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PROTEIN MYSTERIOUS STRUCTURE AND NUMEROUS FUNCTIONS DEPARTMENT

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This overview is dedicated to the history of the Department of Protein Structure and Function at the Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine. It outlines the department's main scientific objectives and highlights its key achievements. In particular, it describes research related to patient blood management, fundamental studies of fibrinogen structure and function, the development of next-generation antithrombotic prototypes, as well as the creation and clinical testing of diagnostic assays. Special attention is given to inventions and studies aimed at addressing pressing social issues, including post-traumatic stress disorder and the consequences of COVID-19. The importance of maintaining continuity in hemostasis research is emphasized, as it enables the generation of unique scientific results and their implementation in medical practice.

K e y w o r d s: protein, enzyme, fibrinogen, fibrin polymerization, blood coagulation, anti-bleeding agents, patient blood management.

The history of the Department of Protein Structure and Function began in 1944, when Volodymyr Belitser arrived in postwar Kyiv at the invitation of the Institute of Biochemistry's director, Oleksandr Palladin. The future academician established the Laboratory of Enzymes, which would go on to become one of the leading centers of hemostasis research in Eastern Europe.

Volodymyr Belitser was already a well-known scientist at that time, with discoveries in the field of cellular respiration [1]. In particular, oxidative phosphorylation was discovered independently by Volodymyr Belitser and Herman Kalckar [2], a fact mentioned by Peter Mitchell in his Nobel lecture [3].

The initial scientific objectives of the department under the leadership of Volodymyr Belitser focused on the functional characteristics of enzymes. These studies made it possible, already in the early 1950s, to disprove the then-widespread concept that the prosthetic group of a molecule was the sole carrier of enzyme specificity. Instead, it was demonstrated that catalytic activity and specificity are determined by the protein, its unique and relatively stable structure.

Another important line of research pursued by the department during those years was the study of denaturation as a process of protein unfolding, accompanied by the release of numerous radicals that, in the native molecule, are tightly grouped within an ordered structure [4]. Theoretical findings enabled the development of methods for producing the blood substitute BK-8, in which a precisely defined

A portrait of Volodymyr Belitser, the founder and visionary of the Department of Protein Structure and Function, created in 1989 by Borys Roitrub, a researcher at the O. O. Bohomolets Institute of Physiology

denaturation of bovine blood components ensured the necessary reduction in the antigenicity of the transfusion agent.

Studies devoted to blood proteases led to the discovery of specific antiproteases, including the identification of α2-macroglobulin. However, the most fruitful line of research proved to be the investigation of the structure and functions of fibrinogen and the polymerization of fibrin. These studies not only laid the foundation for hemostasiology in Eastern Europe but also shaped the modern understanding of the molecular mechanisms governing the blood coagulation system.

In 1963, the Laboratory of Enzymes was divided into the Laboratory of Protein Structure and Function (renamed the Department in 1966) and the Laboratory of Enzymes.

One of the most important achievements of the Department in the 1960s was the development of a method for preparing acidic fibrin monomer and fibrinogen from blood plasma [5, 6]. Both methods were developed by Tamara Varetska and used in the Department for the preparation of fibrinogen and fibrin monomer, which were widely used in subsequent Department's study on the fibrin polymerization process.

The department's key research areas during those years included the study of the structure of the fibrinogen molecule, investigation of the molecular mechanisms of fibrin polymerization, and the development of molecular diagnostic methods for assessing the risk of intravascular thrombosis. Notably, experiments on the thermal unfolding of the fibrinogen molecule led to the most detailed model of its structure at the time and substantiated its domain organization. Methodological approaches were developed to obtain stable proteolytic products of fibrinogen and fibrin, which were subsequently used to explore the functioning of active sites responsible for fibrin polymerization [7]. The proposed approaches for detecting fibrin degradation products and soluble fibrin-monomer complexes as markers of intravascular thrombosis were introduced into diagnostic practice.

In the 1970s, Volodymyr Belitser initiated research on the structural organization of the fibrinogen molecule. At that time, the Department relied solely on biochemical techniques, which were not well suited for structural studies. To overcome this limitation, he established collaborations with Prof. Valentyn Zyma (Head of the Department of Biophysics at Kyiv State University) and Prof. Peter Privalov (who later became a distinguished professor at Johns Hopkins University, Baltimore, USA), both of whom employed biophysical methods to study protein structure.

The collaboration with Valentyn Zyma began in 1976 and led to characterization of the thermolabile and thermostable regions in the fibrinogen molecule by fluorescence spectroscopy. A subsequent collaboration with Peter Privalov, which started in 1979, resulted in the publication of the first detailed model of the domain structure of the fibrinogen molecule, which was then refined and published in Journal of Molecular Biology in 1982 [8]. These collaborations broadened the Department's research scope and increased the Department's visibility on the international level.

Since 1987, the department was headed by Leonid Medved, followed by Yevhen Makogonenko from 1998 to 2001, and then by Georgii Volkov until 2007. A key role during this period was played by Tetiana Platonova, whose efforts ensured the continuity of the department's work from 2001 to 2003.

In 1989, an international collaboration was established between the Department of Protein Structure and Function and Dr. Ken Ingham, Head of the Department of Biochemistry at the Jerom Holland Laboratory of the American Red Cross. This collaboration between the two departments was supported by several grants including those for studying the platelet receptor GPIIbIIIa.

Another important collaboration of the Department was established in 1993 with the Oxford Bioresearch Laboratory headed by Dr. Stewart Cederholm-Williams. His laboratory was developing a technology for producing autologous fibrin sealant using acidic fibrin monomer. Sharing common interests with the Department in the field of blood coagulation and fibrinolysis, Dr. Cederholm-Williams formalized this collaboration by establishing Oxford Bioresearch (Kyiv) in 1995. As part of this collaboration, several scientific projects were carried out by the Department's scientists at the Institute of Biochemistry. These projects were financially supported by Dr. Cederholm-Williams, who also invited several scientists from the Department to visit his laboratory in Oxford to work on some of these projects and learn new research approaches.

Dr. Cederholm-Williams also organized and financially supported the International Conference on Fibrinogen and Fibrinolysis in Yalta (Ukraine) in

Prominent researchers of fibrinogen – John F. Marshall, John Weisel, and Leonid Medved at the conference on fibrinogen and fibrinolysis research in Yalta (Ukraine), 1995

1995 (September 22-28). He invited scientists from the Department, as well as several prominent fibrinogen researchers from the West, including John Weisel, Willem Nieuwenhuizen, Patrick Gaffney, and Garry Matsueda. In recognition of his contribution the development of Ukrainian biomedical research, Dr. Cederholm-Williams was elected a foreign member of the Ukrainian National Academy of Sciences in 1996. Thus, as with the collaboration with the J. Holland Laboratory mentioned above, the collaboration with the Oxford Bioresearch Laboratory provided crucial financial support to the Department's scientists and their research during one of the most challenging periods for Ukrainian science.

The study of snake venom enzymes in the Department, initiated by Dr. Tatiana Ugarova in the 1980s [9], was significantly expanded in the 1990s, resulting in fundamental research on the structure and function of fibrin, coagulation factors, and platelets. Some of the enzymes purified and characterized in the Department formed the basis for the development of laboratory diagnostic methods. In particular, thrombin-like enzymes from the venom of Central Asian snakes of the Agkistrodon genus were used to develop a kit for measuring clotting time in heparinized plasma. This kit, marketed under the trade name "Ancistron-H," was later commercialized. Another enzyme, Ecamulin, a prothrombin activator from the venom of *Echis multisquamatis*, was also produced in the Department. This enzyme was later used in the development of unique anti-bleeding agents.

Under a supervision of Tetiana Platonova, a phenomenon of non-enzymatic activation of prothrombin by fibrin hydrolysis products was discovered. Research into pathological conditions associated with intravascular thrombosis led to the creation of methodological guidelines and numerous publications in collaboration with physicians from leading clinical centers across Ukraine.

In parallel, within the Department of Molecular Immunology, a research group led by Eduard Lugovskoi (a student of Volodymyr Belitser) began studying the structure and function of fibrinogen under the supervision of Serhiy Komisarenko. The researchers succeeded in producing a series of monoclonal antibodies against fibrinogen and its derivatives, including the development of immunodiagnostic tools for the quantitative detection of soluble fibrin and D-dimer. They also obtained numerous fundamental results regarding the functioning of fibrin polymerization centers and the involvement of its coiled-coil region in the self-assembly process.

In 2007, the hybridoma technology group was reintegrated into the Department of Protein Structure and Function, and its leader, Eduard Lugovskoi, became the head of the department. Since 2019 and as of 2025, the department has been headed by Volodymyr Chernyshenko.

A key feature of the Department of Protein Structure and Function is the continuity of research into the blood coagulation system and its individual proteins – research initiated by Volodymyr Belitser. The scientific school founded by academician Belitser remains one of the leading schools in the field and continues to shape the department's identity. His students (Leonid Medved, Tetiana Platonova, Tatiana Ugarova, and Eduard Lugovskoi) formed a new generation of scientists, who in turn have trained a third generation of researchers continuing Belitser's scientific legacy.

Patient blood management

In 1946, immediately after the end of the devastating Second World War, efforts to develop a blood substitute based on bovine blood were initiated under the leadership of Volodymyr Belitser. Fundamental studies on the denaturation of proteins led to the development of a method for reducing the antigenicity of heterologous blood proteins. The blood substitute BK-8, produced using the newly developed technology at the Vinnytsia Meat Processing Plant, was successfully tested at the Kyiv Institute of Blood Transfusion and, in 1955, was introduced into clinical practice. Numerous clinical trial data testify to the widespread use of this product in transfusion medicine [10].

Although the research was brilliantly completed and a cutting-edge product was developed at the time, further progress in this area, both within the department and globally, took a different course. Today, blood transfusion as a primary strategy has largely been replaced by the concept of Patient Blood Management (PBM). PBM is an evidence-based, multidisciplinary approach aimed at optimizing the use of a patient's own blood during treatment. It involves minimizing the need for transfusions, preventing anemia, reducing blood loss, and improving overall treatment outcomes.

In the late 1990s, the department undertook efforts to develop technology for producing factor VIIIa preparations for replacement therapy in patients with hemophilia. A patent published in 2016, obtained by former staff members of the Department of Protein Structure and Function, failed to acknowledge the contribution of the Institute of Biochemistry [11].

In 2014, seventy years after Volodymyr Belitser began his work on blood substitutes, the issue of managing blood loss on the battlefield once again became critically relevant due to Russia's invasion of Ukraine. This time, researchers focused their efforts on developing hemostatic agents based on carbon fiber materials.

As the academic secretary of the Department of Biochemistry, Physiology, and Molecular Biology of the National Academy of Sciences of Ukraine, Serhiy Komisarenko assembled a team of scientists from the Department of Protein Structure and Function at the Palladin Institute of Biochemistry, the Bogomoletz Institute of Physiology, and the Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology. A pivotal role in the invention was played by a blood clotting activator derived from snake venom, which had been developed at the Department of Protein Structure and Function.

Extensive preclinical and subsequent clinical trials demonstrated that Carbohemostate, created from the clotting activator and carbon-based material, outperformed all available analogues in head-to-head comparison in bleeding control.

Importantly, the very concept of activating prothrombin to achieve immediate hemostasis was the outcome of decades of fundamental research on the molecular mechanisms of the blood coagulation system conducted within the department.

Molecular mechanisms of fibrin polymerization

Volodymyr Belitser was one of the first in the world to provide evidence that the process of fibrin polymerization is not associated with denaturation, but rather is a highly ordered process governed by electrostatic and hydrogen bonding interactions.

Refined protein fractionation techniques allowed researchers to develop methods for isolating individual fibrinogen fragments that preserved the

Volodymyr Chernyshenko presents the department's developments at the O. O. Bohomolets National Medical University during the annual scientific-practical conference "Integrative Medicine: Achievements and Prospects." Among the attendees is the Commander of the Medical Forces of the Armed Forces of Ukraine — Major General of the Medical Service Anatolii Kazmirchuk

Staff members of the Department of Protein Structure and Function at the 25th International Annual Conference on Patient Blood Management, Haemostasis and Thrombosis (NATA) in Munich, Germany, April 24–26, 2025: Daria Korolova, Anastasiia Pavlenko, Kateryna Baidakova

active sites of the intact molecule. These fragments became valuable tools for studying the function of fibrin polymerization centers.

Subsequent research by Leonid Medved led to the identification of γ- and β-modules within the D regions, as well as the identification of the connector and domain portions of the αC regions [12].

In the 1980s, a series of publications presented data on the specifics of complex formation between desAB fibrin and the D fragment as well as the D-dimer. Experiments conducted under the guidance of Volodymyr Belitser demonstrated that the composition of complexes between desAB fibrin and the D fragment approaches a ratio of 1:3 – that is, one fibrin monomer molecule can bind three D monomers. In contrast, the D-dimer forms an equimolar complex with desAB fibrin.

It was also shown for the first time that desAB fibrin molecules form an equimolar complex consisting of one molecule of the D fragment and one molecule of the D-dimer, in which three D units correspond to one fibrin molecule [13].

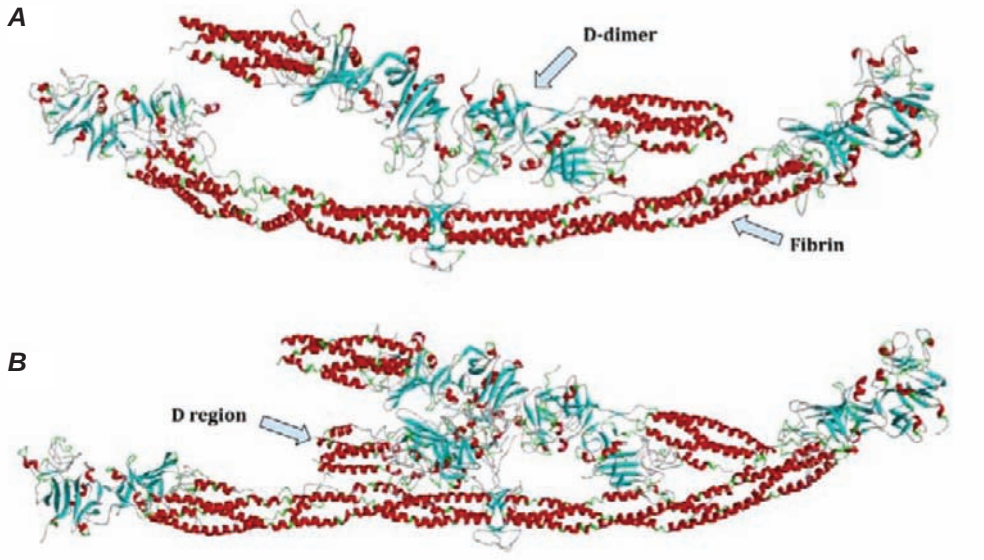
This finding came as a surprise to scientists because, according to the classical model, the DDE triad contains four intermolecular binding sites. It was expected that the stable complex of desAB fibrin with the D-dimer would form through the binding of one fibrin molecule with two D units of the D-dimer via the complementary pairs of sites “A”-knobs, “a”-holes and “B”-knobs and “b”-holes.

In that case, the complex of fibrin with the D-dimer and D-monomer would likely involve not three but four D units [14]. The authors proposed a model suggesting an asymmetric arrangement of one of the fibrin “B”-knob, which allows the attachment of a third D unit in the triple complex desAB:D:DD by means of the fibrin molecule “fitting” to the ligand molecules [15-17].

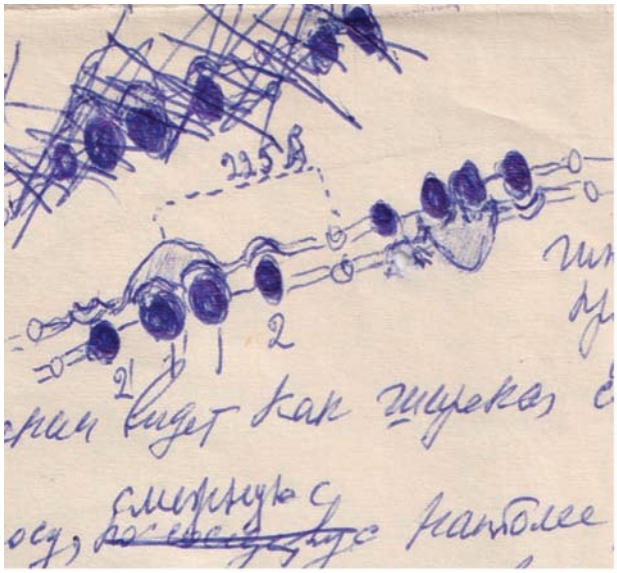
Thirty years after Volodymyr Belitser first proposed the idea of an asymmetric arrangement of one of the “B”-knobs, the combination of *in vitro* experimental approaches with in silico technologies made it possible to demonstrate the involvement of “B”-knobs from molecules within a single protofibril in binding the D regions of molecules from neighboring protofibrils.

Coarse-grained molecular dynamics simulations of the complex formed by desAB fibrin and the D-dimer revealed a shift of the D-dimer toward the coiled-coil region of one half of the fibrin molecule, freeing up space for the attachment of an additional D monomer [18].

Thus, under the leadership of Volodymyr Belither’s scholars, the research cycle was completed, and a model of protofibril branching was proposed. In this model, the polymerization center “b”-hole at



*Snapshots from coarse-grained molecular dynamics simulations. [**A**] complex of fibrin desAB with D-dimer; [**B**] complex of fibrin desAB with D-dimer and D fragment. Coarse-grained structures were firstly converted to all-atom representation using initram.sh script with the minor altering of parameters. During molecular dynamics, D-dimer leans to one half of the fibrin molecule that allows the D fragment to bind to the 'B'-knob on the other half [18]*



Page of a workbook with handwriting and drawing of Prof. Volodymyr Belitser who proposed the asymmetric position of one of B-knobs as the molecular basis for differences of complex formation between fibrin desAB and D-dimer vs D fragment. Arrows indicate B-knobs that are free within the DD-E complex

the sticky end of one protofibril connects with one of the "B"-knobs that remains accessible in the D–E–D complex of the formed protofibril.

Developing of antithrombotic molecules

Intravascular blood coagulation is the cause of more than one-third of deaths related to cardiovascular diseases, various types of trauma and surgical operations, sepsis, burns, oncological diseases, disorders associated with hemostatic pathology, etc. [19, 20]. A particularly interesting area in the development of antithrombotic drugs is the search for methods to directly inhibit the final stage of thrombus formation – fibrin polymerization [21, 22].

Research into the lateral association of fibrin protofibrils prompted the scientists of the Department of Protein Structure and Function to focus on the molecule's supercoiled region, particularly its hinge segment corresponding to the sequences α99-110, β130-155, and γ70-100.

Under the leadership of Eduard Lugovskoi, a monoclonal antibody named FnI-3C was developed. This antibody binds with high affinity to the desAB fibrin molecule and recognizes an epitope within the Bβ118-134 fragment [23]. It was shown that FnI-3C inhibited the lateral association of protofibrils, thereby confirming the important role of the coiled-coil region in fibrin polymerization. Further studies using synthetic peptides that mimic the amino acid sequences of fibrin(ogen) segments Bβ109-126 (QTSSSSQFVMVLLKDLWQ), Bβ121-138 (LKDLWQKRQKQVKDNENV), and its scrambled variant (DKWVQVELKKQKRNDLNQ) demonstrated that the polymerization of fibrin simultaneously involves fragments from each of the three chains of the supercoiled region: Aα, Bβ, and γ [24, 25].

The creation of a spatial model made it possible to explain precisely how these peptides inhibit fibrin formation, as well as to visualize the mechanism of interaction between the supercoiled regions of the fibrin molecule – a mechanism previously proposed by Eduard Lugovskoi [26].

This result is significant from a practical standpoint as well: the inhibition of fibrin polymerization by peptides mimicking the sequences of fibrin fragments γ69-77, Bβ125-135, and Aα91-103 opens up promising prospects for developing an antithrombotic drug based on these peptides – a line of research that has already begun [27, 28].

A new calix[4]arene compound was characterized in the Department of Protein Structure and Function, developed under the leadership of Vitaliy Kalchenko at the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine – calix[4]arene C-145. This compound interacts directly with the fibrin "A"-knobs through its hydrophobic cavity.

As a result, calix[4]arene C-145 directly inhibits the formation of fibrin protofibrils, thereby preventing the assembly of polymeric fibrin [29]. Its effectiveness has been demonstrated both *in vitro* and *in vivo*.

Calix[4]arene C-145 has the potential to become the first antithrombotic agent with a unique mechanism of action, matching or exceeding the effectiveness of previous-generation drugs, while also possessing vasoprotective properties in addition to its antithrombotic effects [30, 31].

The physiological effects of the calix[4]arene C-145 molecule, demonstrated under conditions of administration to laboratory animals, are particularly significant because they are evidently linked to a single well-established mechanism of action – inhibition of fibrin polymerization.

If inflammation (detected by changes in protein C levels) and vascular wall damage (observed

histologically) under pathological conditions can be reduced solely by preventing intravascular formation of polymeric fibrin, then we can truly appreciate the exceptional importance of the hemostatic system and fibrin polymerization in the physiology and pathophysiology of blood circulation [32].

Thus, the fundamental research of the molecular mechanisms of fibrin polymerization, initiated over half a century ago in the Department of Protein Structure and Function, continues to yield practical results. Understanding the key patterns of fibrin polymerization allows the identification of critical checkpoints in this process (such as interactions between polymerization centers and lateral association of protofibrils), whose inhibition can prevent the formation of polymeric fibrin – the core of a thrombus.

Diagnostics of thrombosis

Numerous studies conducted in collaboration with physicians from leading institutions in Kyiv have helped to shape the main task of hemostasis study: thrombosis must be prevented rather than treated after it occurs. Therefore, key efforts of the department's staff were focused on developing diagnostic approaches for the early detection of intravascular thrombosis risk.

To this end, under the leadership of Volodymyr Belitser, a method for detecting soluble fibrin-monomer complexes was developed, also known as the "phosphate buffer method" [33]. With a keen understanding of the nature of pathological intravascular thrombosis, Volodymyr Belitser selected complexes of desA fibrin with fibrinogen (soluble fibrin) as a key marker of intravascular thrombin generation and, consequently, the risk of thrombosis development [34]. This method still impresses today with its elegant simplicity and informativeness, and thanks to its low cost, it continues to be used in clinical settings.

The development of selective antibodies under the leadership of Serhiy Komisarenko opened up new prospects for creating test systems to quantitatively detect markers of coagulation system disorders. In particular, Eduard Lugovskoi's group developed one of the world's first test systems for detecting D-dimer [35]. The monoclonal antibody I-3C, which is specific exclusively to fibrin, but not to fibrinogen or its degradation products, formed the basis of a unique test system for detecting soluble fibrin. This test system was extensively validated in clinical institutions across Ukraine [36, 37].

Leaders of the Department of Protein Structure and Function discussing the pilot batch of test systems for quantitative determination of soluble fibrin: Tetiana Platonova, Eduard Lugovskoi, Yevhen Makogonenko

Under the leadership of Tetiana Platonova and Yevhen Makogonenko, a comprehensive analysis of the hemostatic system in thousands of patients with various pathological conditions identified thrombin generation as a key event in the pathogenesis of intravascular thrombosis.

As an important diagnostic approach, the measurement of protein C levels was proposed, alongside the development and validation of a quantitative method for detecting prethrombin-1.

Prethrombin-1 is an autolysis product of prothrombin by thrombin, formed during pathological activation of the coagulation system, and indicates excessive thrombin production in the bloodstream. Therefore, the detection of prethrombin-1 can serve as an informative marker of the risk of intravascular thrombosis.

The developed method for determining prethrombin-1 concentration is based on the use of a prothrombin activator derived from snake venom. Its creation and implementation would not have been possible without prior expertise in studying venom components capable of acting on human hemostasis, illustrating yet another example of the integration of fundamental and applied research.

Response to the challenges of the times

With the onset of the SARS-CoV-2 pandemic, there arose an urgent need for an in-depth study of the effects of this disease on the hemostatic system, as one of the main complications of COVID-19 proved to be thrombophilia. Importantly, long-term

research, the development of diagnostic algorithms, and the creation of diagnostic approaches prior to the pandemic allowed these studies to begin without delay.

Analysis of the coagulation system status in individuals who had recovered from COVID-19 revealed significant accumulation of thrombophilia markers in the blood plasma. Monitoring the hemostatic system not only provides information about the risk of intravascular thrombosis but also enables prediction of the rehabilitation course – an aspect of particular importance amid the ongoing pandemic [38].

Another significant social challenge addressed by the Department of Protein Structure and Function has been the issue of post-traumatic stress disorder (PTSD), which many Ukrainians have faced since the full-scale invasion of Ukraine by Russia. Numerous studies indicate that, in the presence of other risk factors, stress can trigger a threat of intravascular thrombosis.

The stress response defines a prothrombotic state characterized by autonomic and neuroendocrine dysfunction, platelet activation, impaired regulation of coagulation and fibrinolysis, endothelial dysfunction, and inflammation.

A model of the "perfect storm" was proposed, in which the risk of stress-induced thrombosis manifests only through the combined action of pathophysiological and psychosocial factors, each of which acts in tandem with the others [39]. Taking this interaction into account can aid in developing preventive approaches that improve patient treatment and help avoid the development of intravascular thrombosis.

Currently, research in this area continues under the leadership of Serhiy Komisarenko, in collaboration with the I. Ya. Horbachevsky Ternopil National Medical University (headed by Mykhailo Korda), the Regional Cooperation for Health, Science and Technology Association (under the leadership of Sandor Vari), and other divisions of Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine.

Conclusions. The Department of Protein Structure and Function represents a scientific school dedicated to studying the molecular mechanisms of the hemostatic system, founded by Volodymyr Belitser and further developed by his disciples. The continuous hemostasis research conducted at the Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine ensures not only the preservation of scientific continuity but also the effective advancement of research directions, where methodological innovations enable new scientific discoveries, and a deep understanding of molecular mechanisms facilitates their practical implementation.

Laureates of the O. O. Bohomolets Prize for outstanding scientific work in the field of physiology and theoretical medicine – for the project "Development and Clinical Trials of Innovative Hemostatic Agents": Volodymyr Chernyshenko, Daria Korolova, Serhii Komisarenko

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

ВІДДІЛ ТАЄМНИЧОЇ СТРУКТУРИ І ЧИСЛЕННИХ ФУНКЦІЙ БІЛКА

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Розвідку присвячено історії відділу структури та функції білка Інституту біохімії ім. О. В. Палладіна НАН України. Окреслено основні наукові задачі та висвітлено здобутки. Зокрема описано роботи відділу щодо керування кровопостачанням пацієнта (PBM), фундаментальних досліджень структури та функції фібриногену, створення прототипів антитромботичних засобів нового покоління, розроб-

ки діагностичних тестів та їхній апробації в медичній практиці. Окремо зосереджено увагу на винаходах та дослідженнях, спрямованих на вирішення нагальних соціальних проблем. Описано пошук шляхів запобігання наслідкам посттравматичного синдрому та коронавірусної хвороби. Зроблено акцент на важливості збереження безперервності наукових досліджень гемостазу, що забезпечує отримання унікальних наукових результатів та їх впровадження у практику.

Ключові слова: протеїни, ензими, фібриноген, полімеризація фібрину, зсідання крові, кровоспинні засоби, гемотрансфузія.

References

1. Belitser VA, Tsybakova ET. On the mechanism of phosphorylation associated with respiration. *Biochimia*. 1939; 4(5): 516-535.
2. Prebble JN. The discovery of oxidative phosphorylation: a conceptual off-shoot from the study of glycolysis. *Stud Hist Philos Biol Biomed Sci*. 2010; 41(3): 253-262.
3. Mitchell P. Chemiosmotic Coupling: 1966. In Les Prix Nobel (The Nobel Prizes 1978), Editor Wilhelm Odelberg, [Nobel Foundation], Stockholm, 1979, p. 1-36.
4. Belitser VA, Tsyperovich AS. Intermittency of denaturing conversion of protein molecule. *Dokl Akad Nauk SSSR*. 1952; 83(2): 257-259.
5. Belitser VA, Varetskaja TV, Malneva GV. Fibrinogen-fibrin interaction. *Biochim Biophys Acta*. 1968; 154(2): 367-375.
6. Varetskaya TV. Microheterogeneity of fibrinogen. Cryofibrinogen. *Ukr Biokhim Zhurn*. 1960; 32(1): 13-24.
7. Belitser VA, Varetska TV, Tsinkalovska SN. Estimation of the specific inhibitors of fibrin polymerization. Inhibitory units. *Thromb. Res.* 1973; 3: 251-264.
8. Privalov PL, Medved LV. Domains in the fibrinogen molecule. *J Mol Biol.* 1982; 159(4): 665-683.
9. Ugarova TP, Medved LV, Solovjov DA, Zolotukhin SV. USSR Patent No.: 1476649 titled "A method for preparation of clotting enzymes from the snake venom of Agkistrodon genus". Registered 01/03/1989.
10. Belitser VA. (Ed.) Protein Blood Substitute No. 8 (BK-8). Kyiv: Publishing House of the Academy of Sciences of the Ukrainian SSR, 1957. 242 p.
11. Volkov GL, Havryliuk SP, Krasnobryzha YeM, Havryliuk OS, Zhukova AI. Method for isolating a complex of factor VIII and von Willebrand factor from other plasma proteins using size-exclusion liquid chromatography. Patent of Ukraine No. 110920; published 10.03.2016 (Bulletin No. 05).
12. Medved L, Weisel JW. The Story of the Fibrin(ogen) αC-Domains: Evolution of Our View on Their Structure and Interactions. Thromb Haemost. 2022; 122(8): 1265-1278.
13. Belitser VA, Platonova TN, Pozdnyakova TM. Differences between the complexes formed by monomeric fibrin with fragment D and dimer D. *Ukr Biokhim Zhurn*. 1983; 55(3): 243-249. (In Ukrainian).
14. Belitser VA, Varetskaya TV, Kosterin SA. Mechanism of inhibition of fibrin polymerization by fibrinogen and its active fragments. *Biokhimiia*. 1980; 45(1): 157-164. (In Russian).
15. Ugarova TP, Kalikhevich VN, Ardemasova ZA, Belitser VA.The role of complementary E2 and D2 centers in the reaction between fibrin and fibrinogen. *Biokhimiia*. 1987; 52(2): 255-263. (In Russian).
16. Pozdnyakova TM, Rybachuk VN, Ilyina AV, Davidovich IuA, Rogozhin SV. Effect of peptides – structural analogs of NH2-terminal sites of fibrin alpha- and beta-chains--on specific binding of the NH2-terminal disulfide bond of fibrin with fibrinogen. *Ukr Biokhim Zhurn*. 1986; 58(2): 10-15. (In Russia).
17. Belitser VA, LugovskoyEV, Ugarova TP, Derzskaia SG. Interaction of fibrinogen with two forms of fibrin differing in the degree of activation by thrombin. *Biokhimiia*. 1985; 50(8): 1336-1341. (In Russian).
18. Platonova T, Hrabovskyi O, Chernyshenko V, Stohnii Y, Kucheriavyi Y, Baidakova K, Korolova D, Urbanowicz A, Komisarenko S. Alternative Role of B/b Knob-Hole Interactions in the Fibrin Assembly. *Biochemistry*. 2025; 64(4): 791-800.
19. Shatzel JJ, O'Donnell M, Olson SR, Kearney MR, Daughety MM, Hum J, Nguyen KP, DeLoughery TG. Venous thrombosis in unusual sites: A practical review for the hematologist. *Eur J Haematol*. 2019; 102(1): 53-62.
20. O'Donnell M, Shatzel JJ, Olson SR, Daughety MM, Nguyen KP, Hum J, DeLoughery TG. Arterial thrombosis in unusual sites: A practical review. *Eur J Haematol*. 2018; 101(6): 728-736.

21. Weisel JW, Litvinov RI. Mechanisms of fibrin polymerization and clinical implications. *Blood*. 2013; 121(10): 1712-1719.
22. Chernysh IN, Nagaswami C, Purohit PK, Weisel JW. Fibrin clots are equilibrium polymers that can be remodeled without proteolytic digestion. *Sci Rep.* 2012; 2: 879.
23. Lugovskoy EV, Gritsenko PG, Kolesnikova IN, Lugovskaya NE, Komisarenko SV. A neoantigenic determinant in coiled coil region of human fibrin beta-chain. *Thromb Res.* 2009; 123(5): 765-770.
24. Chernyshenko VO. Men of the molecules. *Ukr Biochem J.* 2020; 92(3): 86-90.
25. Pozniak TA, Urvant LP, Gritsenko PG, Chernishov VI, Pydiura NA, Lugovskoi EV, Komisarenko SV. Inhibition of fibrin polymerization by synthetic peptides corresponding to Aα195-205 and γ69-77 sites of fibrin molecule. *Ukr Biochem J.* 2014; 86(4): 119-125.
26. Lugovskoi E, Pydiura N, Makogonenko Y, Urvant L, Gritsenko P, Kolesnikova I, Lugovska N, Komisarenko S. The fibrin Bβ125-135 site is involved in the lateral association of protofibrils. *Ukr Biochem J.* 2020; 92(3): 33-45.
27. Komisarenko S, Chernyshenko V, Makogonenko Y, Pyrogova L, Lugovska N, Hornytska O, Hrabovskyi O. Patent of the invention. Method for inhibiting fibrin polymerization by synthetic peptides imitating fragments of the coiled-coil region of fibrin(ogen). Patent No. 143853. Application u202002124. Filed 30.03.2020. Published 29.12.2020.
28. Komisarenko S, Chernyshenko V, Makogonenko Y, Pyrogova L, Lugovska N, Hornytska O, Hrabovskyi O. Method of inhibiting fibrin polymerization using synthetic peptides mimicking fragments of the coiled-coil region of fibrin(ogen). International PCT-application WO 2021/201813; filing date 29.03.2021; publication date 07.10.2021.
29. Lugovskoy EV, Gritsenko PG, Koshel TA, Koliesnik IO, Cherenok SO, Kalchenko OI, Kalchenko VI, Komisarenko SV. Calix[4]arene methylenebisphosphonic acids as inhibitors of fibrin polymerization. *FEBS J.* 2011; 278(8): 1244-1251.
30. Chernyshenko VO, Pirogova LV, Didkivskyi VA, Cherenok SO, Dosenko VE, Pashevin DO, Kalchenko VI, Makogonenko EM, Lugovskoy EV. Effects of calix[4]arene C-145 on overall haemostatic potential of blood plasma *in vitro* and *in vivo. J Int Res Med Pharm Sci.* 2016; 10(3): 146-151.
31. Chernyshenko VO, Savchuk OV, Cherenok SO, Silenko OM, Negelia AO, Kasatkina LO, Pirogova LV, Didkivskyi VA, Yusova OI, Kalchenko VI, Garmanchuk LV, Grinenko TV, Lugovskoy EV, Komisarenko SV. Haemostasis modulation by calix[4]arene methylenebisphosphonic acid C-145 and its sulfur-containing analogue. *Ukr Biochem J.* 2018; 90(6): 21-30.
32. Komisarenko S, Chernyshenko V, Didkivskyi V. Creation of a prototype drug "Antithrombotic agent calix[4]arene C-145" and its preclinical studies. In: National Academy of Sciences of Ukraine, editor. Kyiv: Publishing House "Akademperiodyka" NAS Ukraine; 2021. p. 19.
33. Belitser VA. Fibrinogen B (soluble fibrinogen), its nature and methods of determination. *Lab Delo.* 1980; (9): 529-532. (In Russian).
34. Lugovskoy EV, Gritsenko PG, Lugovska NE, Kolesnikova IN, Komisarenko SV. Soluble fibrin: molecular structure and quantitative determination. *Lab Diagnost.* 2006; 3(37): 11-17.
35. Lugovskoy EV, Kolesnikova IN, Gritsenko PG, Zolotareva EN, Gaffney P, Nieuwenhuizen W, Komisarenko SV. A neoantigenic determinant in the D-dimer fragment of fibrin. *Thromb Res.* 2002; 107(3-4): 151-156.
36. Kolesnikova IN, Lugovska NE, Lugovskoy EV, Gritsenko PG, Lyashko KD, Gogolinska HK, Lytvynova LM, Kostyuchenko OP, Komisarenko SV. Monoclonal antibodies specific to human fibrin. *Rep Nat Acad Sci Ukraine.* 2006; (9): 170-174.
37. Komisarenko SV, Dieev VA, Lugovskoy EV et al. Methodical recommendations: "Application of immunoenzymatic methods for diagnosis of the risk of intravascular thrombosis." Kyiv: Publisher Bykhun VYu, 2019. 36 p.
38. Komisarenko SV, Korda MM, Vari SH, Chernyshenko VO, et al. Determination of the risk of intravascular thrombosis in patients recovered from COVID-19: Methodical recommendations. Ternopil: TNMU; 2024. 40 p.
39 Burg MM, Edmondson D, Shimbo D, Shaffer J, Kronish IM, Whang W, Alcántara C, Schwartz JE, Muntner P, Davidson KW. The 'perfect storm' and acute coronary syndrome onset: do psychosocial factors play a role? *Prog Cardiovasc Dis.* 2013; 55(6): 601-610.