Oleg B. Ptitsyn

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Contributor: Alexei V. Finkelstein, Valentina E. Bychkova
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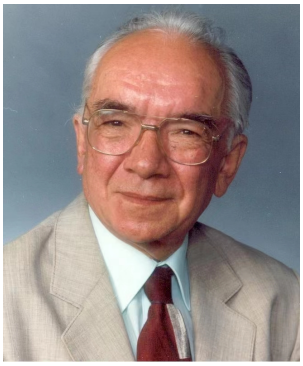
Basic Information



Name: Oleg B. Ptitsyn
(Jul 1929–Mar 1999）

Birth Location:	Leningrad
Titles:	Physicist Biologist Biophysicist Biochemist
Affiliations:	Institute of Protein Research, Russian Academy of Sciences National Cancer Institute National Institutes of Health, USA
Honors:	Pioneer in protein folding studies: Creator of the modern microscopic theory of polymers Founder of the Winter School on Molecular Biology

1. Introduction

Oleg Borisovich Ptitsyn was born in Leningrad, USSR, on July 18, 1929. His mother, Iva Ruvimovna Protas (1904–1976), and father, Boris Vladimirovich Ptitsyn (1903–1965), were chemists. In 1941, after the beginning of the Great Patriotic War, 12-year-old Oleg and his mother, then a scientist for the State Optics Institute, were evacuated to the east, across the Volga River, to the town of Yoshkar-Ola (the capital of the Mari Autonomic Soviet Republic), where Oleg spent his middle school years. In 1946, the family returned to Leningrad. Oleg graduated from high school with honors and became a student of the Physics Department, Leningrad State University. In 1951, after graduating, again with honors, he joined the laboratory of Mikhail Vladimirovich Volkenstein at the Institute of Macromolecular Compounds, the USSR Academy of Sciences. There he began his scientific carrier, ascending from the position of a junior researcher to the head (1964-1967) of the Biopolymer Group doing both theoretical and experimental studies. Oleg received his Ph.D. degree in 1954, having presented a study on "Internal rotation in polymer chains: their dimensions and mechanical properties"; his D. Sc. thesis (1962) was devoted to "Statistical Physics of Macromolecules"; in 1969, he was awarded the title of Professor in Physics and Mathematics.

The 1960s brought a shift in his interests from chemical physics to molecular biology, from synthetic polymers to "living" macromolecules. Together with a group of like-minded people, Oleg Ptitsyn founded the famous Winter School in Molecular Biology, an educational project that brought-up several generations of Russian molecular biologists and initiated the Institute of Protein Research of the USSR Academy of Sciences.

Oleg Ptitsyn contributed much to establishing this Institute in Pushchino, a newly built biological hub upon the Oka River, 100 km South of Moscow. In 1967, he moved from Leningrad to Pushchino and became the deputy director of the Institute of Protein Research; he held this position until 1988. At the same time, he headed the Protein Physics Laboratory where he acted as a scientific advisor till the end of his days (March 22, 1999). Since 1992, he frequently worked in the USA as a visiting research scientist and lecturer for the National Institute of Health (NIH).

From 1967-1991 Oleg Ptitsyn was a lecturer for the Department of Molecular Biophysics, Moscow Institute of Physics and Technology. Also, he lectured for Universities in Paris and Parma, as well as for scientific institutions in many cities of the USSR, Great Britain, France, Germany, Italy, the USA, Belgium, Hungary, Israel, and others.

2. Notable Contributions

His life in science Oleg Ptitsyn, then a university student, began in 1951 at the Institute of Macromolecular Compounds, the USSR Academy of Sciences, under the supervision of Mikhail V. Volkenstein. Two earliest Oleg's projects were devoted to the development of a relaxation theory of glass transitions [1][2] (1954-59) and, co-authored by Tatiana M. Birshtein, the rotational isomeric theory of flexibility of synthetic polymers [3][4] (1952-66).

The latter cycle of works included a statistical theory of macromolecules and the theoretical substantiation of the effect of high elasticity of rubbers, published as the monograph "Conformations of macromolecules" (Russian edition - 1964 [3]; American edition - 1966 [4]). This made him a luminary whose book till now ranks classical in polymer science and is cited in all textbooks on polymers.

The Institute of Protein Research purposed to study protein biosynthesis and self-organization of a protein chain into the native functioning structure was established in 1967 and headed by three outstanding scientists - A.S. Spirin (director), O.B. Ptitsyn (deputy director), and Yu.V. Mitin (deputy director).

A combination of theory and experiment was the distinctive feature of the Laboratory of Protein Physics headed by Oleg Ptitsyn. With only six deciphered protein spatial structures available, Ptitsyn initiated studies of the principles of protein spatial organization and the ways of its achievement. This was the beginning of a novel trend in science - protein physics. A statistical analysis of protein secondary structures, their folding, and amino acid composition of alpha-helices and beta-sheets led Ptitsyn to the conclusions still valid to date, when hundreds of thousands of protein structures have been deciphered.

Specifically, Oleg B. Ptitsyn and his student, Alexei V. Finkelstein proposed a method of prediction of alpha- and beta-structural regions in globular proteins [5] that proved to be efficient and "won" the first international competition on prediction of protein secondary structures [6], and later laid a basis for the theory of the protein secondary structure resulting in the first successful prediction of the protein tertiary structure [7][8].

Back in 1973, Oleg B. Ptitsyn proposed a stepwise model of self-organization of protein molecules [9] implying the existence of intermediate states. It was experimentally confirmed by his team in 1981, when they discovered an intermediate state of the protein chain that was no longer unfolded and loose, but not yet solid and native [10]. The properties of this intermediate, at present widely known as a molten globule, were experimentally studied by O.B. Ptitsyn, D.A. Dolgikh, V.E. Bychkova, G.V. Semisotnov, R.I. Gilmanshin, and their students, and theoretically substantiated by E.I. Shakhnovich and A.V. Finkelstein [11].

Further experimental studies of the intermediate states allowed a hypothesis about the functional role of the molten globule state in the cell [12]. According to this hypothesis, a protein synthesized on the ribosome is in the molten globule state which is recognized by chaperones transporting it to the membrane. This hypothesis received a complete experimental confirmation by several studies, including those carried out in the Laboratory of Protein Physics, and formed the basis of a new direction in cytology.

Ptitsyn and Bychkova experimentally showed that proteins carrying large hydrophobic ligands release them when acquiring the molten globule state near the membrane, that is, the molten globule can be the natural state of a protein near the membrane. In 1995, Ptitsyn and Bychkova suggested that some human genetic diseases caused by point mutations arise due to a delay in protein folding at the molten globule stage. This hypothesis also found its experimental confirmation.

In the 1990s, the folding kinetics of small proteins folding in one step, without visible intermediate states, was a hot topic. Oleg Ptitsyn began studies of transition states, that is, barriers separating the native (folded) and unfolded state of the chain in such proteins. He showed that they might be clusters of the most conserved residues, likely under a strict control of evolution, ensuring rapid and error-free folding of proteins. Together with E.I. Shakhnovich and V.I. Abkevich, Ptitsyn theoretically studied the folding pathways of such proteins, beginning with a detailed comparison of the primary structures of members of two widespread families - cytochromes c and globins. A small number of non-functional conserved residues revealed in both families were suggested to form the folding core necessary for the rapid and correct folding of proteins [13]. The experimental verification of this assumption is not completed yet.

Further development of the theory of protein self-organization (1967–1995) showed that proteins have a limited set of typical packings of their secondary structure elements into the tertiary structure, the so-called folding patterns. This formed the basis for all modern approaches both to the classification of protein structures and prediction of the spatial structure of proteins from their amino acid sequences.

Following this direction, A.G. Murzin, Ptitsyn's and Finkelstein's ex-student, made, together with C. Chothia (at MRC LMB, Cambridge) a unique classification of protein structures, the famous SCOP; the same time, A.V. Efimov, an alumni of the Ptitsyn Laboratory of Protein Physics, developed the concept of "structural trees" formed by evolving protein structures, and O.B. Ptitsyn concluded that the compactness and general shape of a protein is determined by the general physical laws of self-organization of polypeptide chains, while the organization of the active site is a result of "editing" by biological evolution.

This means that in some respects, a protein can be considered as an "edited" random copolymer.

3. Implications for Protein Design

All these findings underlay the occurrence of a new direction — the design of *de novo* proteins. Using the theories of secondary structures and folding patterns developed in his laboratory, O.B. Ptitsyn, together with A.V. Finkelstein, designed an artificial protein "albebetin" with a predetermined spatial structure.

Albebetin was synthesized by A.N. Fedorov, D.A. Dolgikh and M.P. Kirpichnikov [14]. The result was astounding – the *de novo* protein had a rather stable and compact structure of the molten globule type and subsequently displayed various physiological activities.

For his work "Principles of the structural organization of proteins and their application to the design of new protein molecules: theory and experiment", Oleg B. Ptitsyn was posthumous awarded (1999) the Russian Federation State Prize in Science and Technology (together with A.V. Finkelstein, D.A. Dolgikh and M.P. Kirpichnikov). But he never came to know he was awarded...

4. Honors, Awards, Recognition

According to Oleg Ptitsyn himself, over the years of his scientific activity he solved three major scientific problems: 1) He developed a statistical theory of macromolecules which allowed predicting the flexibility and other physical properties of synthetic polymers from their chemical structure; 2) He showed that the general principles of molecular physics strictly limit the number of possible polypeptide chain folds in globular proteins, and proposed a general algorithm for choosing a chain fold from this limited set for each given amino acid sequence; 3) He experimentally demonstrated the mechanism of protein chain folding into a native (functioning) spatial structure, discovered a novel physical state of the protein molecule — the "molten globule" — and showed that this state is the universal kinetic intermediate on the pathway of folding of most globular proteins.

Thus, Oleg Ptitsyn founded a novel trend in science - protein physics, an important component of modern molecular biology. In his field, his team held a leading position in the world.

Ptitsyn, the author of more than three hundred papers, is one of the most cited Russian scientists. He was a teacher to hundreds and a mentor to dozens. He supervised 31 PhD and 10 D.Sc. theses. His contribution to growing a new generation of scientists, now working both in Russia and abroad, cannot be overestimated.

Oleg Ptitsyn acted as a prominent scientific advisor both in Russia and other countries. He was a member of the International Commission on Molecular and Subcellular Biophysics of the International Union of Pure and Applied Biophysics; a Deputy Chairman of the Scientific Council of the Russian Academy of Sciences (RAS) on the theory of polymers and biopolymers; a member of the Scientific Council, RAS, on protein engineering, and a member of the Scientific Council, RAS, on molecular biology and genetics.

He was elected an Associate Editor of the international scientific journal "Protein Engineering", worked for the editorial or supervisory boards of "Biopolymers", "FEBS Letters", "Biophysical Chemistry", "Protein Chemistry", "Folding & Design", "Structure with Folding and Design". Many times, he lectured or chaired scientific meetings, including International Biophysics (1972, 1978) and Biochemistry (1988) Congresses, and Congresses of the Federation of European Biochemical Societies (1975, 1978, 1984, 1987, 1989, 1990, 1993). He participated in the "Conference of Four" of the Nobel Committee (1981), etc.

Ptitsyn's achievements in science are recognized internationally. He is rightfully considered the founder and one of the leaders in research on the protein folding, one of the most important fields of molecular biology. He was awarded the Russian Federation State Prize and the Order of the Badge of Honor; he was a Foreign Member of Trinity College, the New York Academy of Sciences, and the European Academy of Sciences (Academia Europaea), a scientific community which included such world-famous European scientists as J. Kendrew, M. Perutz, A. Klug, and others. Only 15 outstanding Russian scientists were elected members of this Academy at that time, including V.I. Arnold, V.G. Ginzburg, V.I. Gol'danskii, G.P. Georgiev, A.D. Mirzabekov, and A.S. Spirin.

Oleg Ptitsyn was one of the most versatile and accomplished persons, possessing brilliant leadership skills. The laboratory he established and headed years ago keeps working and developing the direction in science he founded — protein physics [15][16][17].

We want to conclude this biographical sketch quoting the opinions of Oleg Ptitsyn by several eminent scientists (adapted from [18]):

… Oleg's exclusivity was that he was bright and lively - in everything related to his intellectual and practical activities. (*A.S. Spirin, Member of the Russian Academy of Sciences*).

... [He] pioneered in the protein folding studies ... revolutionized the field. (*R.I. Baldwin, Member of the National Academy of Sciences, USA*).

... one of those rare scientists who ... advanced new but unfashionable ideas... (*C.M. Dobson, Fellow of the Royal Society, UK*).

... Oleg Ptitsyn had a major influence on our thinking about protein structure, folding and functioning. (*T. Blundell, Fellow of the Royal Society, UK*)

... Ptitsyn is one of the most distinguished Russian physical chemists working on proteins. He has brought scientific and imaginative insight to the extremely difficult protein folding problem. He has been recognized internationally as one of the most original, productive and outstanding scientists in the field... (*Max F, Perutz, the Nobel Prize Winner*).

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