

Celebrating 10 Years in research publishing: scientific traditions of Open-Access Journal **CARDIOMETRY** as the mirror of fundamental and applied biomedical problems

Oleg I. Kit, Alla I. Shikhlyarova*, Elena M. Frantsiyants, Galina V. Zhukova

National Medical Research Centre of Oncology
Russia, 344037, Rostov-on-Don, 14 line ave. 63, building 8

*Corresponding author:
shikhlyarova.a@mail.ru

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The 10th anniversary of the international journal **CARDIOMETRY** is a good opportunity to summarize achievements and highlight the important milestones in the life of the journal with respect to the contents of the journal associated with most advanced research information about the topical issues in cardiology and allied sciences biology and medicine. The ideas on a system-related approach and an integrative assessment of the actual organism status as a whole, which lay the foundation of the journal philosophy, allows covering as wide as possible a great variety of the aspect what is the norm and what is pathology that is a substantial prerequisite for delineating clearly structured themes treated by each issue of the journal and for making in such a manner a collection of the journal issues, with cardiology as a common thread, that

distinguishes **CARDIOMETRY** from all other profiled scientific journals.

We think it is appropriate to take this excellent opportunity to congratulate heartily on behalf of the top management and the staff of the National Medical Research Centre of Oncology, Rostov-on-Don, Russia, the Editorial Team and all the co-workers of the journal **CARDIOMETRY** for the unique possibilities to make presentations of our research topics therein since 2015. We are very appreciative for the kind support and encouragement by the journal in publishing our original research reports that have made possible to submit our breaking-through fundamental concepts in the research work undertaken by our Oncology Center to the international scientific community: first it is a discovery of the law of developing adaptational reactions by a human organism, the theory and practice in complex system control on the basis of the activation therapy principles; second it is development of mechanisms of influence of some factors of electromagnetic nature made on the processes of the tumor growth, including impact by chronic neurogenic pain and studies on the role of comorbid states on the realization of a malignant process; third they are the latest experimental developments in mitochondrial therapy.

In fact, each of the above mentioned topical issues in research has dictated the tonality of the respective **CARDIOMETRY**'s thematic-tuned issue, with not departing from research studies on the cardiovascular system performance states, inseparably linked thereto, with addressing problems of hemodynamics, rather extending the concepts on structural & functional alterations in the heart under the conditions of oncopathology and therapeutic actions, effects and exposures. As a result, we have cleared the philosophy and confirmed the transition from the paradigm of psycho-somatic medicine to a new one: the paradigm implying a dependence of the physical and psychological condition on the archetype of an integral adaptational reaction by an organism in the totality of the mechanisms responsible for the formation of the above reactions.

Adaptation reactions and activation therapy

This theme displaying the new wave of knowledge has been substantially treated in **CARDIOMETRY** Is-

sue No.7 under the topic heading “Treatment and prevention of cardiovascular system diseases: system oriented approach vs. local control”.

The research VIP of that journal issue was Lyubov Kh. Garkavi, an outstanding scientist, who made in cooperation with Maria A. Ukolova and Elena B. Kvakina the discovery of “Pattern of development of qualitatively differing general unspecific adaptational reactions of the organism”, Scientific Discovery Registration Certificate No. 158 issued by the Committee on Inventions and Discoveries at the Council of Ministers of the USSR, 1975.

Undertaking a journey in a space and time continuum “back into the future”, let us turn our eyes on some historical photos captured this great thinker, researcher and absolutely charming lady born in Rostov-on-Don.

Garkavi’s greatest endeavor has been her original concept of **unspecific adaptational reaction of activation**, produced by a human organism as a response to stimulation of a medium intensity, i.e. an intensity of a stimulus in the middle between a strong and a weak stimulation. According to the present-day context interpretation, as against **stress** as a strong response by a human organism according to H.Selye, an outcome of this sort of reactions is a substantial, stable increase in the unspecific resistance of the organism to unfavorable factors of different nature, including the growth

of malignant tumors. Realization of this archetype of the reaction by an organism is performed with participation of control systems in the brain, regulatory impacts made by hypophysis, activation of actuating endocrine and immune organs, under moderate energy consumptions and balanced anabolism-catabolism processes.

It has been just No.7 CARDIOMETRY issue that has made available to the scientific public the conceptual philosophy of the elegant system of the adaptational reactions by a human organism both by unraveling the secrets of their features and offering very simple criteria for an assessment of the reaction type, strategies and technologies of activation therapy, supported by practical recommendation how to carry out them. It has been just CARDIOMETRY that has given us the possibility of the proper scientific justification and a better understanding of a role of quantity in developing qualitatively different types of a systemic response by an organism [1-4].

Nowadays, when we in our everyday life are facing an extremely growing number of the economic, ecological, technical, physiological and psychological problems, accompanied by a permanent nervous tension and stress, requiring a high energy use, there is no need to explain how much would be in demand the scientifically justified approaches and programmed regimes of correction of an adaptation status of a hu-



Lyubov Kh. Garkavi, the greatest theorist in medicine and biology, the originator of the concept of “reaction of activation” in a human organism as the unspecific groundwork for health and life longevity, who has invested all her talents and power into the joint project: periodic system of adaptational reactions by organism at different levels of reactivity



Decades of dedicated research work by the Garkavi's Star Team: Maria A. Ukolova, Lyubov Kh. Garkavi and Elena B.Kvakina, who have made jointly the scientific discovery "Pattern of development of qualitatively differing general unspecific adaptational reactions of the organism", the co-origators of the theory and practice of activation therapy (the left photo from left to right: M.A.Ukolova, L.Kh.Garkavi, E.B.Kvakina; the right photo from left to right: L.Kh.Garkavi, E.B.Kvakina, M.A.Ukolova)

man organism. Long-standing research conducted by L.Kh.Garkavi, M.A.Ukolova and E.B.Kvakina, assisted by their excellent researchers' team, has shown that the cost-effective high-efficient activation therapy is capable of solving the topical problem of a rise in unspecific and anti-tumor resistance of an organism, by applying a small-scale influence, based on the knowledge of the multi-level system of periodic repetition of the same name types of adaptational reactions at different levels of reactivity of the organism. The periodic system of the adaptational reactions can be considered as a biological equivalent of the principle of periodicity in nature, including the well-known periodic table of chemical elements by D.Mendeleyev. In this connection, an identification of the role of high reactivity levels with the greatest degree of an efficient response to small-intensity factors has been treated as that of essential practical value [5-12]. L.Garkavi has illustrated this conceptual idea dramatically in her poem as follows:

Little drops of water wear away a solid stone,
 A small stone may initiate an avalanche,
 So the things are different as some people think sometimes,
 Because we may deal with a lot of consequences and impacts,
 Which might be made by a small cause,
 And sometimes a second may last
 Much, much longer than a year.

Activation magnetotherapy (EMF therapy)

Developing of concepts on high biological value of the law of periodicity of adaptational reactions in a human organism, as established in evolution, and effectiveness of high levels of reactivity therein has been supported by our long-term research and design of new technologies of EMF exposures both of local (tumor-targeted) and central (brain-targeted) type. In our experiments we again and again tested and selected some specific modes of frequencies, intensities and exposures in different ranges of electromagnetic fields: they are ultra-low frequency EMF (ULF EMF), extremely high frequency EMF (EHF EMF), the optical range (laser and incoherent light sources), frequency-modulated with signals of different shapes. It has been resulted in an enhanced informative value of the signal and an increased biotropy with respect to cancerogenesis inhibition. The produced effects have demonstrated that there is availability of ULF EMF and other factors of the wave nature to the key mechanisms responsible for the tumor growth that has been confirmed by our studies on some free-radical, immune and morphological processes [13, 14, 16-20]. We have succeeded in the studies on the most important mechanism of an influence made by some rhythmic broad-band stochastic electromagnetic field patterns on intracellular potentials of a neuron and functional activity of

cardiomyocytes [15]. The above mentioned experimental studies have formed the basis of the topical theme treated by **CARDIOMETRY No.11 released in November, 2017, outlined as “Visible effects of an invisible factor: semi-centennial experience in research on electromagnetic field effects produced on organism and pathological processes”**. This journal issue has presented our top-level solutions to some experimental tasks that have been supplemented by the evidence data obtained in the applied research works as a result of realization of the translational accompanying magnetotherapy in cancer at different clinical hospital units at the Oncology Center in Rostov-on-Don.

From the offered research reports one can now appreciate that the approaches to the problem of how increase the life quality in patients upon applications of ULF EMF at the stages of complex treatment of cancer have been successfully applied in practice. That has been evidenced not only by the significant outcomes of the anti-tumor treatment, but also by the statistically significant data on the reduction in the rate of complications for the part of the functional condition of the brain, the central regulation of homeostasis, the cardiovascular and respiratory system in patients with tumors of the brain, the lungs, the breast, the bladder and the genitals by initiating the required anti-stressor adaptational reactions [21-26]. In infants with complicated forms of hemangiomas, upon their exposure to optical radiation in the infrared region of the spectrum, it has led practically to full regression of the tumor due to removing necrotic masses, sclerosing vessels in hemangioma and activation of the immune defense upon completion of 5-10 Photo-Chromotherapy Method (PCM) sessions [25]. The efficacy of the above mentioned activation magnetotherapy is comparable with that produced by xenon therapy, the programmed regime of which is characterized by a more pronounced recovery actions and effects under deep disorders associated with postcastration syndrome (PCS) in women of reproductive age [24]. In this connection, it should be noted that activation therapy, in addition to oncology and cardiology, has found its application by a large number of specialized medical institutions including those in space and sports medicine, when tracing the line of cardiovascular researchers. So, an exemplary case to illustrate this has been published by **CARDIOMETRY No.15 in November 2019 [27]**.

So, it can be stated that the theory of adaptational reactions has been properly supported by the clinical practice of activation therapy as the most valuable, essential, criterion for justification of the accompanying therapy approaches being designed nowadays.

Cardiotoxicity and cardiometric approach in oncology

An important point is that **CARDIOMETRY** always publishes evidence data and outcomes pertaining to most topical research themes, which are in the spotlight of the leading researchers. **CARDIOMETRY No.13, November, 2018, titled as “Cardiology in Oncology”** is no exception: this issue has taken up the baton in releasing fresh publications discussing the discovery of adaptational reaction by a human organism and their developing patterns, made by Prof. L.Kh.Garkavi, Prof. M.A.Ukolova and Prof. E.B.Kvakina in 1975 at the Oncology Center in Rostov-on-Don. Adhering to this promising way in science, it should be noted that much thought is being given to the promotion of the fundamental sciences: cardiometry, adaptational medicine, mitochondrial energy of the heart, biochemistry and hormone-related research by Prof. Oleg I. Kit, MD, General Director of the National Medical Research Centre of Oncology at the Ministry of Healthcare of the Russian Federation, Full Member of the Russian Academy of Sciences.

The widest range of the expertise of Prof. Oleg I. Kit and his high professional level in surgery provide always the required support and assistance in conducting pilot experimental studies, targeted at revealing the mechanisms responsible for hemodynamics disorders and cardiotoxicity. It is because of the cardiometric approach that permits pioneered qualitative and quantitative assessments of a toxogenic impact made by a malignant tumor and effects produced by anti-tumor therapy on hemodynamics and metabolic processes in the cardiac muscle cells, considering the categories of the interconnected electrophysiological, metabolic and adaptation processes.

The challenging issues associated with the mechanisms of hemodynamics disorders and cardiotoxicity have become an important focus in oncology. Some unsolved problems have been discussed therein: what importance has a cardiometric control and monitoring at the stages of the anti-tumor treatment in onco-



Prof. Oleg I. Kit, MD, General Director of the National Medical Research Centre of Oncology at the Ministry of Healthcare of the Russian Federation, Full Member of the Russian Academy of Sciences, research architect, mastermind and inspirer of fundamental scientific concepts and their clinical applications in the context of most advance solutions to topical biomedical problems

logical patients? Can monitoring of cardiotoxicity and thrombotic complications be used as an instrument to correct and improve the quality of cancer treatment? What are electronic resources of cardiometry in oncology?

Most solutions to the above listed problems have been presented in detail in *CARDIOMETRY* No.13, 2018 where first of all given are an analytical review of the interplay between cardiology and oncology and evidence that cancer and cardiovascular diseases possess a similar biological mechanism of their development. During the complicated process of cancerogenesis, the cells are subjected to several “knock” impacts that initiates the full neoplastic transformation with starting execution of the program of the growth, invasion and metastasizing. Similarly, the pathogenesis of the cardiovascular diseases is a multiple step process with identical risk factors [28].

As it has been already noted, one of the best *CARDIOMETRY*'s traditions is an integration of the theory and practice. So, some fundamental reports have been published by the journal which discuss research works on free-radical and hydrolytic processes in car-

diomyocytes in rats upon actions and effects made by doxorubicine and protective action produced by pre-ductal and trimetazidine. Some clinical aspects of cardiometry have found their reflection in an assessment of cardiotoxicity in anthracycline class medication in breast cancer patients. The researchers have submitted the relevant data on complex monitoring of electrophysiological, metabolic and adaptive criteria, which have a great prognostic value just with respect to cardiotoxicity [29, 31, 32, 35, 36].

Prediction of complications in case of other cancer localizations, in particular under operable tumors in the gastrointestinal tract, has made it possible to determine a high risk of thrombotic complications, and, based on the blood coagulation test data, parameters of an extended coagulogram and a new global homeostasis test, to offer a fresh model of predicting venous thrombosis development and using direct oral anticoagulants, direct oral anticoagulant agents (DOACs), absorbed in the proximal gastric regions [33, 34].

The journal has provided a rare analysis of psychopathophysiological aspects of cardiovascular diseases in lung cancer patients [37]. Original innovative research reports on cardiotoxicity have been published in *CARDIOMETRY* No.16 (May, 2020), where a clear-cut morphological portrayal of some specific markers of cardiovascular pathology in breast cancer patients under systemic chemotherapy is completed [38].

Cardio- and neuro-physiological aspects of oncology. Chronic neurogenic pain

Scientific interfaces constructed by *CARDIOMETRY* in the area of oncology are linked through pathological connections to the initial law-based alterations in CNS. There is no doubt that the cardio- and neuro-physiological components may exist independently, but however, in the context of oncology, they construct some specific “alliances”, which may aggravate the tumor disease. Considering this conceptual idea, *CARDIOMETRY* No.17, November, 2020, with its headline “Cardio- and neurophysiology” has revealed some secrets of complex mechanisms responsible for development of malignant tumors against the background of chronic neurogenic pain.

It is well known that neuropathic pain is defined as that caused by damage or a disease of somatosensory nervous system. It is theorized that chronic pain can be treated not as a symptom of a disease, but represents by itself an independent disease requiring its own

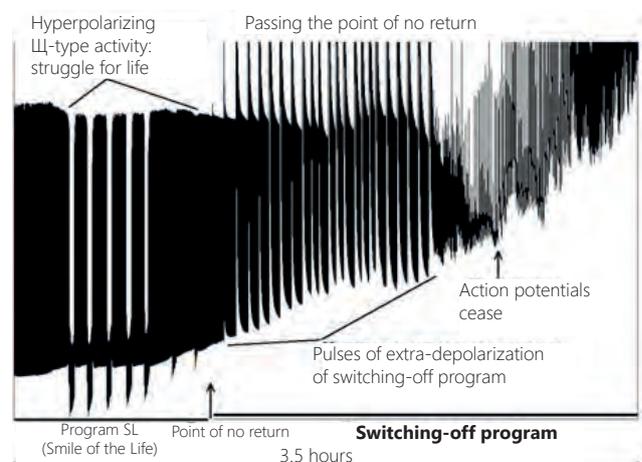
etiopathogenic treatment. The pathophysiological mechanisms of chronic pain are of combined nature and include both a nociceptive (somatic and/or visceral) component and the neuropathic (neurological) one. It has been shown that pain impacts of different nature induce changes in the main types of metabolism, mobilization of adaptive metabolic mechanisms, tissue lesion and, that is especially important, dysfunction of the vascular system. Neuropathic pain, occurring even under a short-time damage of a tissue or nerves, initiates a great number of adaptational reactions, which are maintained at the cell and at the molecular level, and which, in their turn, may prolong the pathological process of other etiology against the background of the already formed symptom complex of chronic pain.

This challenging issue is the concern of many medical doctors and researchers, which make their great efforts to identify the primary cause of the CNP appearance and initiation as well as reveal mechanisms responsible for protection with chronic neurogenic pain (CNP) some other pathological processes, oncology as leader among them. This exclusive theme has been in the spotlight of the research work conducted by the Rostov Oncology Research Center according to the Governmental Task assigned thereto. The completed studies have demonstrated convincing results in an understanding of the determining role of CNP in stimulation of a tumor process, beginning with molecular-genetic, biochemical, energetic, morphological and up to and included gender-related levels in the evidence for the interplay between the mechanisms of separate pathologies.

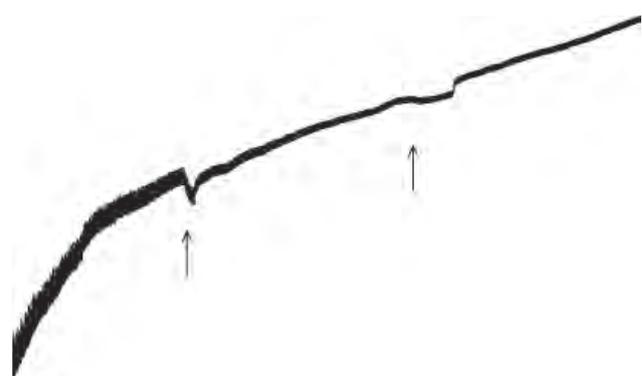
So, we decided “to unspool the coil of the mystery” of the mixed pathological events by searching “in the ball for the red twine” to find the way out of the above mentioned research labyrinth. For the purpose of our experimental studies, the model of chronic neurogenic pain (CNP) was reproduced by applying a ligature to the sciatic nerve from both sides in an animal that was followed by further investigation of the entire range of changes, alterations and modifications found in the organism under the conditions. To gain insight into what is the matter with the pain source has become possible by unique intracellular electrophysiological experimental studies of active neurons in the grape snail *Helix pomatia*, as an integral part of the organism in vivo, which were conducted by **Valeri I.Orlov**, a passionate Russian researcher in the field of

electrophysiology, who departed this life reaching the peak of his research efforts in 2021 in the pandemic. For the purpose of experiment, used has been the Orlov’s original electrophysiological method of continuous recording of intracellular bio-potentials of animal neurons by applying a long-term low-threshold action (LTA) to the main nerves due to a graded pressure to produce a pain effect of the subthreshold level that over time turns into increasing pain [39].

For the first time in the world science, objective evidence for the long-term low-intensity action of pain on the electrophysiological characteristics in a CNS neuron has been obtained. Revealed are the changes in the amplitude and the action potential firing rate, the membrane potential level and the pattern of the neuron pulse activity, traced continuously, up to full neuron potential turning-off. It has been detected that, when removing the pain factor, there are some points of return to the norm available, and, in case of longevity of the pain action, the functional state of the neuron passes the point of no return, after which the neuron electrophysiological potentials reach zero value, indicating the cessation of its life.



Dynamics of passing the point of no return by the command neuron in CNS



Termination process

Thus, the dynamics of the functional state of a neuron in vivo, under prolonged action of the pain factor, reflects nonlinear changes in the membrane potential, firing rate, and amplitude of AP. This characterizes the phase process of the formation of a pathologically stable pain state of the neuron, despite the readiness of the membrane mechanisms at the points of transition to a response aimed at returning to life. So, the complications that occur in various diseases, including those in cardiology and oncology, can be associated with chronic pain due to prolonged compression stimulation of neurons, which develop at the site of the nerve compression or in areas with impaired nervous regulation because of the compression effect of the tumor. It can often be observed that in cardio- or oncological patients, pain first appears as flashes, and then it transforms into a repetitive one with an increasing force, or into a continuous pain sensation, as was shown in continuous long-term (up to 5 days) recordings of experiments on living neurons under study. The obtained material reveals opportunities for an understanding of the electrophysiological component of the mechanisms of chronic neurogenic pain and may be of interest for predicting the effectiveness of accompanying pain therapy.

In the process of studying the combined effect made by CNP and the growth of experimental tumors, a *concept has been formulated according to which the neuropathic nature of pain resulting from the compression of the command neuron or the ligation of the sciatic nerves is essentially identical to the implementation of genetic programs for the control of life and death, repeating events in carcinogenesis with the progression of the malignant growth.* In other words, the initiation and chronicization of pain at the local level of the nervous system can lead to a generalization of the pain syndrome and contribute to the *cancelation of the genetically predetermined programs of carcinogenesis.*

Evidence for this postulate was presented when studying the mechanisms of the cancellation by pain of the genetically determined inhibition of the growth of a malignant tumor in an experiment on mice of the C57BL/6-PlautmI.IBug-ThisPlau6FDhu/GFDhu line, which had a knockout in the urokinase gene, and the C57BL/6 line with the normal genotype [41, 42, 44]. When modeling in mice of both lines the process of B16/F10 melanoma growth under conditions of CNP, it has been found that only in experiments on mice with the uPA gene knockout, neuropathic pain causes

a double acceleration in the formation of the melanoma tumor, stimulation of the growth of primary tumor nodes, multiple metastasizing to lungs, shortened life span, the appearance of pronounced gender characteristics of the malignant process course. In other words, CNP initiates the operation of the mechanisms for the cancellation of the genetically programmed process of the urokinase inhibition control of the tumor growth in genetically modified mice.

What signaling pathways can be involved in the knockout of the urokinase gene, which itself contributes to the inhibition of the tumor growth and metastasizing?

Firstly, some components of the kallikrein-kinin system were studied, namely, the content of prekallikrein, kallikreins 1 and 14 (KLK1 and KLK14), involved in the processes of carcinogenesis, pain and inflammation. It turned out that the urokinase gene knockout mice had significantly higher baseline levels of kallikreins and prekallikrein in the skin, with males having especially elevated KLK1 levels and with females having the higher KLK14 content. This suggests that with a deficiency of urokinase in the body, some compensatory changes occur in the system of tissue kallikreins. This has been clearly demonstrated in the study of tumor tissue in knockout animals, where a lower content of all studied enzymes has been determined, especially pronounced for KLK14, confirming the existence of complex proteolytic cascades between the families of the uPA/uPAR, kallikreins, and metalloproteinases which modulate the cellular signaling pathways [42].

Secondly, the study of the effects made by CNP on the content of biogenic amines in the brain in tumor-bearing mice with a knockout of the urokinase gene (uPA) has indicated that one of the factors leading to the cancelation of the genetically determined inhibition of the growth of transplanted B16/F10 melanoma is the suppression of the noradrenergic, serotonergic and dopaminergic systems of the brain, which had been initially activated to compensate for urokinase deficiency. The data on enzyme linked immunosorbent assay have formed the evidence base for such a conclusion, based on the determination of the content of adrenaline, norepinephrine, dopamine, histamine, serotonin and 5-hydroxyindoleacetic acid as factors reflecting the change in the state of the neurotransmitter systems of the brain during the modulation of the tumor growth program with CNP [30, 41].

It is easy to see that a situation, in which two or more pathological processes take place in their combination, can be attributed to the concept of comorbidity. Most often, comorbid conditions are defined as referred to the existing main disease, as, for example, in oncology, when diagnosing with cancer as the main disease, one or more systemic disorders are necessarily recorded, including diabetes mellitus, hypothyroidism, obesity, hypertension, heart and lung diseases, etc. However, there are practically no studies of the pathogenetic aspects of comorbidity and no relevant experimental models: a malignant tumor against the background of obesity, diabetes mellitus, thyroid dysfunction that seems to be a very urgent problem. Behind the lack of development of complex pathogenetic therapy for complicated and modified forms of common diseases (CVD, malignant neoplasms, endocrine and immune pathologies), there is the absence of fundamental developments that reveal the mechanisms of cross-influence of various nosological conditions.

This “untrodden path” in science is attracting scientists now who are facing a complex clinical picture of concomitant pathology against the background of the main disease. The question arises, how to decode a system that demonstrates high complexity, for example, cancer, in order to determine the factors that modify this process? Modeling of combinations of the corresponding “driving factors” in the model system of the main process comes to the rescue. Thus, modeling of various pathological processes in one object seems to be the key to understanding complex inter-system relationships.

In the special issue No. 21 CARDIOMETRY, February 2022, Modeling of Pathological Processes has been announced as the headline thereof with making attempts to discover the relationship between the growth of malignant tumors and their environmental associates, i.e. some comorbid conditions. In the presented experimental works, bold attempts were made to implement the idea of how the mechanism is initiated and actuated, which is responsible for the behavior of tumors of various types is, up to genetically modified ones, under strictly specified conditions, in the presence of another pathological condition in the body: chronic pain or hypothyroidism, obesity or diabetes mellitus. The same profile of research, “model in model”, has been revealed through the involvement of biochemical, electrophysiological, hormonal, morphological methods, the totality of the results of which

states the possibility of predicting the ways of regulating the tumor process, metastasizing, life expectancy and gender differences [44-48].

So, a logical transition from the study of the effect made by CNP on the tumor growth has become the next stage in the creation of experimental models of the tumor growth in diabetes, the prevalence of which continues to increase many times over. The most convincing were destructive changes in organs outside the area of the primary tumor node (the kidneys, the ovaries, the peritoneum), which could serve as a strong evidence for the implementation of the mechanism of the tumor progression when modeling the comorbid state of diabetes mellitus. At the same time, the aggressive nature of the tumor progression was manifested in the pattern of blood filling of the vessels and hemorrhage, followed by the release of tumor cells, their settlement, higher proliferation, the formation of strands and compaction of cell aggregations throughout the volume of the affected organ. The process of the secondary intra-organic generalized growth in the ovary, the kidney, and peritoneum of Guerin's carcinoma, initially transplanted under the skin of an animal under the conditions of diabetes, bears witness to the commonality of the target determining influence of diabetes [45].

However, some gender-specific features of the tumor progression in female and male rats were noted: in females it was the case with active metastasizing with small primary tumors, and in male rats we recorded stimulating the growth of the primary focus of the tumor without metastasizing. It has been found that the above differences are associated with varying degrees of saturation of the tumor and perifocal zone with glucose and determined by the state of the insulin/insulin-like growth factor (IGF) axis. Thus, the morphological examination of the organs subjected to metastatic lesions of Guerin's carcinoma in female rats with diabetes mellitus makes it possible to establish not only the synergy of both pathological processes, but also a powerful pro-oncogenic effect of the comorbid state of diabetes in the implementation of the tumor growth program.

In the same issue of the journal, the modifying effect of obesity on the concentration of sex hormones and their receptors in endometrial adenocarcinoma and its surrounding tissue is considered. It has been found that obesity exacerbates hyperestrogenism and progesterone deficiency in adenocarcinoma and en-

riches the latter with androgen and estrogen receptors, with the prevalence of estrogen receptors ER α over ER β , which can cause autocrine-paracrine regulation of the growth and metastasizing of the malignant process in patients with endometrial cancer [47].

Among the comorbid conditions detected during the growth of malignant tumors, thyroid dysfunctions being an integral part of the pathogenesis of cancer not only in women, but also in men demonstrate a high occurrence rate and are accompanied by paraneoplastic disruptions in the content of thyroid hormones and cortisol. An experimental model of hypothyroidism in male and female rats, reproduced for 30 days using Mercazolil, followed by modeling of 2 variants of the tumor process (Guerin's carcinoma and sarcoma 45), made it possible to compare gender differences in the dynamics of the tumor progression and the level of thyroid hormones: triiodothyronine (T3), total thyroxine (T4) and pituitary thyroid-stimulating hormone (TSH). Against the background of hypothyroidism in female rats, the volumes of tumors were significantly lower, and the survival rate was higher compared to the reference. In male rats, the parameters did not differ from the reference. The explanation for the above gender differences is that due to the appearance of the T3 and T4 deficiency against the background of an increase in the TSH level differently have a proliferative and anti-apoptotic effect on cancer cells, regulating gene expression and stimulating estrogen-like effects. Therefore, the pronounced effect detected in females is due to the prevalence of estrogens involved in the regulation of the thyroid gland [48].

In addition, certain gender differences in the processes of lipid peroxidation and the redox status of the heart and the tumor in rats with combined pathology have been revealed that contributes to the features of oncogenesis in males and females and their life expectancy.

We have come to the most important question of the prospects for solving the key problems of the role of comorbid pathology in cancer, and, possibly, to a new bio-therapeutic approach, which is gaining immense research popularity throughout the world.

The 21st century has boldly declared itself by penetrating into "the holy of holies" - compartmentalization of intracellular structures, mitochondria, and accumulated scientific data confirming their unique role in the regulation of energy metabolism, stem cell dif-

ferentiation, proliferation, migration, apoptosis, and necrosis. It is known that under the conditions of high loads, mitochondria carry out the process of complex formation of large associates, the transfer from one cell to another, with retaining the mitochondrial DNA code. Recent evidence has shown that the physiological properties of healthy mitochondria provide their ability to replace damaged mitochondria, suggesting that replacing damaged mitochondria with the normal ones may protect cells from further pathological changes. Moreover, mitochondria can also be actively released into the extracellular space and potentially be transferred from cell to cell in the central nervous system. This enhanced interest in mitochondrial therapy calls for a better understanding of the mechanisms responsible for mitochondrial transport, integration, and cellular defense, especially in human diseases such as cardiovascular disease, metabolic syndrome, neurodegenerative diseases, immune system disorders, and cancer.



Prof. Elena M. Frantsiyants, Deputy General Director for Science, Doctor of Biology, Chief of the main scientific development projects according to the National Governmental Task, including the development of methods for mitochondrial transplantation, the research philosophy pioneer and driving motivator of the developments in mitochondrial therapy at the National Medical Research Center of Oncology at the Ministry of Health of the Russian Federation.

At present, mitochondrial transplantation has attracted the attention by many scientists in the world. Mitochondrial transplantation is considered as a potential therapeutic method that can be used to treat specific diseases associated with mitochondrial dysfunction or mtDNA damage. Previous studies have shown that isolated mitochondria from a variety of sources, including cultured stem cells or autologous tissues, yield successful results when applying to injured tissues, organs, or cells in developing mitochondrial therapy approaches.

In a complete set of our papers presented by us in CARDIOMETRY Issue No. 22, May 2022, we review the latest evidence data on the involvement of mitochondria in the mechanisms of malignant transformation, mitochondrial dynamics of metabolic programming, features of mitochondrial transplantation in vitro and in vivo in models of ischemic reperfusion injury of the heart, the lungs, the spinal cord, and the liver [49]. Another article published therein, devoted to the biological effects of mitochondrial therapy, shows the possibility of preventing from the development of myocardial infarction and blocking the metastatic activity of B16 melanoma in mice with intraperitoneal transplantation of intact heart mitochondria, against the background of chronic neurogenic pain. The heart is an organ with high energy requirements, hence it is not surprising that mitochondria account for 30% of the total volume of cardiomyocytes and generate approximately 95% of ATP in the organism. However, in order to understand how the structure of the myocardium changes in an extreme situation, when pathological processes overlap (a bi-model system of chronic neurogenic pain and melanoma growth), a morphological analysis of the heart muscle was carried out and a real structural catastrophe was revealed, demonstrating deep damage to cardiomyocytes [50]. This article specifically precedes the research work, which reports the results of a symmetrical study in experimental mitochondrial therapy, where one can visually verify the possibility of preventing from ischemic damage and necrosis the heart tissue using intraperitoneal transplantation of live mitochondria [51].

The result of repeated intraperitoneal infusion of a suspension of living mitochondria was not only the prevention of myocardial infarction, but also the blocking of the metastatic aggression of B16/F10 melanoma, growing against the background of chronic neurogenic pain. Complete blocking of metastatic lesions of internal organs was revealed in animals with mitochondrial therapy, while in animals of the reference group, metastases in the lungs were observed in 100% of the cases, and in the spleen - in 95% of the cases, respectively [52,53]. To explore the mechanisms of influence produced by mitochondrial therapy, the content of factors, which induce apoptosis, free radical oxidation, the self-organization processes in the mitochondria of the heart and other somatic organs (brain, liver, skin, tumors) during the growth of melanoma B16 and CNP was investigated.

Issue No. 22 of the journal also presents the results of mitochondrial therapy using allogeneic liver mitochondria in the BALB/c Nude mice with B16/F10 melanoma with slowing down the tumor growth in mice of both sexes. The knowledge gained of the state of mitochondria in pathologically altered cells and the degree of their dysfunction represents important information for a better understanding of the pathophysiology of cancer that gives impetus to the development of mitochondrial pharmacology. In this regard, the data from the article on the content of cAMP in the mitochondria of heart cells and blood serum in the C57BL/6 mice during the growth of B16/F10 melanoma associated with chronic neurogenic pain may be very useful [54].

Thus, mitochondrial transplantation is an innovative treatment strategy for mitochondrial dysfunction to overcome the limitations imposed by agent-based therapies. Mitochondrial transplantation is aimed at transferring functional exogenous mitochondria into mitochondrially defective cells to restore or prevent mitochondrial diseases, when, in other words, the old “engine” is replaced with a new one in order to restore the required performance.

This experimental project to identify the biological effects made by transplantation of functionally active mitochondria into animals with melanoma growing against the background of chronic neurogenic pain is our pilot project. Nevertheless, it can serve as the basis for large programs for the use of MC therapy in the field of oncology not limited thereby, with further in-depth study of the mechanisms of action of healthy mitochondria on pathological processes in the organism.

Completing our essay with running through the pages of some issues of the *Cardiometry* journal, where reflected are many exciting topical aspects of fundamental oncology that are directly related to cardiological issues to integrate an assembly of pathogenetic events, it is necessary to comment on the applied value of the discussed research topics. The highest value and logic of any targeted scientific research is its translation into clinical practice to optimize specialized treatment, functional rehabilitation and rehabilitation therapy.

The time has come when not only in oncology or cardiology, but in almost all areas of healthcare, from pediatrics and gerontology up to sports and space medicine, it is necessary to use the theoretical foundations of the organism’s adaptive control as a self-or-

ganized integrated system. As a result of many years of scientific research on general non-specific adaptational reactions, a new strategic approach has been developed to increase the unspecific and anti-tumor resistance of the organism, an original therapeutic technology has been created: activation therapy: its strategy and tactics have been defined, the principles and criteria for assessing the state of the organism and its systems have been formulated in detail, and applicable guidelines and recommendations have been prepared [6-10].

The translation of fundamental developments into the clinical practice has shown the effectiveness of activation therapy as an accompanying treatment in patients with a malignant process of different prevalence and localization [40]. In addition, under the influence of weak electromagnetic radiation and low doses of biologically active substances, used according to activation therapy algorithms, the possibility of enhancing the action of anti-tumor chemotherapy drugs and reducing their dose, as well as a pronounced activation of the anti-tumor resistance mechanisms in the early postoperative period, has been demonstrated that significantly has reduced the number of complications and improved the quality of life [36].



Prof. Alla I. Shikhlyarova, Doctor of Biological Sciences, Prof. Garkavi's heiress and successor to carry on the research traditions referred to the development of the adaptational reactions theory, moderator of the translation of activation therapy to the clinical practice at the National Medical Research Center of Oncology at the Ministry of Health of Russia, research advisor at the Center for Rehabilitation and Accompanying Therapy of Cancer Patients

Thus, the disclosed typological features of anti-stress ARs, the developed strategies and digitally programmed modes of exposure, simple and adequate criteria for assessing the state of the organism can define the reference points for the use of effective methods of rehabilitation of cancer patients, both together with, between and after courses of anti-tumor treatment. In the latter case, the possibilities of telemedicine can be used.

In November 2021, Issue No.20 CARDIOMETRY appeared and offered some results of the use of unspecific activation therapy in the treatment of cancer of the breast, the cervix, the lungs, the bladder, the primary high-grade brain gliomas and metastatic brain lesions and common colorectal cancer [55]. At the stages of complex anti-tumor treatment, various types of accompanying therapy were used: technologies of central (the hypothalamic region of the brain), local (the bed of the resected tumor), extracorporeal (blood) exposure to electromagnetic radiation of ultra-low frequency (ULF), extremely high frequency (EHF), optical range, pulsed (PMF) and scanning magnetic fields (SCMF). We used new programmed modes of xenon therapy (XT) using a therapeutic circuit for xenon inhalation with gas flow control (GFC). It is important that, regardless of the nature of the acting factors, both electromagnetic and pharmacological effects in the developed programmed modes are addressed to the triggers of the organism's integral response, the formation of unspecific adaptational reactions of an anti-stress nature. This serves as a fundamental basis for the implementation of activation processes at all hierarchical levels of the organism and contributes to the regenerative dynamics of the regulatory systems (the nervous, the endocrine, the immune and the antioxidant defense systems). Of course, the evidence-based arguments for the effectiveness of accompanying therapy are based on the data on the direct anti-tumor effect, life quality and life expectancy of patients.

In the above mentioned issue of the journal, other types of accompanying therapy were also discussed, the implementation of which was carried out via selective plasmapheresis in the chemotherapy of multiple myeloma [57]. That approach made it possible to significantly reduce the toxic manifestations of the disease and chemotherapy and increase the level of the anti-stress reactions. Of great interest is the method of interval hypoxia, which improves cardiac me-

tabolism and hemodynamics [58]. It should be noted that both xenon therapy and controlled hypoxia are unique forms of targeted access to the regulatory centers of the brain that trigger the development of integral reactions of the organism; therefore, the use of exponential modes of activation therapy with gaseous agent exposures has a great future for oncology and cardiology.

Convincing data on the use of other non-specific factors of accompanying therapy, such as cytochrome C, cAMP, or the iodine-containing drug Stellanin, are presented in the articles which discuss the mechanisms and models of the development of lymphoproliferative processes and lung cancer [54,56]. A complete set of highly effective compounds based on succinic acid makes a huge contribution to the development of a new applied branch of the regulation of bio-energetics and adaptive responses [43], which undoubtedly corresponds to the principles of poly-modality of influence and multi-level control of the hierarchically subordinated organism's systems.

In conclusion of our thematic journey through the pages of *CARDIOMETRY*, we can recall the well-known classic expression that scientists often have numerous facts in their hands, but unfortunately, they sometimes are not capable of finding the proper connecting thread. Let us hope that the theoretical heritage left by L.Kh. Garkavy, M.A. Ukolova, E.B. Kvakina will become the very connecting thread that will connect the fundamental laws of adaptation by a living organism with real possibilities and approaches to control the organism's state. The availability of such a scientific platform will make it possible to make a powerful breakthrough in providing targeted recovery, improving the quality of life and rejuvenating the population of our beautiful planet Earth.

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