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REVIEWS

To the 100th Anniversary of A.S. Danilevsky

The Immune System of Maggots of the Blow Fly (*Calliphora vicina*) as a Source of Medicinal Drugs

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Abstract—Studies of cellular and humoral immunity of the blow fly *Calliphora vicina* maggot revealed three groups of pharmacologically active substances that are perspective for use in medicine: alloferons, allocations, and antimicrobial peptides. Alloferons are the *C. vicina* peptide family selectively stimulating cytotoxic activity of the natural killer cells, an evolutionary ancient group of immunocompetent cells playing the key role in antiviral and antitumoral immunity of mammals. Alloferons are used in medicine for treatment of herpes viral infections and viral hepatitis B. Allostatins are synthetic peptides combining structural characteristics both of alloferons and of some mammalian immunoactive proteins. Allostatins, like alloferons, stimulate cytotoxic activity of the natural killer cells and interferon production, but, unlike alloferons, have pronounced adjuvant properties, i.e., the ability to enhance immune recognition of alien (non-self) antigens. At present, allostatins are used to enhance resistance of skin and mucous membranes to viral infections; in future, they might find use in immunotherapy of cancer and other diseases. One more group of proteins and peptides of the *C. vicina* maggot immune response, which are promising for use in medicine, serve antimicrobial peptides. The study of the preparation whose composition inclusdes defensins, cecropins, diptericins, and proline-rich peptides of *C. vicina* show that this type of drugs has great potential for treatment and prevention of antibiotic-resistant infections.

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Key words: *Calliphora vicina*, immune system, antimicrobial peptides, alloferons, allostatins.

INTRODUCTION

Insects and their life activity products are widely used in traditional medicine since antiquity [1, 2]. Although the ethnopharmacopeias of China, Tibet, India, South America, and other regions describe therapeutic application of hundred insect species, the experience of traditional medicine, with few exceptions, remains undemanded by scientific medicine. These exceptions include use of calliphorid maggots for treatment of infected wounds and sores referred to as "maggot debridement therapy" (MDT) or "biosurgery." In this case, the living *Lucilia sericata* maggot and, less frequently, other representatives of blow flies that lyse necrotic tissues, sterilize wounds, and accelerate their healing. The therapeutic efficacy and safety of MDT has been clinically proved [3, 4]. This method gained official recognition in the United States, Great Britain, and many other countries.

Introduction of new drugs into arsenal of modern medicine needs performance of several conditions that have little in common with practice of

traditional entomotherapy. First of all, the drug active substance must be produced in chemically pure form, characterized structurally and, as a rule, reproduced through chemical or biological synthesis. Then it has to pass pre-clinical test to establish full spectrum of its biological activity, mechanism of action, toxicity, and stability in the composition of the tentative drug. The overwhelming majority of candidates for an active substance are eliminated at this stage. The remaining ones must be further verified in the course of multistage clinical trials for their therapeutic efficacy and safety. They also have to prove their advantage over the existing counterparts with the same indication. As few as one of thousands of candidate molecules has a chance to cross finishing tape in this competition. Just a handful of substances produced by insects, such as mellitin, an active peptide component of the honey bee venom [4], gained an official drug status.

Progress in insect immunology opens new avenues for the search for potential drugs meeting criteria of scientific medicine [5, 6]. The mechanisms by which insects recognize and inactivate pathogenic microorganisms are considered in reviews based mainly on studies of immunity *Drosophila melanogaster* [7–10]. Peculiarities of organization of the immune system in other insects are either investigated fragmentarily or remain unknown. Nevertheless, a large body of evidence allows revealing general regularities characteristic of the class of insects. It is commonly accepted that anti-infectious immunity in insects is based on phagocytosis and mechanical isolation of pathogens realized by the specialized hemolymph cells [11], the hemolymph phenoloxidase system [12], and the antimicrobial peptides [13–15]. In the context of the subject of this paper it is important to note that the natural immune system developed in the evolution of insects by combining both the ancient conservative elements common to different types of metazoans and the mechanisms specific to certain orders, families, and even species [16–19]. The mosaics of evolutionary conservatives and variable cell-molecular components creates the practically unlimited diversity of variants of the insect immune system organization.

The goal of the present paper is to generalize results of the many-year studies on the *C. vicina* maggot immune system as a source of medicinal drug substances.

THE *C. VICINA* MAGGOT IMMUNE SYSTEM

Hemocytes. The *C. vicina* maggot immune system includes a complex network of regulatory and effector mechanisms aimed at recognizing and eliminating pathogens. The principal cell-based effectors of the immune system are hemocytes and fat body. There are several classifications of the *C. vicina* hemocytes [20–23]. One of them divides the hemocytes into four morphological types: prohemocytes, plasmatocytes, thrombocytoids, and oenocytoids [21]. Plasmatocytes (or histiolysocites by terminology of [23]) comprise the main part of hemocytes in the end of the larval development and during larval diapause [22].

The *C. vicina* plasmatocytes have the cytotoxic activity analogous to that of mammalian natural killer cells [19]. Like the latters, the *C. vicina* maggot plasmatocytes recognize their target cells (in this case, the K562 human leukemia cells) as the alien (non-self), form a transient conjugate with them, and induce the apoptosis process leading to death of the attacked target. The natural killer cells are found not only in vertebrates, but also in many invertebrate phyla, and seem to represent one of the most ancient mechanisms of natural immunity in metazoans [24]. Although the natural killer cells are not described in other insects so far, in the *C. vicina* maggots at the period of preparation for metamorphosis the cytotoxic activity of hemocytes reaches very high level and exceeds by one order the similar activity of murine splenocytes or human blood mononuclears. At this period, the natural killer cells (cytotoxic plasmatocytes) appear to form the main mass of hemocytes in the maggot hemolymph. Detection of the natural killer cells poses quite few fundamental questions as to organization and function of the insect immune system [19]. First of all, the question arises of the mechanism of the "self—non-self" recognition, which allows the cytotoxic hemocytes to attack mammalian cells. The known mechanisms of recognition of the pathogen-associated molecular patterns (lip polysaccharides or peptidoglycans of bacterial cell membranes) during phagocyto-

Structure and functional properties of peptides included in the composition of the *Calliphora vicina* antimicrobial peptide complex

Peptides	Amino acid sequence	Antibacterial activity
Defensin	Ala-Thr-Cys-Asp-Leu-Leu-Ser-Gly-Thr-Gly-Ala-Asn-Hys-Ser-Ala-Cys-Ala-Ala-Hys-Cys-Leu-Leu-Arg-Gly-Asn-Arg-Gly-Gly-Tyr-Cys-Asn-Gly-Lys-Ala-Val-Cys-Val-Cys-Arg-Asn	Gram-positive bacteria
Proline-rich peptide	Phe-Val-Asp-Arg-Asn-Arg-Ile-Pro-Arg-Ser-Asn-Asn-Gly-Pro-Lys-Ile-Pro-Ile-Ile-Ser-Asn-Pro- ... (N-terminal sequence)	
Cecropin	Gly-Trp-Leu-Lys-Lys-Ile-Gly-Lys-Lys-Ile- Glu-Arg-Val-Gly-Gln-Hys-Thr-Arg-Asp-Ala-Thr-Ile-Gln-Gly-Leu-Ala-Val-Ala-Gln-Gln- Ala-Ala-Asn-Val-Ala-Ala-Thr-Ala-Arg	Gram-negative bacteria
Diptericin	Asp-Ser-Lys-Pro-Leu-Asn-Leu-Val-Leu-Pro-Lys-Glu-Glu-Pro-Pro-Asn-Asn-Pro-Gln-Thr-Tyr-Gly-Gly-Gly-Gly-Gly-Ser-Arg-Lys-Asp-Asp-Phe-Asp-Val-Val-Leu-Gln-Gly-Ala-Gln-... (N-terminal sequence)	

sis most likely do not operate, as in this case the animal cells do not contain such structures. At the same time, the natural killer cells of mammals are known to have the unique system of the feedback recognition that allows them to attack any cells that lack the specific markers of "self", proteins of the main histocompatibility complex (MHC) of the type I. Detection of the natural killer cells in *C. vicina* maggots allowed to suggest that the cytotoxic hemocytes in insects also have the system of the negative feedback "self—non-self" recognition and, hence, the markers of "self" analogous to the mammalian MHC proteins [19]. The functions of the cytotoxic hemocytes in insects remain obscure. By analogy with the mammalian natural killer cells, it may be suggested that the *C. vicina* cytotoxic hemocytes provide elimination of the virus-infected cells. However, it is remarkable that plasmatocytes become most abundant in hemolymph of the maggots at the period of preparation for metamorphosis. This fact allows suggesting that during metamorphosis, plasmatocytes induce apoptosis of maggot cells via the same cytotoxic mechanisms as with alien cells [19]. In this case, the cells destined for self-annihilation probably shed the "self"'s surface markers and become susceptible for the attack from cytotoxic hemocytes.

The natural killer cells play a leading role in human antiviral and antitumoral immunity and are considered as one of the most promising pharmacological targets in combatting viral infections and oncological diseases [25]. The detection of the counterpart system in insects opens up new sources for the search for pharmacologically active substances able to increase functional activity of the natural killer cells. Among these substances are alloferons—stimulators of the human natural killer cells isolated from the *C. vicina* maggot hemolymph and used in medicine to treat some viral infections (see Alloferons section).

Fat body. The insect fat body performs multiple functions related to synthesis of various proteins including antimicrobial peptides [26, 27]. In norm, synthesis of antimicrobial peptides in intact *C. vicina* maggots is maintained at the minimum level, but rises dramatically after introduction of bacteria into the maggot's body cavity [28, 29]. The involvement of the fat body in synthesis of antimicrobial peptides determines some peculiarities of the maggot immune response important in view of the perspectives of application of pharmacological use of these substances. First of all, the fat body antimicrobial peptides act as extracellular factors and perform protective functions in the direct contact with host tissues. Such mechanism implies a high selectivity of the cytotoxic effect towards microorganisms and, accordingly, the absence of toxicity toward host cells. In mammals, similar antimicrobial peptides (alpha-defensins) are located in blood cells and produce antimicrobial effect in the composition of specialized intracellular organelles [30, 31]. On finding themselves

in the non-characteristic milieu, such as the extracellular space or blood plasma, α-defensins are submitted to fast inactivation by the specialized plasma proteins. From this point of view, the *C. vicina* extracellular antimicrobial peptides are more suitable candidates for the role of drugs.

Antimicrobial peptides. In response to introduction of bacteria, *C. vicina* maggots synthesize and accumulate in hemolymph a complex of antimicrobial peptides [29] that include defensins, cecropins, diptericins, and proline-rich peptides (see Table).

Defensins are represented by at least three isoforms with molecular masses of 4032.0, 4091.3, and 4114.3 Da, respectively. The complete amino acid sequence is established for the 4032.0 Da peptide. Defensins in *C. vicina*, like in other insects, are characterized by six cysteine residues forming three disulfide bridges and selectively toxic for Gram-positive bacteria. Defensins are widely spread among the majority of winged insects (Pterygota) and apparently appeared as long age as in common ancestors of arthropods and molluscs [17].

Cecropins in *C. vicina* are represented by a linear 4156.0 Da peptide composed of two amphipathic alpha-helices and selectively toxic for Gram-negative bacteria. Cecropins are spread among representatives of Diptera and Lepidoptera orders, while are unknown in other insects. The diptericin family of *C. vicina* is represented by four isoforms with molecular masses of 8886.2, 8913.9, 8999.7, and 9029.1 Da. The N-terminal site of *C. vicina* diptericin consisting of 43 amino acids, including the 5-glycine repeat, shows homology to the known dipteran diptericins and have no close homologues among antimicrobial peptides in other animals. Diptericins are selectively toxic for Gram-negative bacteria.

Proline-rich peptides in *C. vicina* include four isoforms with molecular masses of 2987.0, 3025.7, 3040.0, and 3048.6 Da. The N-terminal sites is currently sequenced and contains 23 amino acids including four proline residues. By the formal character (the high proline content), they can be ascribed to the family of proline-rich peptides; however, their amino acid sequence has no homology with proline-rich peptides in other insects. Functionally they also differ radically from the known members of this heterogeneous group. Unlike the latter affecting mainly the Gram-negative bacteria, the proline-rich peptides in *C. vicina* are selectively toxic for Gram-positive bacteria.

Thus, the complex of antimicrobial peptides in *C. vicina* was formed over a long period of time, probably for no less than the half a billion years, i.e., exactly the time of separation between ancestral arthropods and molluscs. The most anxious element of this complex, defensins, was gradually added by other antimicrobial peptide families—cecropins chrematistic of Diptera and Lepidoptera, diptericins found in muscoid Diptera, and, finally, by the original variant of proline-rich peptides that have no obvious evolutionary analogs.

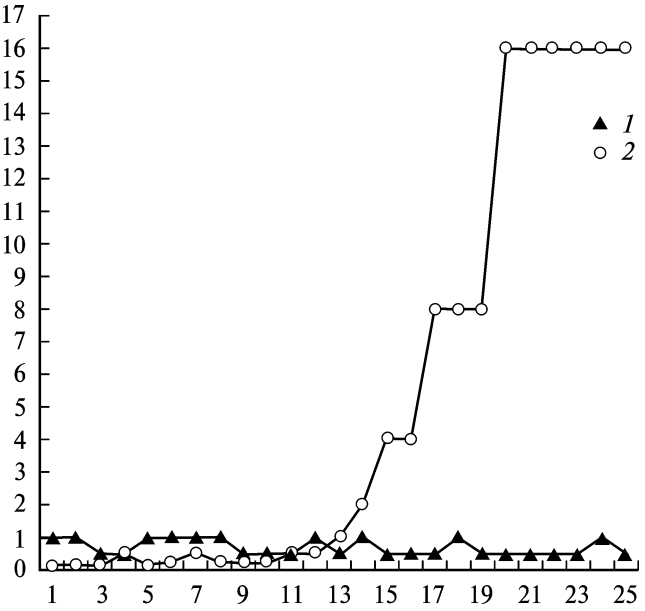
COMPLEX OF THE IMMUNE RESPONSE PEPTIDES IN *C. VICINA* MAGGOTS AS A BASIS FOR CREATION OF ANTIBACTERIAL DRUGS

The modern medicine survives the complex period that is often called "the end of the antibiotics era." Indeed, the situation in therapy of bacterial infections is becoming ever more alarming due to spreading of "superbacteria" resistant to the majority or to all known antibiotics [32, 33]. A special danger is the expanding of the antibiotics-resistant bacteria in medical institutions where they compose the principal cause of infectious complications and the associated lethality.

At present, the main way to overcome the drug resistance is the use of an empirically found combination of two or more antibiotics with different structure and mechanism of action. The combination of antibiotics is presumed to increase the therapeutic efficacy and to prevent development of resistance of bacteria. However, such complication of the therapeutic schemes is far from always giving positive results. Negative properties of each antibiotic (toxicity and other side effects) frequently sum up; sometimes one component suppresses the other rather than produces a synergistic effect. It is experimentally shown that use of combination of antibiotics can provoke development of resistance even to the greater extent than each antibiotic separately and promotes formation of the most dangerous multi-resistant bacterial forms [34, 35].

The search for approaches to rational therapy of bacterial infections remains one of the global tasks of pharmacology and of the public health system on the whole. In the present section, we propose a variant of solving the problem, based on studies of mechanisms of insect antibacterial immunity. The proposed approach, like the known methods of combination antibiotic therapy, includes the simultaneous action on the bacterial cell of two or more components differing by their structure and mechanism of action. The main distinction consists in that the proposed approach implies use of the evolutionary co-adapted complex of active substances. In this case, by the co-adapted complex we mean a combination of two or more antimicrobial peptides, formed during biological evolution and optimized by natural selection with respect to the compatibility of its components. The analysis of the *C. vicina* antimicrobial peptides described in the previous section shows formation of this complex to have occurred over hundred millions of generations by introduction into its composition of new active components with preservation of the evolutionary old ones. The latter remain practically unchanged structurally and functionally. For example, fixation of point mutations in the defensin primary structure occurred, on average, once per 10 million years and did not affect the functionally important properties of their molecular organization [17]. We believe that in the process of evolution of ancestors of the modern insects, such complex organization variants were found, which made bacterial adaptation extremely slow or even impossible. Accordingly, the drugs made on the basis of the co-adapted complex of insect antimicrobial peptides, unlike the currently known antibiotics, can retain antibacterial activity over the unlimited period of time.

To check this hypothesis, we performed a series of experiments, in which different bacteria were submitted to selection for resistance to the *C. vicina* complex of antimicrobial peptides. The complex contains hydrophobic maggot hemolymph components in the phase of active immune response. The complex major antibacterial components represent defensins, cecropins, diptericins, and proline-rich peptide, as described in Table I [29]. As positive control, the common antibiotics were used in these experiments. In all cases the result was unequivocal: all the examined bacteria easily produced resistance to usual antibiotics, whereas the resistance to the drug containing the *C. vicina*



Changes in resistance of several generations of the bacterium *Klebsiella pneumonia* to the *C. vicina* antimicrobial complex (1 mg/ml) and to the antibiotic meropenem (2 μg/ml). *Abscissa*: the passage number, *ordinate*: minimal inhibiting concentration. To obtain the antimicrobial complex, the *C. vicina* diapausing maggot immune response was activated by administration of the bacteria, as described previously [29]; the obtained hemolymph was acidified by 0.05% trifluoroacetic acid (TFA, final concentration) and centrifuged for 5 min at 5000 g. The supernatant was applied onto Sep-Pak C_{18} classic (Waters) cartridge, washed in 0.05% TFA, and eluted with 50% acetonitryl in 0.05% TFA. The eluate was submitted to lyophylization and used as the antimicrobial complex. The multi-resistant hospital *K. pneumonia* wild type strain (resistant to amikacin, netilmicin, gentamicin, ciprofloxacin, cefaperazone, cefoperazone/sulbactam, ceftazidime, cefotaxime, cefepim, levomycetin and amoxiclav, sensitive to imipenem, meropenem, and polymyxin) was used. Minimum inhibitory concentration (MIC) measured by serial dilutions in Luria-Bertany medium served as a resistance criterion. Bacteria were incubated in the presence of the tested complex at 37°C for 24 h and transferred daily from the medium with sub-threshold antibiotic concentration to fresh media with consecutive twofold dilutions of the *C. vicina* antimicrobial complex or meropenem antibiotic (Astrazeneca). The MIC value was measured after each passage.

complex of antimicrobial peptides was preserved at the initial level. As an example, Figure presents results of one of experiments, in which the multi-resistant strain of *Klebsiella pneumonia* (resistant to amikacin, netilmicin, gentamicin, ciprofloxacin, cefaperazone, cefoperazone/sulbactam, ceftazidime, cefotaxime, cefepim, levomycetin, and amoxiclav and sensitive to imipenem, meropenem, and polymyxin) was selected for resistance to meropenem or the *C. vicina* maggot antimicrobial complex. Cultivation of *K. pneumonia* with meropenem led to an active rise in resistance to this antibiotic. Resistance of the strain obtained after 25 passages with meropenem was 128 times higher than initially. At the same time, no changes in resistance to the *C. vicina* maggot antimicrobial complex was found. The results confirm the above-mentioned hypothesis and simultaneously demonstrate that the *C. vicina* maggot antimicrobial complex effectively suppresses development of the antibiotic-resistant strain of *K. pneumonia* and can probably be used to treat infections caused by such bacteria. The same results were obtained in experiments with multi-resistant forms of *Escherichia coli* and *Acinetobacter bumannii* [36–38]. On the whole, the spectrum of the complex antibacterial activity includes representatives of many groups of Gram-positive and Gram-negative bacteria, such as Enterobacteriacea, Bacillaceae, Coccaceae, Enterococcaceae, Pseudomonadaceae, Moraxellaceae and Corynebacteriaceae families.

The preparations based on the antimicrobial complex of *C. vicina* or related species of calliphorid flies might considerably expand the drug arsenal for treatment of infectious diseases caused both by usual and by antibiotics-resistant bacteria. The first preparation of this type in the world practice was the purified *C. vicina* maggot peptide complex called FLIP7 (from Fly Larvae Immune Peptides) containing defensins, cecropins, diptericins, proline-rich peptide, and other biologically active substances synthesized by larvae in the process of immune response. Specifically, FLIP7 is used as an active component of the hydrogel designed to protect skin from pathogenic bacteria, including antibiotics-resistant forms. The clinical efficacy test showed that hydrogel has a pronounced antibacterial and anti-inflammatory effect in purulent skin streptococcal/staphylococcal infections.

ALLOFERONS

Alloferons, an olygopeptide family with antiviral and antitumoral activity, represent another group of pharmacologically active substances isolated from the *C. vicina* larval hemolymph [39]. The mechanism of their action is associated with a cytotoxicity activation of the natural killer cells, a lymphocyte subpopulation that recognizes and eliminates tumor or virus-infected cells [39, 40], an increase in production of leukocytic interferon [39, 41], an activation of the NF-kB transcription factor [42], and a decrease in activity of p38 MAP kynase involved in synthesis of anti-inflammatory cytokines [43]. Alloferon-1 is also characterized by a growth-modulating effect on tumor cells [44]. Alloferons form a novel group of immunotropic pharmacological substances synthesized by insects and showing a cytokine-like activity toward the natural killer cells and other cells of the immune system of mammals including human [45, 46]. Currently, alloferon-1 is produced by chemical synthesis [47]. Based on synthetic alloferon-1, there is developed an injection able drug form was manufactured under the name Alloying-alpha and aimed at treating recurrent genital herpes and hepatitis B (Federal Drug Application Guide, issue V, Moscow, 2004, section 20.1.2.2.3.2). Allokin-alpha has passed comprehensive clinical trial at Gamaleya Institute of Epidemiology and Microbiology, Institute of Immunology and Institute of Virusology of the Russian Academy of Medical Sciences, Sechenov Moscow Medical Academy, Central Research Institute of Dermatology and Venerology. Specifically, allokin-alpha showed a high therapeutic efficacy in treatment of relapses of chronic genital herpes [41, 48, 49]. As compared with acyclovir, the "golden standard" of anti-herpetic drugs, allokin-alpha eliminates herpes eruptions much faster and, which is particularly important, provide the longer remission time. The study of immune status of patients treated with allokin-alpha confirmed that the drug mechanism of action included activation of the natural killer cells and the interferon system [41]. The potential sphere of the allokin-alpha use also includes other virus diseases, specifically those caused by oncogenic types of human papilloma virus [50, 51].

ALLOSTATINS

Alloferons, apart from their direct use in medicine, are of interest as prototype molecules for developing new drugs with improved pharmacological properties as compared with the natural peptide. An essential result of studies in this direction became development of allostatins, the synthetic oligopeptides that combine structural features of alloferons with functionally important fragments of some proteins involved in activity regulation of the mammalian immune system cells [6, 46]. Like alloferons, allostatins have pronounced antiviral and antitumoral effects based on enhancement of the natural killer cell cytotoxicity. Comparative studies of antitumor activity of alloferon-1 and allostatin-1 showed, specifically, that the latter has more pronounced adjuvant properties by providing effective recognition and elimination of tumor cells by the cytotoxic lymphocytes. Allostatin-1 also has the higher antiproliferative and anticlonogenic effects on tumor cell population, particularly when combined with cytostatics [52]. Currently, allostatin-1 is used for protection of skin and mucosae against herpes simplex virus (HSV) and human papilloma virus (HPV) as an active substance of allomedin [46, 50, 51, 53–55]. HSV and HPV infections of skin and mucosae are the most common infectious diseases affecting, in clinically obvious or latent forms, practically the entire Earth adult population. HSV is characterized by a lifelong virus persistence and a disease recurrence due to defects in the antiviral immunity System. Use of allomedin either prevents recurrence or decreases its duration and intensity [46, 53, 54]. The HPV infection is also characterized by the chronic course of the disease. Especially dangerous are oncogenic HPV types well known to cause uteral cervical and other cancers. In this context, of special interest is the experience of use of allomedin for treatment of HPV infections with high oncologic risk. Specifically, a high efficacy of the drug was shown in treatment of cervical lesions caused by the most oncologically dangerous HPV types 16 and 18 [50, 51]. It is important to note that use of allomedin provided not only elimination of the disease clinical symptoms, but also led, by the data of PCR analysis, to virus elimination in the absolute majority of patients. These results allow hoping that the allostatin-based drugs would also open the way in perspective to prevention and treatment of the virus-dependent oncological diseases.

CONCLUSION

The study of the *C. vicina* maggot immune system, whose results are summarized in this paper, has allowed revealing two groups of pharmacologically active substances—alloferons and the complex of antimicrobial peptides.

From the point of view classification of medicinal substances, alloferons belong to the large class of immunomodulators, but differing from the known immunotropic drugs (cytokines, chemokines, interferons, interferon inducers, etc.) in their structure, origin, and mechanism of action. In the system of human antiviral and antitumoral immunity, the main pharmacologic target of alloferons serve natural killers—one of the most ancient groups of immunocompetent cells in metazoan animals. Probably, it is the evolutionary antiquity of these cells which accounts for the fact that among the insect immune response peptides there was discovered the substance able to regulate activity of this chain of the mammalian immune system. Another target of alloferons is the interferon system playing the key role in the vertebrate antiviral immunity, but unknown in insects. At present, alloferons are used in medicine for treatment of some chronic viral infections, while results of preclinical studies show that in future they might find the wider use including treatment of oncologic diseases.

The discovery of alloferons stimulated development a new group of immunotropic drugs—allostatins. Allostatins are synthetic peptides whose structure was "calculated" by comparative analysis of amino acid sequences of alloferons and immunologically active mammalian proteins/peptides. The resulted obtained hybrid molecule, like alloferons, produces stimulating effect on cytotoxic activity of the natural killer cells and interferon production, but differs from alloferons in pronounced adjuvant properties—i.e., the ability to enhance immune recognition of alien antigens, for example, in the process of antitumoral vaccination. This property makes the application of allostatins particularly promising for oncology, specifically in treatment and prevention of virus-

dependent forms of cancer. Currently, allostatins are used to increase resistance of skin and mucosae to viral infections caused by viruses of human simple herpes and papilloma.

Antimicrobial peptides are another promising group for use in medicine; they include immune response proteins and peptides in *C. vicina* maggots and in other calliphorid flies. An investigation of antimicrobial peptides in insects and other animals already has more than 30-year history. Nevertheless, none of the known peptides so far has found application in medicine. The preliminary studies of FLIP7 whose composition includes the *C. vicina* larval defensins, cecropins, diptericins, and proline-rich peptides allow hoping that drugs of this type will replenish the antimicrobial drug arsenal aimed at treating and preventing bacterial infections, including those caused by the antibiotics-resistant "superbacteria."

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