pharmacokinetic tests for newly generated medications
- Bioequivalence tests for brand name medications and the generics by pharmacokinetic parameters

Publications

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5. A.M. Asrorov, N. Sattorov, E.M. Sultanova, V.V. Uzbekov, Sh.T. Khodjayev, Sh.I. Salikhov Effects of different classes of insecticides on some secondary metabolites of cotton leaves The Asian and Australasian Journal of Plant Science and Biotechnology, Special Issue 1, 2013, pp. 43-47
6. Vyacheslav V. Uzbekov, Samat A. Talipov, Bakhtiyar T. Ibragimov, Robert D. Stipanovic and Alois A. Bell Lacinilene C 7-methyl ether(Structure Report)// Acta Crystallographica Section E (2013). E**69,** o1392 **[**doi: 10.1107/S1600536813021430**]**
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