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To the 90th Anniversary of the Birth of Academician Yuri Anatolievich Ovchinnikov

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Yuri Anatolievich Ovchinnikov (1934–1988). Photo from the personal archive of T.V. Ovchinnikova.

August 2, 2024, will mark the 90th anniversary of the birth of Academician Yuri Anatolievich Ovchinnikov, the founder and first editor-in-chief of the journal *Biologicheskie Membrany*. Yuri Ovchinnikov was an outstanding Soviet scientist, one of the founders of bioorganic chemistry and biotechnology, the creator of the Russian school of bioorganic chemists and biotechnologists. From 1970 to 1988 he was the permanent director of the Institute of Bioorganic Chemistry, now named after its founders—Academicians M.M. Shemyakin and Yu.A. Ovchinnikov. The scientific-educational and scientific-manufacturing complex created by him in Moscow on Miklukho-Maklaya Street and in Pushchino on Nauka Avenue remains one of the leading scientific centers in the world up to the present time. The high level of personnel training and scientific research, first-class equipment, amazingly beautiful architectural solution of the complex—all this was laid and created thanks to the leadership character and outstanding qualities of Yuri Ovchinnikov's personality.

During his short life, Yuri Ovchinnikov published more than 500 scientific papers, which were highly appreciated by the world scientific community. Membrane biology always was his main priority. Academician V.P. Skulachev in his article *Membranologist in the main role* [1] wrote: "Yuri Ovchinnikov and his team made a number of outstanding discoveries, first of all in the field of biological membrane studies. In fact, Ovchinnikov is the founder of Russian membranology."

The first steps in the study of membrane-active substances were made by Yuri Ovchinnikov in the newly established Institute for Chemistry of Natural Compounds of the USSR Academy of Sciences, where Academician M.M. Shemyakin invited him to study the unusual composition of antibiotics-depsipeptides, containing hydroxy acid residues along with amino acid ones. Yuri Ovchinnikov and his collaborators solved the difficult problems of obtaining optically active N-methylated amino acids, reversible protection of hydroxyl groups in hydroxy acid residues, synthesis of linear depsipeptides and their cyclization. As a result, depsipeptides enniatins A and B, sporidesmolides I–IV, valinomycin, angolide, serratamolide, esperin, and beauvericin were synthesized. These works formed the basis of Yuri Ovchinnikov's habilitational dissertation, which he defended in 1966.

Using the ability of depsipeptides to induce the permeability of lipid membranes to alkali metal ions, Yuri Ovchinnikov and his collaborators carried out a series of studies on the mechanism of action of antibiotics of this class. In particular, they established the spatial structure of valinomycin in solution and showed it to be specifically selective to K^+ ions when complexing with monovalent cations. This explained the K^+ specificity of transmembrane ion transport induced by this ionophore. As a result of these comprehensive studies, molecular mechanisms of selective ion transport across biological membranes mediated by synthetic transporters were established for the first time. In addition, the neologism "ionophore" owes its origin to the studies of antibiotic-depsipeptides. The results of these works were presented in a number of experimental articles and reviews, reports at international forums, and in the monograph *Membrane-active complexones*, published in 1974 in Russian and English in the publishing houses Nauka and Elsevier [2]. This monograph allowed academicians Yu.A. Ovchinnikov

and V.T. Ivanov to win the Lenin Prize award in 1978. To commemorate this exciting period in the study of membrane-active peptides, a sculptural image of the complex of the antibiotic valinomycin with potassium ion was installed in front of the Institute of Bioorganic Chemistry.

A logical extension of the study of depsipeptide ionophores was the study of ion-transporting membrane proteins. These studies necessitated the development of special methodology, since membrane proteins differ fundamentally from globular proteins in a number of their properties (low content in cells, poor water solubility, structural lability, and significant molecular mass). Yuri Ovchinnikov and his team achieved the greatest success in the study of photoreceptor proteins—bacteriorhodopsin from halophilic bacteria and the light receptor rhodopsin from photoreceptor cells of the retina. The development of this work was hampered by the lack of information about the amino acid sequences of the proteins of the visual cascade. Yuri Ovchinnikov's decision to decipher the primary structure of bacteriorhodopsin, as well as rhodopsin and other proteins of the phototransduction cascade in retinal rods was strategic one. Ahead of the team of Nobel Prize winner G. Korana (USA), the laboratory under the leadership of Yuri Ovchinnikov published the complete amino acid sequence of bacteriorhodopsin in 1978 and the complete primary structure of rhodopsin, in 1981. Ovchinnikov and coworkers showed that the structures of both molecules include seven transmembrane alpha-helical domains linked by short extra-membrane peptide loops. Thus, bacteriorhodopsin became the world's first membrane protein, and rhodopsin became the first G-protein-coupled receptor with a fully determined primary structure and membrane topology.

This was followed by work to establish the structure of other proteins of the visual cascade—transducin and cyclic GMP phosphodiesterase. To accomplish these works, Yuri Anatolievich created and headed the interdepartmental research program *Rhodopsin* and mastered a high-class creative team, which included, in addition to the team he headed, the laboratories of Academician M.A. Ostrovsky, Academician V.P. Skulachev, and Professor L.P. Kayushin. The history of the initiation and development of the Rhodopsin Project is detailed in the review by Academician Mikhail Arkadievich Ostrovsky included in this special issue of the journal.

The last brilliant series of works by Yuri Ovchinnikov aimed at exploring the structural and functional properties of membrane proteins included the study of systems of active ion transport across the membrane, such as the Na^+,K^+-ATPase and a number of related adenosine triphosphatases. The oligomeric organization of the functionally active enzyme in the membrane was proved. The complete primary structure of Na^+,K^+-ATPase from pig kidney was determined. The spatial structures of the beta subunit and the complete enzyme were established for the first time, allowing one to propose the first topological model of the enzyme polypeptide chains inside and outside the membrane. This was largely facilitated by the use of an original approach—limited proteolysis of the enzyme directly in membranes.

In the course of joint studies conducted in laboratories under the leadership of Academicians Yu.A. Ovchinnikov and E.D. Sverdlov, the regions of the human genome encoding active transport systems were identified. It was shown that the human genome contains a multigenic family encoding different isoforms of the catalytic subunit of Na^+,K^+-ATPase, as well as subunits of related ion-transporting enzymes. The structure of an extended region of the human genome was determined, allowing one to obtain complete information on the enzyme structure, particularly including a previously unknown form of the catalytic subunit of Na^+,K^+-ATPase. Establishment of the chemical structure and spatial organization of Na^+,K^+-ATPase in combination with elucidation of the basis of genetic regulation of their functional activity opened a qualitatively new page in understanding the mechanisms of active ion transport in human cells.

The pioneering works of Yuri Ovchinnikov, which were aimed at structural and functional studies of membrane-active peptides and their synthesis, at elucidation of the structure of membrane proteins and the relationship between structure and function, as well as at analysis of the molecular mechanisms associated with their physiological activity, are widely known and appreciated throughout the world. The scientific legacy of Academician Yu.A. Ovchinnikov has received well-deserved recognition. He was a laureate of the Lenin and State Prizes of the USSR, the Russian Federation Government Prize in the field of science and technology (posthumously), the A. Karpinsky Prize (Germany). He was an honorary foreign member of 13 academies of sciences and a number of scientific societies, including the German National Academy of Sciences Leopoldina, the European Academy of Sciences, Arts and Humanities (France), the Spanish Royal Academy of Exact, Physical and Natural Sciences, the World Academy of Sciences and Arts (Sweden), the Japanese Biochemical Society, the American Philosophical Society (USA). He was a professor at the Lomonosov Moscow State University, honorary doctor of 8 foreign universities, including the Pierre and Marie Curie University of Paris (Sorbonne, France), Uppsala University (Sweden), and Friedrich Schiller University of Jena (Germany). This is by no means a complete list of scientific awards of Academician Yuri A. Ovchinnikov.

Nobel Prize winner in Chemistry John Ernest Walker (UK) wrote in his memoirs: "His name will long be remembered for the significant contribution made by

him and his colleagues to the study of membranes, a field in which he was a pioneer and a leader" [3].

The Editorial Board of the journal *Biologicheskie Membrany* expresses sincere gratitude to all contributors to the special issue dedicated to the memory of the founder of the journal, Academician Yuri A. Ovchinnikov.

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