



DOI: <https://doi.org/10.56936/18290825-2023.17.2-95>

BIOCRISTALLOMICS AS THE BASIS OF INNOVATIVE BIOMEDICAL TECHNOLOGIES

MARTUSEVICH A.K.^{1,2}, KOSYUGA S.YU.¹, KOVALEVA L.K.³, FEDOTOVA A.S.¹, TUZHILKIN A.N.¹

¹Privolzhsky Research Medical University, Nizhny Novgorod, Russia

²Nizhny Novgorod State Agrotechnological University, Nizhny Novgorod, Russia

³Kuban State Medical University, Krasnodar, Russia

Received 14.10.2022; accepted for printing 10.01.2023

ABSTRACT

The phenomenon of biocrystallization has been recorded by researchers for over a century. At the same time, despite the presence of numerous empirical data in this area, there is no unified theoretical basis for the direction under consideration. On this basis, the purpose of the review is to systematize the concepts of biocrystallomics as a new synthetic biomedical science that considers in detail and integratively the processes of bio-associated crystallization occurring both in vitro and in vivo. In this paper historical basis and current status of Russian investigations, which associated with human and animal's biological fluids free and initiated crystallogenesis, are shown. Main stages of building, fundamental rules and problem aspects of biocrystallography as a transformation it to biocrystallomics causes are demonstrated. The definition of this science is presented, its main tasks are characterized. The main directions of biocrystallomics are described, which include experimental biocrystallomics, crystallopathology, crystallotherapy (crystallotherapy), pharmacobiocrystallomics and crystal indication. The existing methods of studying biocrystallogenesis are considered in detail, which are grouped into 3 categories: crystalloscopic, tezigraphic and experimental crystalloscopic. Special attention is paid to the factors that determine the features of the crystallization of biological fluids, among which physical, chemical, biological and mixed are distinguished. The 5 main functions of biocrystallogenesis in biological systems are revealed: protective, nutritive-metabolic, pathogenetic, informational and synthetic-biogenic. The holistic theory of biocrystallomics and its main provisions are presented. So, biocrystallomics as a new integrative science about biocrystals is characterized, and its general ways are given.

KEYWORDS: biocrystallomics, biocrystallization, biological fluids, structurization, dehydration

INTRODUCTION

It is known that many living organisms have the ability to form crystalline or pseudocrystalline bodies inside themselves and/or in the external environment. Thus, for representatives of the microcosm, the latter option is predominant [Volchetsky

A et al., 1999; Golovanova O, 2006], whereas endolithogenesis prevails in higher living organisms [Rikhvanov L et al., 2004; Minsky A et al., 2002; Artishevskaya N, Pavlovich O, 2000]. In addition, the interest of many researchers, primarily miner-

CITE THIS ARTICLE AS:

MARTUSEVICH A.K., KOSYUGA S.YU., KOVALEVA L.K., FEDOTOVA A.S., TUZHILKIN A.N., (2023). Biocrystallomics as the basis of innovative biomedical technologies; The New Armenian Medical Journal. 17(2): 95-104; DOI: <https://doi.org/10.56936/18290825-2023.17.2-95>

ADDRESS FOR CORRESPONDENCE:

Andrew K. Martusevich, PhD
Sechenov University
8-2 Trubetskaya str. Moscow, Russian Federation
Tel.: +7-909-144-91-82
E-mail: cryst-mart@yandex.ru

alogists, is attracted by the alleged “intermediate” role of crystals as intermediates of living and inanimate nature. This thesis is confirmed by the long-term research of the Academician RAS N. P. Yushkin, devoted to the hypothesis of the origin of life on primary organo-mineral aggregates [Yushkin N, 2007], as well as numerous facts of the genesis of crystalline bodies by living beings [Bakulin M et al., 2006; Gerasimenko L et al., 1996; Golubev S, 1981]. The most striking examples are the formation of an egg shell by a chicken, the presence and nature of precipitation as a result of the vital activity of ice-forming bacteria, the formation of a pearl by a mollusk, etc. At the same time, attention is drawn to the fact that this information is extremely fragmented, being the property of various disciplines, and there are practically no attempts to apply a systematic approach to the analysis of general patterns of bio-associated crystal formation. The prerequisites for generalizing ideas about certain aspects of the problem are the theory of “functional morphology of biological fluids” proposed by acad. RAMS. V.N. Shabalin and Prof. S.N. Shatokhina (2001) [Shabalin V, Shatokhina S, 2001], as well as the theory of self-organization of the protein “Protos”, developed for about 40 years by Prof. E.G. Rapis (2003) [Rapis E, 2003].

On the other hand, it should be noted that each of the above theories, despite the observed trend towards globalization (primarily with regard to the functional morphology of biological fluids), concerns only some particular patterns of the formation of biogenic crystals. So, the concept of V.N. Shabalin and S.N. Shatokhina, based on the diagnostic value of individual marker structures formed as a result of dehydration of biological media and, according to the authors, are highly specific indicators of specific pathological conditions [Shabalin V, Shatokhina S, 2002], can be applied exclusively to the study of its own (without the participation of any chemical modulators) structure formation of the biosubstrate.

The essence of the theory of E.G. Rapis is the prerogative of protein as an organizing principle in the processes of structure formation of drying droplets [Rapis E, 2005]. This hypothesis is substantiated by the author and collaborators from experimental and theoretical positions using methods of mathematics, physics, and physical

chemistry [Shabalin V, Shatokhina S, 2002], however, the information obtained by the developers cannot be directly extrapolated to biological objects, since the conducted surveys were mostly carried out only on protein-water model systems [Yakhno T et al., 2004].

An extremely important and fundamental aspect overlooked by the creators of the above theories is “spontaneous” crystallogenesis in real conditions (in vivo), the presence of which is confirmed by numerous observations described in sufficient detail in the literature of various profiles (physico-chemical [Rapis E, 2003; Gilinskaya L et al., 2003], biological [Volchetsky A et al., 1999; Golovanova O, 2006; Rikhvanov L et al., 2004; Minsky A et al., 2002] and medical [Volchetsky A et al., 1999; Artishevskaya N, Pavlovich O., 2000; Shabalin V, Shatokhina S., 2001; Shabalin V, Shatokhina S, 2002; Gilinskaya L et al., 2003; Martusevich A et al., 2010]).

In addition, the moment of the functional role of biogenic crystals formed by beings of different levels of organization in different periods of the life cycle is unaccounted for. There are practically no works devoted to the disclosure of the laws of coexistence of living organisms and crystalline bodies [Golubev S, 1987]. Even the presentation of this incomplete list of questions suggests the need to create a new direction that directly studies bio-associated crystals. Considering that the problems under consideration are interdisciplinary in nature, because at the same time, the interests of physicians, biologists, chemists, physicists, mathematicians, etc. are affected, then this direction should be synthetic.

To denote this integrative science, we propose the term “biocrystallomics”, indicating the immediate object of research and emphasizing the biological bias of the discipline [Martusevich A, 2008]. From our point of view, the direction being formed can become a qualitatively new stage in the development of ideas about biogenic crystals, logically continuing the previously proposed theories interpreting the phenomenon of biocrystallization.

Biocrystallomics is the science of the structure, properties, mechanisms and conditions of formation and degradation, as well as the functional significance of bio-associated crystalline and pseudo-crystalline bodies.

The main goal of biocrystallomics as a new synthetic science should be a comprehensive, multilateral decoding of the nature and essence of the phenomenon of crystallization associated with the vital activity of organisms. The range of primary tasks of the discipline may include: study of the structure and properties of biogenic crystals themselves.

1. clarification of the mechanisms and conditions that ensure the formation of biocrystals.
2. disclosure of the functional significance of the phenomenon under consideration.
3. investigation of the information capacity of biogenic formations of crystalline and pseudocrystalline structure.
4. evaluation of the possibilities of using the information contained in biocrystals.
5. consideration of the prospects and features of biocrystallogenesis management both in the external environment (in vitro) and inside the body (in vivo).
6. disclosure of the general biological role of biogenic crystals.

The listed set of tasks requires careful selection and classification of methodological approaches used in biocrystallomics. Since this discipline is synthetic in nature, it is advisable to divide the entire range of methodological techniques into specific and non-specific ones.

Currently, more than 20 different specialized methods of biocrystallomics have been proposed, shown in Figure 1. It is important to note that in principle they can be divided into three groups according to the estimated properties of the dehydration structuring of biological substrates.

The first group, from our point of view, should include methods based on the study of the crystallogenic properties of biological objects directly (crystalloscopic methods). The currently proposed approaches assigned to this group differ mainly in the peculiarities of the mode of obtaining structures during drying of a biological substrate on a solid substrate (using a closed cell [Antropova I, Gabinsky Ya., 1997], vacuuming the sample [Savina L, 1999], exposure to different temperatures [Martusevich A, Zimin Yu., 2008], the use of a wide range of substrates [Barer G et al., 1998] and their modification with different coatings [Shatokhina S, Shabalin V, 1999] etc.).

The second group combines methods of biocrystalloscopic research (topographic methods),

which allow analyzing the initiating properties of biosubstrates. The general principle embedded in this group of approaches is the dehydration of the studied liquid biological object and modulator, a priori having high crystallogenic activity (basic substance) [Kidalov V et al., 2004; Martusevich A, Kamakin N, 2007]. 0.9% aqueous solution of sodium chloride can act as the simplest and most affordable basic substance. It is interesting to emphasize that a simple or composite dye (chromocrystalloscopy method) can act as a basic substance, which, acting as an initiator of structure formation, is capable of selectively staining components of a dehydrating biomaterial [Martusevich A et al., 2010].

As the most general parameter characterizing the initiating properties of a biological substrate or organism in relation to the whole set of potential basic substances, we propose the term “initiator potential” [Martusevich A, 2008]. Its implementation for a specific basic substance (or their system) is an “initiator profile”. The introduction of these concepts seems significant to us due to the fact that, as shown by some authors [Kidalov V et al., 2004] and in our works [Martusevich A, 2008; Martusevich A, Zimin Yu, 2008; Martusevich A, 2008] the initiativeness of biological objects varies significantly depending on the basic compound used. This is due to the fact that the introduction of various substances into the biological medium differentially changes its microenvironment, changing the conditions for the course of dehydration structuring [Martusevich A, Zimin Yu, 2008]. Therefore, the completeness of the extraction of the information capacity of the biomaterial is determined by the correctness of the selection of the complex of basic substances (the initiated series) [Martusevich A, Zimin Yu, 2008; Martusevich A, Kamakin N, 2007; Martusevich A et al., 2008].

Finally, the last group includes a small number of methods that allow manipulations of varying complexity to be carried out with a drying biosystem. Thus, the methods of substrate congruence [Korotko G.G., 2000] and model composites [Savina L.V. et al., 2003] have in their essence isolated crystallization of individual components of biological media (proteins, lipids, carbohydrates, inorganic and organic salts) in individual form and in various combinations [Savina L et al., 2003].

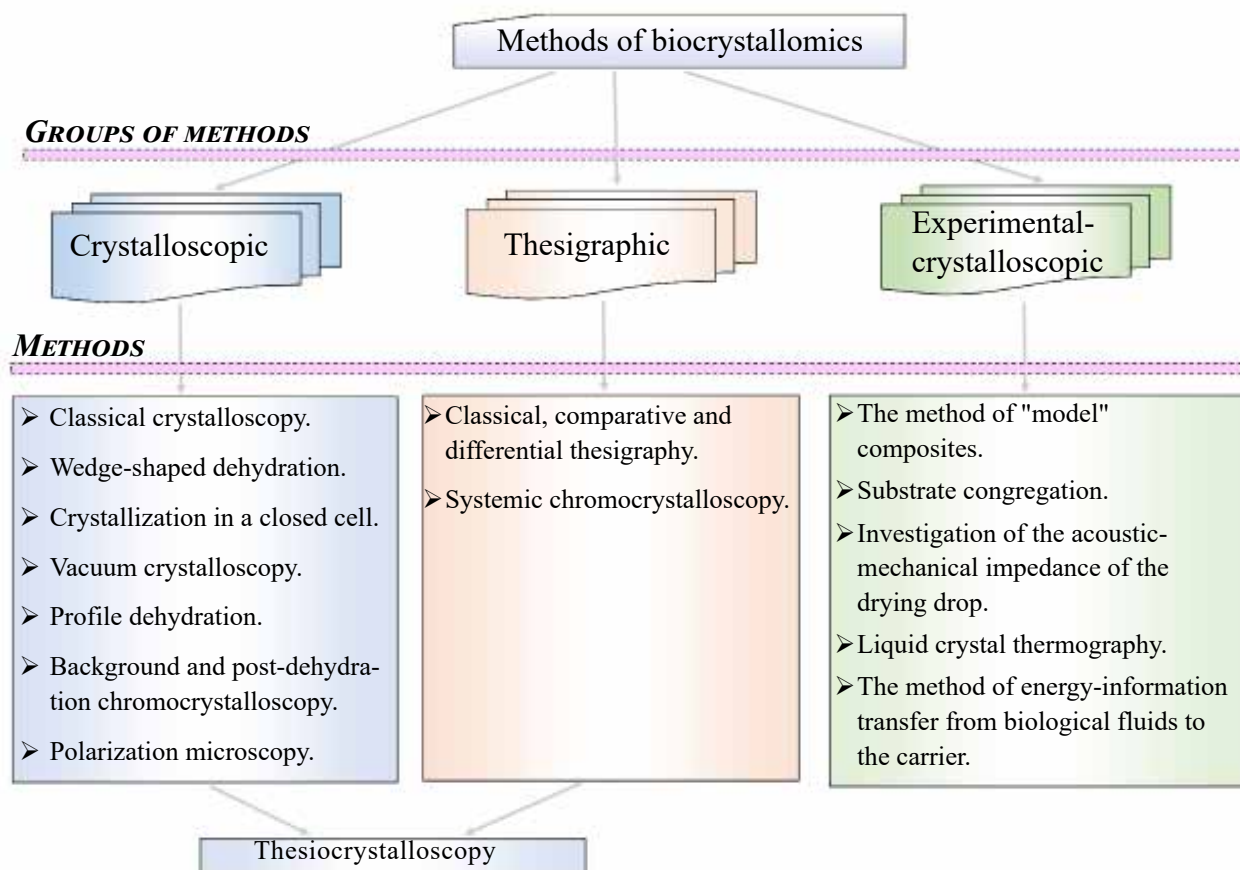


FIGURE 1. Structure of biocrystallomics methods

The approaches of experimental biocrystallomics, initially being exclusively research, are designed to solve one of the most fundamental tasks of the discipline – the development of ways to create controllability of biocrystallogenesis [Martusevich A, 2008; Martusevich A, Zimin Yu, 2008]. In our opinion, such modeling and study of the influence of a wide range of modulators (physical, chemical, biological and mixed) of this process will allow us to form experimental and theoretical foundations for the directed qualitative and quantitative modification of bio-associated crystallization (Fig. 2).

Regarding the next component of the newly formed science, the object of research, it is necessary to emphasize that at present the main attention of specialists is drawn to biological fluids [Volchetsky A et al., 1999; Shabalin V, Shatokhina S, 2001; Shabalin V, Shatokhina S, 2003; Martusevich A, 2008; Antropova I, Gabinsky Ya, 1997; Savina L, 1999; Martusevich A, Zimin Yu., 2008; Barer G et al., 1998; Shatokhina S, Shabalin V,

1999; Kidalov V et al., 2004; Martusevich A, Kamakin N, 2007; Martusevich A. et al., 2010; Martusevich A, 2008; Martusevich A, 2008; Savina L et al., 2003]. Only a few works are aimed at studying the products of spontaneous crystallogenesis associated with the vital activity of organisms, and these publications in most cases represent structural studies of the resulting biocrystals [Golovanova O, 2006; Rikhvanov L et al., 2004; Gilinskaya L et al., 2003], while their functional significance remains undisclosed [Martusevich A, 2008; Martusevich A, 2010]. Therefore, the subject of further research should be a comprehensive assessment of biocrystals from the standpoint of natural science as a whole [Minsky A et al., 2002; Martusevich A, 2010].

As part of the implementation of the task, based on the generalization of extensive factual material of the literature and the results of many years of his own research [Martusevich A.K. et al., 1998-2020], the cornerstone is the clarification of the general biological functions of biocrystallogene-

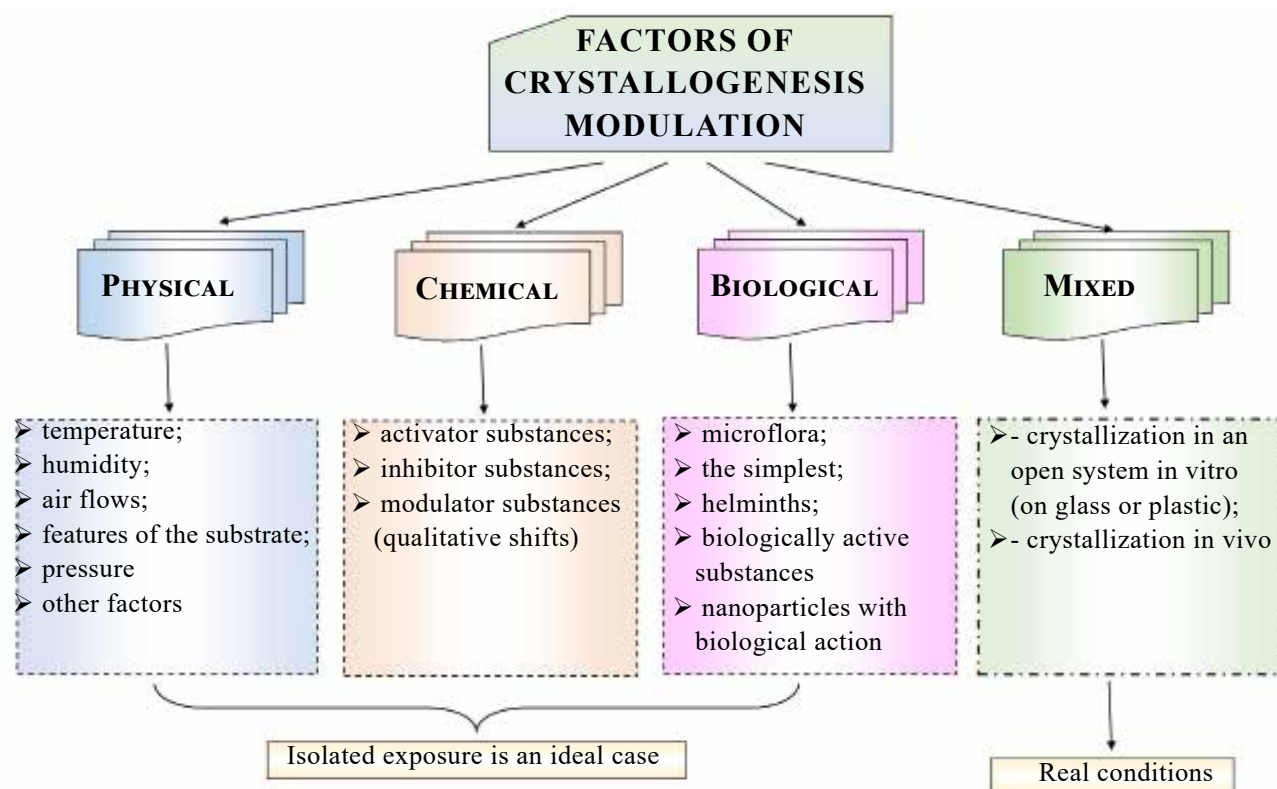


FIGURE 2. Classification of biocrystallogenesis modulators by the nature of the acting agent.

sis, which at this stage include 5 main:

A) **protective** – crystals act as structural elements of the protective system of the whole organism (mainly in agents of the microcosm) and/or its parts (organs, tissues, cells, subcellular structures). To date, this function has been studied most fully, on the basis of which it is possible to identify several options for its implementation:

✓ *the protective function itself*, when crystal formation directly allows the microorganism to maintain its structure in an inviolable state. An example of such a phenomenon is the formation of protein capsules from a specific RecA protein around the genetic material of *Pseudomonas aeruginosa*, which allows the bacteria to prevent UV radiation and other damaging effects [Namsaraev E et al., 1998]. The need for this is due to the absence of karyolemma in bacteria and the diffuse distribution of nucleic acid in the intracellular space, which significantly reduces its tolerance to external and internal negative factors. Similar information is presented regarding the Dps protein in other microorganisms (*Listeria innocua*, *Agrobacterium tumefaciens*) [Bozzi M et al., 1997; Ceci P et al., 2003]. It is important to emphasize that both

compounds are synthesized specifically to perform a protective function [Nair S, Finkel S, 2004].

In addition, crystal formation can provide protection for individual bacterial cell organelles. Thus, there is evidence of the ability of ribosomes to crystallize, which is also included in the concept of the projective function of MAC [Shirokov V, 1991].

Crystallization at the next, higher level of organization of living matter makes it possible to form a protective crystalline “framework” for the entire bacterial cell [Minsky A et al., 2002; Lanzov V, 2002], and complex multi-element biosystems containing a significant number of microorganisms connected exclusively by a structure resembling a crystal lattice can be recreated in this way.

✓ *protective-cumulative function*, which consists in the accumulation of certain compounds by a microorganism. This is a fairly general function associated with the formation in the cell of a bacterium or hyphae of a fungus of an accumulation (deposit) of a substance in crystalline form. The prevailing localization of these inclusions is the primemembrane region. An example is the formation of magnetosomes in magnetotactic bacteria [Schüler D, 2008]. This function is heterogeneous

and may be a summation of several. In addition to detoxification, inclusions foreign to the microorganism can be used to ensure their metabolism (nutritional and metabolic function), act as structural or signaling elements of a bacterium, virus or fungus, etc. [Chubukov V, 1982].

√ *detoxification function*, which is a special but physiologically significant case of cumulative function, and provides neutralization of toxic substances coming from outside. The special allocation of this function is determined by the fact that bacteria are capable of paradoxical (at first glance) phenomena – the accumulation of heavy metals, which were supposed to suppress their growth and reproduction. The study of the nature of the inclusions of microorganisms demonstrates the presence of metal atoms in a cell-neutral reduced form [Chernyh N et al., 2007]. Thus, microorganisms not only have detoxification systems for heavy metals, but also accumulate them, preventing their re-entry into the external environment and oxidation before the formation of a toxic ion. This feature of the physiology of bacteria of individual ecological groups has already found application, in particular, in wastewater treatment technologies [Chernyh N et al., 2007].

An important aspect of studying the protective function of the MAC is the study of ways to implement it. Thus, by using the intracellular type of microorganism-associated crystallogenesis, the previously considered DNA protection in pseudomonads is provided [Namsaraev E et al., 1998; Nair S, Finkel S, 2004], as well as the crystallization of ribosomes and other bacterial cell organelles [Schüler D, 2008]. The involvement of the extracellular type of MAC is required if it is necessary to protect the entire microorganism, also with prolonged forced presence of microagents in unfavorable conditions. The primembrane type is directly related to the cumulative and detoxification functions of MAC, since most intracellular inclusions have a similar localization, which is explained by the presence there of most enzyme complexes that form the formation of the crystalline state of the accumulated substances. A separate aspect of the problem is the special forms of MAC, for example, the transformation of viral particles into a crystal structure. In this case, crystallization takes on the character of one of the stages

of the life cycle of the virus in a negative environment for it, resembling the process of capsule formation and sporulation in bacterial cells. These facts indicate the manifestation of the protective function of the MAC [Martusevich A et al., 2012].

B) **nutritive-metabolic** – first of all, it manifests itself at the cellular level in the form of accumulation of nutrients and metabolites, and at the tissue and organism level – in the form of participation in biochemical processes). It is directly related to the projective-cumulative, since perimembranous deposits of a crystalline structure can contain both products of the detoxification function and metabolites in their composition. We assume that the protective and cumulative function can in some cases be performed simultaneously by the same crystalline elements serving as the depot of individual crystallizing metabolites and the “supporting framework” of the microbial cell, which may occur in magnetotactic bacteria [Schüler D, 2008; Schüler D, 2004].

C) **pathogenetic** – associated with the possibility of direct or indirect participation of crystal formation in the development and/or progression of pathological processes (at the level of inter-organizational connections [Minsky A et al., 2002; Martusevich A, 2010; Namsaraev E et al., 1998], as well as at the organizational level – in the form of urinary and cholelithiasis [Shabalin V., Shatokhina S, 2010; Gilinskaya L et al., 2003]). Depending on the evolutionary level of each of the interacting organisms, there will be significant features of the implementation of this function. Thus, for microorganisms, the most preferable is the use of biocrystallization for antagonism purposes [Martusevich A, Zhdanova O, 2013], whereas in the process of interaction of micro- and macroorganism, crystallization can act as a mechanism for occupying a certain ecological (including pathological) niche [Martusevich A, Zhdanova O, 2013].

At the same time, from the standpoint of assessing the functional significance of the resulting biocrystals, from our point of view, it is reasonable to divide them into groups according to the degree of activity of participation in the development of the pathological process:

√ *direct* (crystal formation acts as a direct agent of the process development). In particular, this type includes the destruction of the helico-

bacter-associated microflora of the gastrointestinal mucosa by initiating the formation of rosette-shaped crystals on the surface of microorganisms [Martusevich A, 2007; Martusevich A et al., 2008], as well as the destruction of plant leaf tissue under the influence of ice formation from intracellular and extracellular water with the participation of bacteria [Trunova T, 2006].

√ *mediated* (crystal formation does not directly lead to the appearance of pathology, but only is its trigger mechanism). The most illustrative example of such a variant can be all types of lithogenesis in the mammalian body (the formation of stones in the gallbladder and bladder, salivary and pancreatic glands and their ductal system, etc.).

√ *mixed* – involves a combination of both of the above options.

D) **informational** – is determined by the possibility of accumulation and translation of biologically significant information [Martusevich A, 2008; Martusevich A, Zhdanova O, 2008]. At the same time, crystals can play the role of “accumulators”, “archives” or “transporting substances” in the information cycle. This makes it possible to consider crystals as a new natural element of recording, storing and transmitting various information.

E) **synthetic-biogenic** – is considered as the property of biogenic crystals to form separate tissues and organs (otolith apparatus, bones, tooth enamel, etc. [Golovanova O, 2006; Rikhvanov L et al., 2004; Golubev S, 1981; Golubev S, 1987; Martusevich A, 2010; Babenko O et al., 2007]). It should be noted that this function is found in living organisms at all levels of the organization. At the same time, it is less important for microorganisms compared to their role for animals and humans.

All of the above general experimental and theoretical information and factual material have been integrated by us in the form of a holistic theory of biocrystallomics, which includes three main provisions:

1. The phenomenon of bio-associated crystallization is a general biological phenomenon and is inherent in living matter at all levels of its organization.
2. The shape, composition and functional significance of the biogenic crystals formed depend on the mechanical properties and metabolic activity of living beings and are determined by their function.

3. Biocrystallogenesis is a complex cascade of physicochemical processes regulated by a system of biogenic and xenogenic modulators, which makes it possible to control it.

For biocrystallomics as a discipline of natural sciences, a fundamentally important aspect is the possibility and scope of practical application of previously developed methodology and methodological apparatus. Currently, the broadest prospects for the use of this information are viewed for biocrystallomics in relation to medicine and biology, and the medical and veterinary aspects of biocrystallomics are based on the following provisions [Martusevich A, 2008]:

- A) The nature of the dehydration structure formation of the biological fluid is determined by its physico-chemical properties, reflecting the functional state of the patient's body.
- B) The features of dehydration structure formation of biological fluid specific to specific physiological and pathological conditions can be distinguished.
- C) The established features of the structure formation of liquid biological substrates have diagnostic significance.

Currently, it seems possible to identify several of the most significant and promising areas of biocrystallomics:

1. *Experimental biocrystallomics* is a field of biocrystallomics that deals with deciphering the mechanisms of biocrystallogenesis and its modeling.
2. *Crystallodiagnostics* – studies the diagnostic prospects for assessing the own and initiated structure formation of the biological environment of humans and animals.
3. *Crystallopathology* is a field that studies pathological processes, the course of which is directly or indirectly related to crystal formation.
4. *Crystallotherapy* is a branch of biocrystallomics, the main purpose of which is to study and apply methods of controlling biocrystallogenesis in vitro and in vivo for the development of fundamentally new technologies for the treatment of human and animal diseases, in the pathogenesis of which crystal formation plays an essential role, by means of modulation (towards inhibition or activation) of the biocrystallization process.

5. *Pharmacobiocrystallomics* is a branch of biocrystallomics that studies the possibilities of biocrystalloscopic methods in the study of pharmacodynamics, pharmacokinetics, individualized selection, as well as current and final monitoring of the effectiveness of drugs.
6. *Crystal indication* is a direction of biocrystalomics that studies the ability of biogenic crystals to act as markers of individual states of the organism (in particular, intoxication, sensitivity of a microorganism to antibiotics) or an object (for example, contamination by microorganisms).

It is important to emphasize that all of the above directions and areas of practical use of the discipline in question are based on the thesis about the

information function of biocrystals [Martusevich A, Zhdanova O, 2008].

In our opinion, attention should be paid separately to the fact that the biotechnology of crystallogenesis is essentially a natural nanotechnology, since it allows manipulations at the level of structures having dimensions of 10^{-10} - 10^{-7} m (0.1-100 nm) [Rapis E, 2005], which is of considerable interest for various fields of modern science and technology [Martusevich A, 2007; Martusevich A, Kamakin N, 2007].

Thus, by now the foundation for the birth of a new synthetic discipline – biocrystallomics - has been fully formed.

This study was supported by Russian Science Foundation (grant №22-25-00652).

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The Journal is founded by
Yerevan State Medical
University after M. Heratsi.



Rector of YSMU

Armen A. Muradyan

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU

(+37493 588697 Editor-in-Chief

Fax: (+37410) 582532

E-mail: namj.ysmu@gmail.com, ysmiu@mail.ru

URL: <http://www.ysmu.am>

*Our journal is registered in the databases of Scopus,
EBSCO and Thomson Reuters (in the registration process)*



SCOPUS



EBSCO

REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "LAS Print" LLC
Director: Suren A. Simonyan
Armenia, 0023, Yerevan,
Acharyan St. 44 Bulding,
Phone: (+374 10) 62 76 12,
E-mail: las.print@yahoo.com

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