R.E. KAVETSKY INSTITUTE OF EXPERIMENTAL PATHOLOGY, ONCOLOGY AND RADIOBIOLOGY

R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (IEPOR) is an academic center with significant material and technical resources and cadre, which has a many-year experience in the fields of experimental pathology, biotechnology, molecular and clinical oncology. The Institute was established in 1960 by an outstanding Ukrainian scientist, Member of the USSR Academy of Sciences, Rostislav Evgenievich Kavetsky as the Ukrainian (Kiev-based) Research Institute of Experimental and Clinical Oncology under the USSR Ministry of Health.

Nowadays, scientific research is focused on the following areas:

- Studying the biology of a tumor cell and its microenvironment in the development of molecular and cellular mechanisms of carcinogenesis in order to manage the tumor-host relationships;
- Identification of molecular and cellular markers of the initiation, promotion and progression with the view of developing methods for early and differential diagnosis of malignant neoplasms;
- Studying molecular aspects of pharmacological management of carcinogenesis and formation of drug resistance in malignant cells and epigenetic approaches to modifying it with account for the impact of environmental factors;
- Studying the effect of nanoparticles and nanocomposites on the metabolism of normal and tumor cells and developing approaches to targeted therapies and sorptive detoxification. .

Focus on fundamental and applied studies in the priority areas has enabled the institution to considerably succeed in resolving the pressing issues in the fields of experimental and clinical oncology, which deal with identifying molecular and cellular features of neoplastic disease and correction of the established alterations; identifying and structuring a number of links in the molecular genetic changes associated with the progression of malignancy; developing innovative technologies for differential diagnosis of precancerous and neoplastic processes; developing approaches to resolving the pressing issues in the field of ecology, incl. environmental protection; and developing modern methods for treatment and diagnosis of pathological processes of different origins using nanotechnology.

The following units successfully operate under the institute's aegis: SECTOR FOR SCIENTIFIC/METHODOLOGICAL AND EQUIPMENT PROVISION OF SCIENTIFIC RESEARCH, which includes:

- **Center for Shared Use of Research Unique Instruments / Equipment «Molecular Oncology and Biotechnology»;**
- **Center for Expertise and Determination of Carcinogenic Factors and Molecular Biological Markers of Tumor Growth** (Certificate of Qualification dated 02.12.2011, No. PT-455/11 issued by the State Enterprise «All-Ukrainian State Research and Production Center for Standardization, Metrology, Certification and Consumer Protection»).

CELL BANK OF HUMAN AND ANIMAL CELL LINES. The IEPOR's Cell Bank of Human and Animal Cell Lines was included by the Regulation (Decree) of the Cabinet of Ministers of Ukraine No. 1709 dated December 19, 2001 in the State Register of Scientific Objects that Make up the National Estate. (Certificate of the Ministry of Health of Ukraine No. 41 date 19.02.2009)

EXPERIMENTAL RESEARCH BASE (vivarium).

SCIENTIFIC LIBRARY.

The institute has a permit for **training (postgraduate education and doctorate)** based on government contracts and for specific purposes in the fields of 14.01.07 — «Oncology» and 03.00.01 — «Radiobiology» (Order of the Presidium of the National Academy of Sciences of Ukraine No. 368 dated June 6, 2002).

In the Institute, the National Academy of Sciences' Scientific Council on «Malignant Neoplasm» works.

The Institute publishes **scientific journals**:

- International scientific journal **«Experimental Oncology»** and
- Scientific and practical journal **«Oncology»** (supplement to «Experimental Oncology»).

A series of books **«Seminars on Hematopathology»** is published on a regular basis. Also, the Institute published a series **«IN MEMORIAM OF UKRAINE'S OUTSTANDING SCIENTISTS IN THE ONCOLOGY FIELD.»**

The Institute developed a **Database «Specifics of Functional Oncogenome»** (Certificate of registration of the copyright No. 43893, Database «Specifics of Functional Oncogenome» dated 21.05.2012, Certificate of registration of copyright No. 43894, Computer Software Database «Specifics of Functional Oncogenome» dated 21.05.2012). The database summarized optimally formalized and structured information necessary to understand the key theoretical principles of modern oncology, and functional features of oncogenome and proteome. It is designed to help apply this knowledge in clinical practice.

The Institute pays much attention to cooperation with foreign partners from Austria, Belarus, Cuba, Germany, Poland, Russia, USA, Turkey, France, Sweden, Japan, Italy, and the Netherlands. This cooperation includes joint research with leading academic and medical institutions in these countries in the areas of Experimental Pathology and Oncology. In recent years, research has been carried out as part of a number of international projects and grants, including:

- 7th Framework Program: FP-7 -People- IRSES Mead-Et No 247547 «Novel Medical Adsorbents for Extracorporeal Treatment of Life Threatening Conditions» (Scientific panel: Life Sciences)
- Grant Program VISBY Sweden (Svenska Institutet The Visby Programme) «Identification of cell signaling cascades involved in Epstein-Barr virus induced transformation» (Center Microbiol. Tumor Cell Biol. Karolinska Institute, Stockholm) (2008-2010)
- Grant FEBS – INSERM U 758-TNS de Lyon, France «CD150 receptor on gliomas cells as a target for measles virus» (2009-2011)
- INTAS Grant 04-82-7065 «Implementation and evaluation of a new generation of carbon hemosorbent in treatment of acute and complicated forms of viral hepatitis in Uzbekistan» (Brighton University, UK) (2005-2008)
- CRDF GUKB2-2831-KV-06 Cooperative Grants Program «Expression and function of protein kinase PKD2 in human B-cell lymphoma» (Univ. Washington, Children's Hospital & Reg. Med. Center, Seattle, USA) (2006-2008)
- Fogarty International Center Grant FIRCARTW-01 «The role of PKD2 in Btk-PKCBeta-NFkappaBeta signaling cascades in B-lymphocytes» (Univ. Washington, Children's Hospital & Reg. Med. Center, Seattle, USA) (2005-2008)
- INTAS 05-1000007-418 «Development, patenting and pre-registration of new combined hemosorbent based on mass-fractal carbonic piropolimer and diffuse transparent albumin coating (Brighton University, UK) (2005-2008)
- «Agreement on an Inter-laboratory comparison of the in ovo carcinogenicity assay (IOCA)» (Bundesinstitut fur Arzneimittel und Medizinprodukte, Germany; New York Med. Coll. Valhalla, USA; Nagoya City Univ. Grad. Shc. Med. Sci., Japan) (2005-2011)
- «Molecular pathology of gastrointestinal tumors and improvement of diagnosis» (Dept Surgery Techn. Univ. Munich, Germany) (2009-2013)
- «Development of biological products (biomolecules) based on RNA-based molecular technologies for the correction of violations detected in tumor cell» (Lab. Epigenetics Natl. Center Toxicology, USA) (2010-2014)

As part of **international activities**, IEPOR is actively involved in projects of Organization of European Cancer Institutes-European Economic Interest Grouping (**OECI-EEIG**). The Institute is Ukraine's only one OESI-EEIG member since 1994. This organization is aimed at implementation of innovative, competitive, quality methods of cancer treatment based on the principles of evidence-based medicine. To this end, OESI-EEIG coordinates clinical and scientific studies and helps European cancer institutes to increase the level of training.

The IEPOR's membership in the OESI-EEIG lays an important foundation for greater integration of Ukrainian oncologic science in the European space.

The IEPOR's leading specialists are active members of international organizations, such as ASCO, EACR, ESMO, International Clinical Hyperthermia Society (Indiana, USA), European Society for Hyperthermic Oncology (Rotterdam, The Netherlands), indicating a high ranking of the Institute in international scientific community.

In order to improve the forms of interaction between science, education and production, creating a single scientific and educational/methodological mechanism for training as envisioned in the cooperation agreements with universities and secondary institutions, **the scientific educational complex** was established

under the IEPOR's aegis. This unit is responsible for promoting scientific knowledge, valeological education of the youth, attracting students to scientific work and training of young specialists of high level.

The leading scientists of the institute created a training manual «Oncology. Selected Lectures for Students and Physicians» / Editor V.F. Chekhun — Kyiv: Zdorovya Ukrainy, 2010 — 770 pp. The publication of «Oncology. Selected Lectures for Students and Physicians» as a handbook for students, physicians and lecturers of higher medical educational establishments of III-IV accreditation levels (protocol No. 4 dated October 1, 2010) was approved by the Central Methodological Cabinet on Higher Medical Education of the Ministry of Health of Ukraine.

The Institute has a **Council of Young Scientists**.

The Institute's staff regularly take active part in national and international exhibitions and fora: the International Trade Club, the International Fora «Complex Support of Laboratories» (annual plenary and section presentations at the conference «Medical Laboratory and Innovation in Medicine»); exhibitions with international participation «Ecology»; exhibition of specialized equipment and technologies «From Science to Production»; All-Ukrainian Exhibitions «Barvysta Ukraina»; international specialized exhibitions «High Technologies 2011»; international specialized exhibitions «LABCompLEX-2011»; international specialized exhibitions «Nanotehnologies-2011»; international fora of the pharmaceutical industry «PHARMCompLEX-2011,» etc.

The IEPOR is represented in the global computer networks in three languages, Ukrainian, Russian, and English. The official website of the institution contains the following sections: **General Information** (information about the staffing of the institution, the Center for Shared Use of Research Instruments / Equipment, the Center for Expertise and Determination of Carcinogenic Factors and Molecular Biological Markers of Tumor Growth, the Cell Bank of Human and Animal Cell Lines, Scientific Library, Council of Young Scientists, and Post-Graduate School); **Activities** (Research Priorities, Specialized Scientific Board, International Cooperation, Conferences, Seminars, Courses), **Proposals from Oncologists** (studies that can be performed under contracts or through economic agreements), Structure (presents the management and all the scientific departments of the Institute, their main research areas, staff with individual pages for each employee, major accomplishments, publications, patents and participation in scientific meetings), and other sections — **Public Procurements, Charity Foundation «Uniting Against Cancer,» Contacts,** and **Useful Links**.

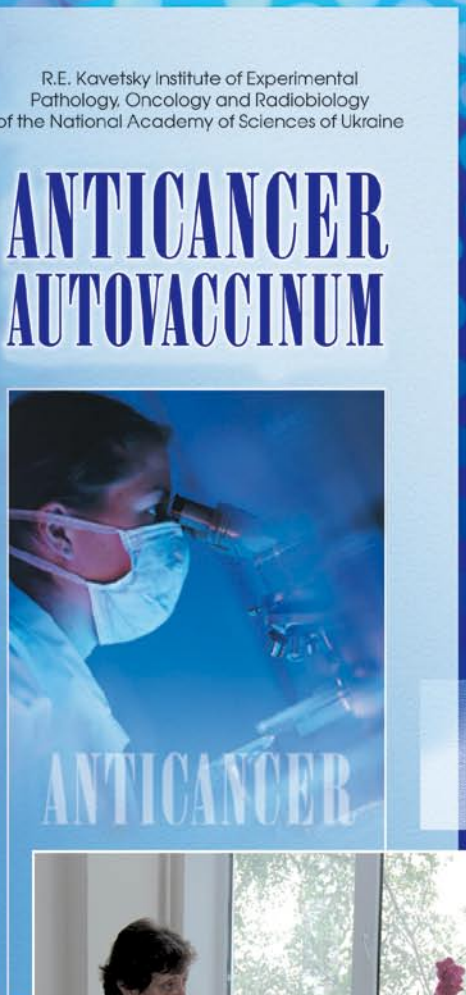
To learn more about IEPOR, please visit our official web-site at: **http://www.onconet.kiev.ua/**

CATALOGUE OF INNOVATION PROPOSALS

of the R.E. Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology of the National Academy of Sciences of Ukraine









Content of the innovation:

A METHOD FOR FORECASTING THE RISK OF MALIGNANT NEOPLASM

It has been established that the majority of malignant neoplasms (MN) are multifactorial diseases and develop as a result of an additive effect of both genetic component, which is highly variable and depends on the nosological form of cancer, and region-specific environmental factors. The risk of MN in families with polygenic inheritance of the disease progressively increases as the degree of burden in the family history increases.

A well-known way to predict the development of MN involves clinical examinations, but in many cases, this approach does not allow obtaining objective information about the risk of MN in the offspring.

The risk of MN in relatives of the proband is assessed using a comprehensive clinical and genealogical study with subsequent genetic-mathematical analysis of the pedigrees (see Figure), which is used as a basis to determine the likelihood of cancer occurrence in the offspring and the contribution (%) of hereditary and environmental components in the occurrence of cancer pathology (Table 1).

As an example, the table below shows estimates of the recurrency risk of endometrial cancer for probands with endometrial cancer. Thus, in families, where the proband's parents were negative, the risk of PN in offsprings is 0.2%, but if one or both parents are positive for cancer, the risk increases to 14.2% (Table 2).

The proposed technology of genetic counseling as a first step in examination of cancer patients has a socio-economic importance, since it allows identifying the hereditary form of the disease and forming groups at risk for malignant tumors.

Table 1. **Technology for genetic-mathematical analysis**

Algorithm for estimating recurrency risk of PN in the offspring	Algorithm for estimating the contribution of genetic and environmental determinants in the occurrence of cancer
I. Classify patients on the basis of clinical and genealogical data, depending on the type of marriage of the proband's parents (mother-father): negative-negative, negative-positive, positive-positive.	I. Determine the number of positive-negative patients in a «parent-offspring» pair on the basis of clinical and genealogical data;
II. Calculate the segregation frequencies.	II. Conduct genetic correlation analysis using monogenic and multifactorial models.
III. Compare the empirical and theoretical segregation frequencies to identify the type of inheritance of the disease.	III. Calculate the contribution (%) of genetic and environmental components in causing cancer.
IV. Calculate the recurrency risk (%) of cancer in the offsprings.	

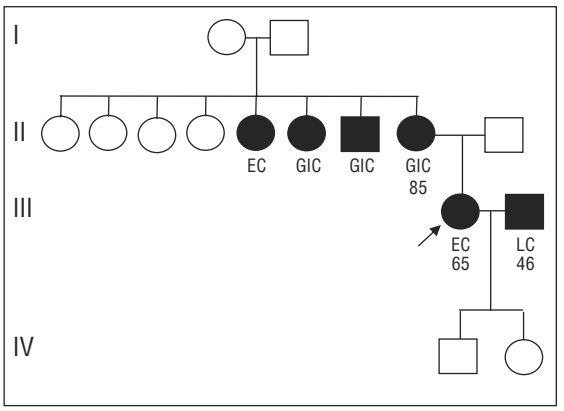


Figure. ***Pedigry of patient S., 65 years old, with endometrial cancer.***

Notes: the proband is marked with an arrow. Arabic numerals indicate the age when the disease appeared, Roman numerals indicate generation.

Table 2. **Evaluation of the recurrency risk (%) of PN for offspring in families of patients with endometrial cancer**

Sequence number of the expected child in the family	Number of offsprings of MN patients				
	0	1	2	3	4
If both parents are negative					
1	0,2				
2	0,2	4,1			
3	0,2	3,9	7,7		
4	0,2	3,8	7,4	11,0	
5	0,1	3,7	4,2	10,7	14,2
If one or both parents are positive					
1	14,2				
2	13,2	19,8			
3	12,4	18,6	24,7		
4	11,7	17,5	23,3	29,1	
5	11,1	16,5	22,0	27,5	32,9

Content of the innovation:

APPROACH TO EVALUATE PRIMARY TREATMENT RESISTANCE IN PATIENTS WITH LOW-RISK NON-HODGKIN'S DIFFUSE LARGE B-CELL LYMPHOMAS

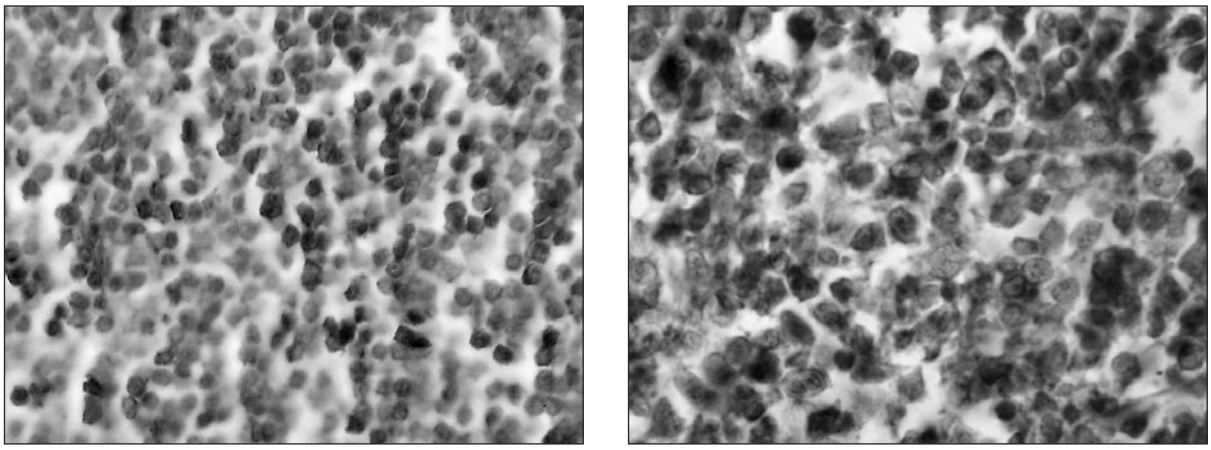
(Developed in collaboration with National Institute of Cancer)

Non-Hodgkin's diffuse large B-cell lymphomas represent a heterogeneous group of malignant tumors that vary in biology, morphological structure, clinical features, therapy response, and prognosis. Diffuse large B-cell lymphoma diagnostics and revealing the factors that allow evaluating the efficiency of therapy, prognosis, and patients' survival continue to be pressing problems of modern oncology.

Despite significant achievements in the therapy of this group of patients, selection of prognostic factors is still a problem to be solved. To define the prognosis in patients with diffuse large B-cell lymphoma, the practical significance of several clinical factors is evaluated. These include: intoxication symptoms, baseline levels of hemoglobin, total proteins and albumin, tumor size, molecular and immunohistochemical markers. Considerable attention is paid to the prognostic significance of protein kinase CβII (PKCβ II).

A method based on the Prognostic Index, which includes the patient's age, performance status, tumor stage number of extranodal sites and serum lactate dehydrogenase level is routinely used for prognosis of treatment response for patients with diffuse large B-cell lymphoma. However, this approach has a limitation: it is not possible to predict the primary treatment resistance in patients with low-risk non-Hodgkin's diffuse large B-cell lymphoma. The authors improved this approach for patients with low-risk non-Hodgkin's diffuse large B-cell lymphoma by additional the evaluation of PKCβ II expression level. This allows identifying patients with poor prognosis, which is defined as a high PKCβ II expression level in more than 80% of tumor cells.

Taken together, the measurement of PKCβ II expression level gives a possibility to predict the primary treatment resistance in patients with low-risk non-Hodgkin's diffuse large B-cell lymphoma (according to the International Prognostic Index). This allows enhancing the first-line therapy and prolonging the relapse-free survival.



PKCβII expression in neoplastic cells of diffuse large B-cell lymphoma

Content of the innovation:

A METHOD TO PREDICT THE COURSE OF DISEASE IN GASTRIC CANCER PATIENTS

Gastric cancer (GC) is one of the most common malignancies. The main method of treatment in gastric cancer is surgery. Assessment of the possible course of GC helps improve the effectiveness of treatment and survival rates of patients.

The authors propose a method to predict the course of gastric cancer by identifying a set of molecular markers in tumor cells, which characterize the biological features of the tumor, including: apoptosis-regulating proteins (p53 and Bcl-2), receptor tyrosine kinases belonging to the ErbB family (EGFR and Her-2/neu), intercellular adhesion molecules (α- and β-catenins), and vascular endothelial growth factor (VEGF). This set of markers helps predict the course of disease and identify appropriate treatment regimens. Immunohistochemical study of the expression of p53, Bcl-2, Her-2/neu, EGFR, E-cadherin, α- and β-catenin, and VEGF is carried out by way of application of monoclonal antibodies to dewaxed slices of tumor samples. Positive expression of p53, Bcl-2, EGFR, Her-2/neu, and VEGF predicts a survival of up to 1 year, while positive expression of α-catenin predicts a survival of more than 3 years.

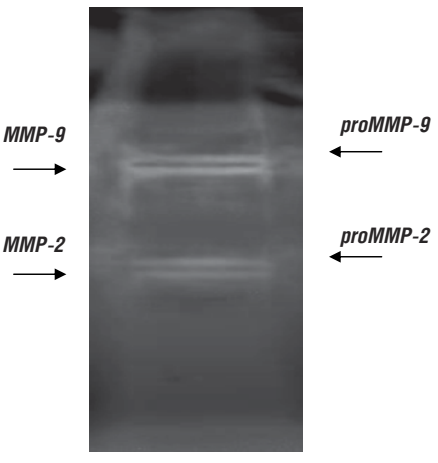
In order to predict the course of GC, it is also possible to use a non-invasive method of determining the level of activation of A and B gelatinases (matrix metalloproteinases 2 and 9). The above mentioned enzymes are synthesized by cells of the tumor, surrounding tissue, endothelial, and immune cells and are engaged in the degradation of extracellular matrix during metastasizing.

Suppression, stabilization, and increased degradation of the extracellular matrix are critical characteristics of malignant growth.

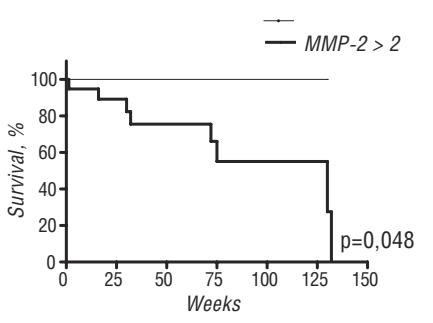
Generally, the levels of A and B gelatinases are measured in the serum of melanoma patients by ELISA and by polyacrylamide gel zymography, and are associated with the overall survival and the level of metastasizing.

The authors propose to determine the ratio of active to latent forms of matrix metalloproteinases 2 and 9 in sera of patients with gastric cancer, which helps monitor the efficacy of anticancer therapy, adjust treatment regimens, and improve survival rates. The ratio of levels of active to latent forms of A and B gelatinases is determined in the serum; and ratios lower than 0.2 for gelatinase A and 0.5 for gelatinase B are associated with a favorable prognosis, while ratios above the aforesaid levels are associated with unfavorable prognosis.

The methods proposed can be used to monitor the effectiveness of anticancer therapy and to predict the course of disease in patients with gastric cancer.



Zymogram of gastric cancer patient serum



Overall survival of gastric cancer patients in accordance with tumor MMP-2 activity (μg/g) (Kaplan-Meier curves, log-rank тест).

Activation index of serum MMP

Favourable prognosis	Unfavourable prognosis
MMP-2 < 0,2 MMP-9 < 0,5	MMP-2 > 0,2 MMP-9 > 0,5

Content of the innovation:

A METHOD TO PREDICT SURVIVAL IN PATIENTS WITH SEROUS OVARIAN CANCER BASED ON Ki-67 PROLIFERATION MARKER AND ESTROGEN-PROGESTERONE STATUS OF THE TUMOR

(Developed jointly with A.A. Bohomolets Medical University)

Ovarian cancer is known to belong to a group of hormone-dependent tumors. This implies an important role of hormonal imbalance in the pathogenesis of this disease. Hormonal imbalance leads to hyperstimulation of ovulation and chronic hyperestrogenia accompanied by reduced secretion of progesterone.

Methods for diagnostics and treatment of ovarian cancer (OC), which are used in clinical practice, are primarily focused on characteristics such as tumor stage, histological structure of the tumor and its degree of differentiation. They do not satisfy physicians, because the degree of differentiation of ovarian tumors, frequency of metastasis and survival of patients do not directly correlate to one another.

The above shows that it to needed to identify additional indicators that objectively reflect the biological characteristics of the tumor. Such indicators may include proliferative activity and expression of steroid hormone receptors.

Mitotic activity can be assessed using flow cytofluorimetry and concentration of hormone receptors in ovarian tumor tissue can be assessed by biochemical radioligand method. These methods, however, are not free from shortcomings. The method of flow cytofluorimetry needs expensive equipment, and ovarian tissue samples used for biochemical assessment of hormone receptor may contain both tumor cells and unaltered epithelium; as a result, it is not possible to determine the concentration of steroid hormone receptors in tumor cells as such.

In the last decade, thanks to the development of new molecular biological methods, it has become possible to assess protein products of genes using specific monoclonal antibodies (mAbs). This method allows evaluating the proliferative potential and receptor status in a tumor tissue with a specific morphological structure.

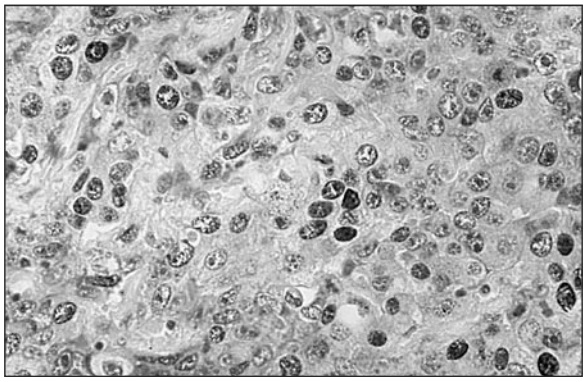
There are integral indicators of the proliferative potential of the tumor and its estrogen-progesterone receptor status. These include expression of Ki-67 antigen and estrogen and progesterone receptors determined using immunohistochemical method. This method makes it possible to objectively evaluate the proliferative activity and the presence of steroid hormone receptors in epithelial cells of ovarian cancer. The method is also instrumental in determining the sensitivity of tumors to hormone therapy.

The task to predict the survival of patients with serous ovarian cancer, who did not receive neoadjuvant chemotherapy, can be approached by immunohistochemical detection of the expression of indicators such as biomolecular markers of cell proliferation: Ki-67 (MIB-1 clone), estrogen receptor (1D5 clone) and progesterone (PgR636 clone) in tumor tissue determining the number of positively stained cells (%).

To establish a statistically reliable 5-year survival prognosis for patients with serous ovarian cancer, the obtained values of markers' expression in ovarian tumors should be compared with the values of their medians (Me):

- if the value of proliferation marker Ki-67 expression is below Me, the 5-year survival rate for patients with ovarian cancer is 75%;
- if the value of estrogen and progesterone receptors expression is above Me, the 5-year survival rate for patients with ovarian cancer is 70%.

The proposed method helps make more accurate statistically reliable prediction of survival in patients with serous ovarian cancer after surgery and can be used in clinical practice.



Expression of proliferative marker Ki-67 in serous ovarian cancer, x400

Content of the innovation:

USE OF CANCER AUTOVACCINES IN A COMBINED THERAPY OF CANCER PATIENTS

While various methods of biotherapy are recommended to enhance the efficacy of classic methods of cancer therapy, achieve complete recovery, and prevent recurrences and metastases, cancer autovaccines (CAVs) are considered to be especially promising.

The authors have developed special approaches to the construction of CAVs on the basis of antigens from patient's tumor tissue modified with cytotoxic lectins (CLs) produced by saprophytic bacterium B.subtilis B-7025. This technique ensures a high specificity and immunogenecity of CAVs due to the presence of modified tumor-associated antigens and microbial adjuvants. The use of CAVs in a combined therapy of malignant tumors of a wide range of localizations and histological forms significantly increases the survival time and improves both immunologic indices and the quality of life.

CAVs are used in the post-surgical period to increase the survival time, improve the quality of life, and prevent recurrences and metastases due to improved anticancer resistance. Depending on the patient's state and necessity of other therapies, the course of autoimmunotherapy includes 3 injections with 7-day intervals followed by re-vaccination (1 and 6 months after the last vaccination); the vaccination is typically performed on day 10 to 14 after the surgery or on day 18 to 21 after the completion of chemo-/radiotherapy. The vaccine is always administered subcutaneously.

The vaccine is indicated for stage 1 to 3 cancer patients after surgical removal of the tumor. The use of the vaccine has no age limitations. It can be used as a means to restore the immunity after surgical intervention or as a means of immunologic correction after surgery or chemo-/radiotherapy.

CAVs provide anticancer effects, help the patient better tolerate chemo-/radiotherapy, and prevent cytopenia. In various nosologic forms of malignant tumors, CAVs prevent recurrence and metastasizing. Also, autovaccine is indicated for treatment of functional immunodeficiency, suppression of phagocytic and cytolytic functions of immunity. CAVs are prescription only agents, and should be administered under close control.

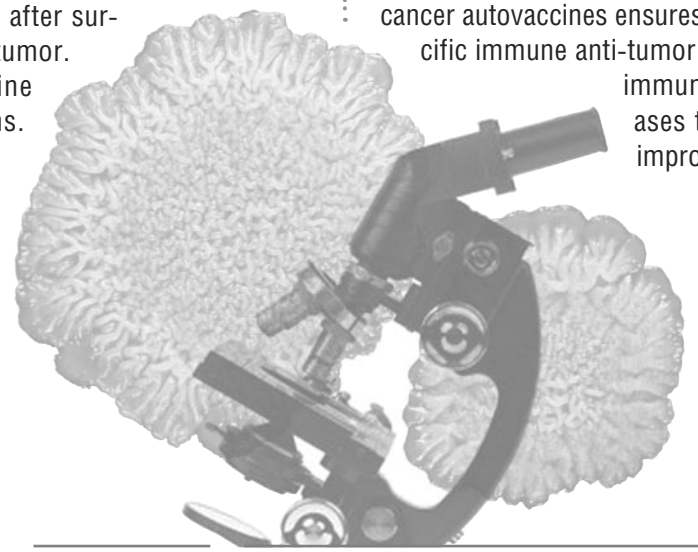
In a combined therapy of gastric cancer, CAVs improve the survival time even in the presence of metastases ($T_{3-4}N_{1-3}M_0$).

In the treatment of lung cancer, CAVs improve the survival time and normalize immunological indices and the quality of life of patients with squamous cell carcinoma and other histological forms.

In a combined therapy of colorectal cancer, CAVs improve the 5-year survival rates. In particular, vaccinated patients with stage $T_{3-4}N_0M_0$ colon adenocarcinoma showed an average 5-year survival rate of 88.37% and a recurrence-free rate of 79.67 versus 74.44% and 63.91%, respectively, in patients treated with surgery only.

In a combined therapy of breast cancer, CAVs improve the 5-year survival rate, normalize immunologic indices, and improve the quality of life.

To sum up, immunotherapy with the use of cancer autovaccines ensures the formation of specific immune anti-tumor response, normalizes immunologic indices, increases the survival time, and improves the quality of life.



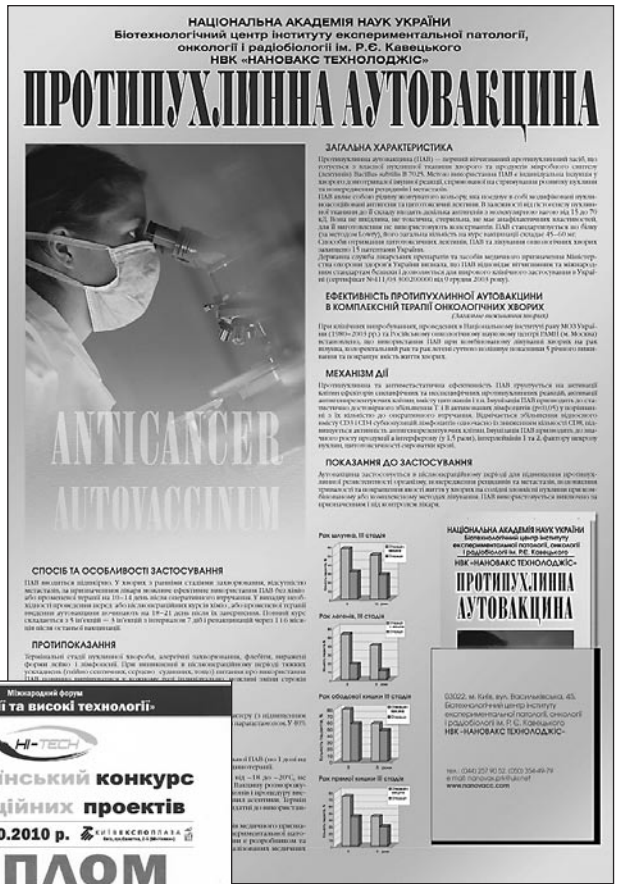
Content of the innovation:

A METHOD TO INCREASE THE EFFICACY OF ANTITUMOR VACCINES

Recent years have seen an intensive development of new ways and means of tumor immunotherapy (vaccines, immunoadjuvants, cytokines, etc.) based on the specific induction of antitumor resistance in the host. One reason for the interest in immunotherapy is that the efficiency of traditional anti-cancer methods (surgery, chemotherapy, radiology) has largely reached its maximum. At the same time, possibilities for enhancing immunotherapy results based on defining the regulation patterns of tumor immunity and optimized biotechnological processes are far from being exhausted in oncology. Therefore, the development of all-round technologies for the production of antitumor vaccines from tumors of different origins for specific immunotherapy is a very promising approach.

The authors developed a method for increasing the effectiveness of anticancer vaccines through successive application in combined therapy regimes of a cytotoxic lectin isolated from the cultural liquid of B. subtilis B-7025 and antitumor vaccine produced on its basis with the view of improving the life expectancy and quality. An advantage of the invention is that the bacterial lectin is used not only for the production of the anticancer vaccine, but also as an immunomodulating agent that is injected in intact mice or tumor-bearing animals before surgical removal of the tumor only several times. Due to a rapid antigen presentation and stimulation of the activity of immunological reactions, the antitumor resistance increases. This not only increases the therapeutic effectiveness of anticancer vaccines and helps improve the quality of life but also makes the treatment less expensive.

Thus, the proposed method allows obtaining a higher therapeutic efficacy in mice compared to anti-tumor vaccine alone and thus saving on the purchase of appropriate adjuvants. The method does not require additional special equipment and can be widely used to increase the efficacy of anti-tumor vaccines. The high efficiency and lack of adverse side effects make this method a promising approach which can be used in cancer therapy and justifies implementing it in the clinical practice with the view of improving the treatment efficacy in post-surgery patients to prevent recurrences and metastases as well as to increase survival.





INNOVATE OFFERS

Content of the innovation:

ANTITUMOR VACCINE BASED ON MICELLAR GLYCOPEPTIDE — CPG-DNA COMPLEX

A glycopeptide-based vaccine in a complex with a bacterial DNA of certain composition contains a built-in adjuvant fragment of a bacterial DNA molecule with non-methylized cytosine residues, unlike the anticancer autovaccine developed in the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine, which demonstrates best therapeutic effect in the presence of adjuvants that enhance it.

The laboratory technology for the production of glycopeptide-based vaccine in a complex with the bacterial DNA of certain composition is mainly a micellar complex of a 50 kDa glycopeptide fraction isolated from tumor cells containing tumor-associated antigens and CpG-DNA of bacterial origin with non-methylized cytosine obtained from the cultural liquid of Bacillus subtilis GP1-807-03, which is a potent natural adjuvant that enhances the antitumor and antimetastatic effects of the vaccine.


УКРАЇНА UKRAINE

ПАТЕНТ

НА КОРИСНУ МОДЕЛЬ

№ 48694

ПРОТИПУХЛИННА ВАКЦИНА НА ОСНОВІ МІЦЕЛЯРНОГО КОМПЛЕКСУ ГЛІКОПЕПТИД-CPG-ДНК

Видано відповідно до Закону України "Про охорону прав на винаходи і корисні моделі".

Зареєстровано в Державному реєстрі патентів України на корисні моделі 25.03.2004.

Голова Державного департаменту інтелектуальної власності М.В. Паладій

The micellar complex, glycopeptide-based vaccine-CpG-DNA, contains a built-in adjuvant molecule — a fragment of the plasmid DNA of Bacillus subtilis and is an effective anticancer and antimetastatic agent which is effective in animals with transplantable tumors, in particular, murine melanoma B-16. Should the glycopeptides faction be isolated from the surgical material of cancer patients, the vaccine based on the micellar complex of this fraction and bacterial CpG-DNA can be used in clinical practice.

Content of the innovation:

A METHOD TO INCREASE ANTITUMOR RESISTANCE

It is known that lectins synthesized by saprophyte bacteria are involved in the processes of carbohydrate-protein recognition, and ensure intra- and inter-cell interactions. Bacterial cytotoxic lectins can be used to create effective anticancer drugs and unique immunomodulators of directed action capable of stabilizing the tumor process and preventing the emergence and spread of metastases after surgical removal of tumors, which may contribute to the effectiveness of treatment and improve the quality of life in cancer patients.

The authors proposed a way to enhance the antitumor resistance of animals by using extracellular lectin from the culture medium of Bacillus subtilis, strain B-7025. The application of lectin for the inhibition of tumor growth and preventing the emergence or inhibiting the growth of metastases after the surgical removal of the tumor helps increase the survival and improve the quality of animals' life. The scheme is as follows: bacterial lectin of Bacillus subtilis B-7025 in concentrations of 2,5-5,0 mg/kg is injected every day or every other day, 4-5 times a day subcutaneously or intravenously to mice before the inoculation of tumor cells or several days before the removal of the tumor. This increases the antitumor resistance of mice resulting in the inhibition of tumor growth of different genesis and prevention/inhibition of metastases after surgical removal of tumors. Lectins show no toxic effects.

The high efficiency and safety of bacterial extracellular lectin provides experimental basis and warrants implementing this agent in the clinical practice.

Content of the innovation:

USE OF MICROSOMAL OXIDATION INDUCTORS TO INCREASE THE SELECTIVITY OF ANTITUMOR DRUGS

As a rule, the presence of a tumor reduces the activity of liver enzymes involved in the metabolism of various drugs. Antitumor compounds as such affect the functional activity of monooxygenases, change the biotransformation of substances in the host, and exhibit their pharmacological properties depending on the type of the monooxygenase system. Therefore, the functional status of the microsomal oxidation in patients with malignant tumors is essential. Drugs that cause the induction or inhibition of monooxygenases can be used to correct the functional state of the microsomal oxidation system and the process of biotransformation of endogenous substances.

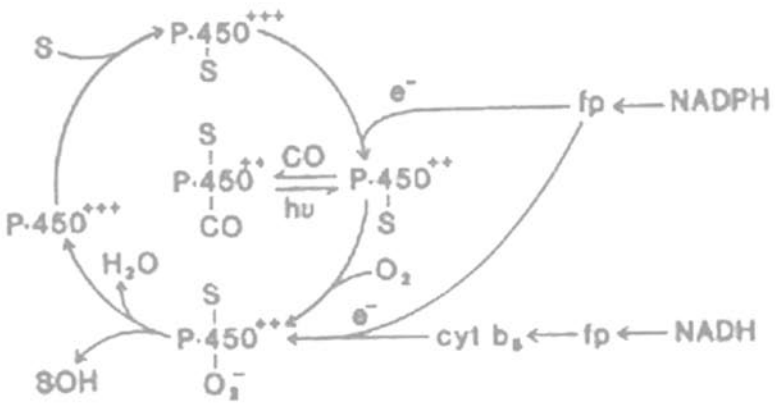
It has been shown in tumor-bearing animals that inclusion of phenobarbital, an inductor of microsomal oxidation, in the treatment scheme increases the activity of main enzyme systems involved in microsomal oxidation of hepatocytes i.e. demetylase and hydroxylase systems. Phenobarbital added to the treatment schemes based on most commonly used anti-tumor drugs typically reduces their toxicity in animals with transplantable tumors.

It should be noted that the monooxygenase induction, along with the reduction of toxic effects of antitumor drugs, has never led to any reduction in the antitumor activity. Thus, we can assume that most anticancer drugs undergo metabolic biotransformation in the cytochrome P450-dependent oxidation system.

In an attempt to reduce the toxicity of cytostatics and phenobarbital's inhibitory action on the CNS, the authors studied two new domestic original products synthesized on the basis of phenobarbital — benzonal and halonal. Both drugs are inductors of the monooxygenase system in the liver, but they are not hypnotic. Adding these inducers to the scheme of anti-tumor treatment of animals with transplantable tumors, either in loading doses or as a course, leads to improved selectivity of cytostatics.

Based on experimental data, more preferential is benzonal, which causes a more pronounced modifying effect. In our study, we did not find any anticancer drugs, whose selectivity might be decreased as a result of induction of microsomal oxidation enzymes. In these conditions, most of them showed a decreased toxicity without reduction of the antitumor effect.

It is considered appropriate to include inducers of microsomal oxidation – phenobarbital or benzonal –in the treatment scheme, whether it is a monochemotherapy or a polychemotherapy. The inductors should be prescribed for the entire course of antitumor therapy, starting 2-3 days before the course begins in the following doses: phenobarbital — 0.2 g once a day, benzonal — 0.1 g twice a day (every other day).





Content of the innovation:

A METHOD FOR PHOTODYNAMIC THERAPY OF MALIGNANT TUMORS

Among antitumor therapies, photodynamic therapy (PDT) occupies a special place due to its low invasiveness and maximal selectiveness in the destruction of tumor tissues.

The PDT method consists in the introduction of tumor-tropic photosensitizers into a tumor-bearing organism, for example, one of porphyrin compounds, which can accumulate in malignant cells making them photosensitive and inducing their selective damage under subsequent light irradiation.

The authors enhanced the tumor destruction effectiveness of PDT using tumor-tropic photosensitizing substances (e.g., hematoporphyrin) in a form of their complexes with antibodies against angiogenic factors. The complexes accumulate in tumor tissues in a higher concentration as they bind not only to tumor cells as such (which is a characteristic of porphyrin compounds) but also to tumor angiogenic factors. Besides, light (laser) irradiation of tumors is performed at time points, which are selected with account for the circadian oscillations in the angiogenic processes and in the formation of angiogenic factors by tumor tissues. This modification of PDT gives a 1.5-fold better therapeutic effect in comparison with the traditional PDT method.

Thus, the proposed original modification of PDT helps improve the results of tumor treatment owing to the enhanced accumulation of the photosensitizing agent in the tumor tissues and to the fact that the PDT procedure is carried out at the optimal circadian time.

Content of the innovation:

A TECHNIQUE TO MODIFY THE GOLDEN SURFACE OF A SENSOR CHIP FOR IMMOBILIZATION OF GLUTATHIONE-S-TRANSFERASE FUSION PROTEINS

In the sensor chips used for biosensor devices based on surface plasmon resonance (SPR), one of the binding partners should be immobilized on the sensor surface. SPR-based biosensors are widely used in medicine and veterinary (diagnostics), pharmaceutical and food industries (quality control of raw materials, semi-finished products and processed products), as well as in biotechnologies. Time variation of the SPR angle makes it possible to study the formation of macromolecular complexes without labeling procedures in a real time. This greatly simplifies the experiment design.

SPR-based biosensors for studies of intermolecular interactions consist of a total internal reflection prism, a gold-flashed quartz chip, a monochromatic light source (laser), photosensitive element that records optical signals, and an electronic device that processes information automatically.

The authors developed a new technique for the modification of the sensor chip golden surface that helps immobilize recombinant protein molecules with glutathione-S-transferase (GST) in a defined surface concentration without detriment to spatial conformation. For this purpose, the complex of carboxythiol-acetate with cadmium-glutathione is formed on the sensor chip golden surface. This complex immobilizes GST-recombinant proteins. After these modifications, chips can be used in domestic biosensor devices with available and inexpensive reagents.

This technique for the modification of sensor chip for immobilizing GST-fusion proteins is suitable for experimental scientific studies, namely, analysis of protein-protein and protein-nucleic interactions. Moreover, taking into account the simplicity and relatively low cost, this technique may also be used in medicine for screening diagnostics of specific antibodies in biological fluids.

Content of the innovation::

CORRECTION OF DISTURBED METABOLISM OF HOMOCYSTEINE IN BREAST CANCER

Determination of diagnostic indices that allow predicting the course of pathologic process in a human body is an important aspect of the studies in various fields of medicine, including oncology. Of special interest is the search for marker products of metabolism, whose deficiency or excess in the blood or tissues could be neutralized by physiologic or medicinal correction.

An importance of such purposeful search in oncology is determined by conclusive data that suggest that malignancy may develop not only as a result of irreversible alterations in the cell genome but also as a result of epigenetic disorders, first of all, changed DNA methylation status. Since the latter is potentially reversible, its correction is possible.

Among such marker metabolic products, one could mention homocysteine (HC), a well-known factor involved in the regulation of important biochemical processes. Numerous studies have shown that the HC level in the human blood plasma is a labile index responsive to numerous factors. Disturbed HC metabolism and elevated plasma levels is a risk factor of the development of a number of somatic diseases, in particular cardiovascular pathologies, and cancer. In this context, a special attention should be paid to the determination of HC status in patients with breast cancer (BC) as this pathology is presently very common in women.

The presented research work is aimed at the correction and prevention of hyperhomocysteinemia (HHC) in BC patients on the basis of the data of mathematical analysis of associative relations between HC plasma level and individual indices of the development and clinical course of cancer process.

There is a direct relationship between the state of important elements of HC metabolism (deficiencies of folic acid (FA), vitamin B_{12}, and coenzymes of vitamin B_6) and the elevated HC level in the blood. Insufficient level of FA is among the causes of cancer development, in particular BC. In case of a combined a B_{12} and FA deficiency and disturbed folate metabolism, the plasma level of HC significantly increases. In this case the risk of cancer development is also elevated. For the correction of these disorders, it may be necessary to use FA, vitamins B6 and B12 in doses that exceed physiologic doses.

The following is recommended for the prevention and correction of hyperhomocysteinemia:

- Give preference to food of plant origin balanced in terms of the contents of B group vitamins and micronutrients as well as break away from bad habits (smoking, high coffee consumption).
- At least two times per year, take polyvitamin complex with sufficient spectrum and normative dosage of vitamins B_6, B_{12} and FA.
- All BC patients with co-morbidities (cardiovascular, endocrine, gastrointestinal, reproductive organ pathologies) and bad habits that contribute to chronic HHC, should avoid methionine loading. In order to increase the efficacy of anticancer therapy, they should take vitamins B6, B12 and FA before and during the therapy.
- For normalization of HC metabolism, elevation of tumor sensitivity to anticancer preparations and radiotherapy, normalization of the content of FA, vitamins B_6 and B_{12}, individualized prescription of the above-mentioned vitamins should be included in the treatment protocols of BC patients, starting from physiologic doses or using them supportively.


УКРАЇНА

(19) (UA)

(11) 66134 A

(51) 7 A23L1/29, A23L1/302

МІНІСТЕРСТВО ОСВІТИ І НАУКИ УКРАЇНИ

ДЕРЖАВНИЙ ДЕПАРТАМЕНТ ІНТЕЛЕКТУАЛЬНОЇ ВЛАСНОСТІ

Деклараційний патент на винахід

Голова Державного Департаменту інтелектуальної власності М. Пилипій

(21) 2003087305

(22) 04.08.2003

(24) 15.04.2004

(46) 15.04.2004, Бюл.№ 4

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(73) ІНСТИТУТ ЕКСПЕРИМЕНТАЛЬНОЇ ПАТОЛОГІЇ, ОНКОЛОГІЇ ТА РАДІОБІОЛОГІЇ ІМ. Р.Є. КАВЕЦЬКОГО НАЦІОНАЛЬНОЇ АКАДЕМІЇ НАУК УКРАЇНИ

(54) ЕКСПЕРИМЕНТАЛЬНА МОДЕЛЬ ГІПЕРГОМОЦИСТЕЇНЕМІЇ

INNOVATE OFFERS

Content of the innovation:

A METHOD TO SYNTHESIZE A STABILIZED SOLUTION OF MAGNETITE NANOPARTICLES FOR TARGET DELIVERY OF ANTITUMOR DRUGS

(In collaboration with the E.O. Paton Electric Welding Institute, NAS of Ukraine)

Magnetic nanoparticles feature a high level of magnetization and magnetic sensitivity in magnetic field. They are of interest as a promising field of biotechnology and medicine. Of special importance is their use as a means of targeted drug delivery into specific sites of the body.

Success in this field is to a considerable extent dependent on the stabilization of magnetic nanoparticles, particularly Fe_3O_4, because their high surface activity causes nanoparticles to aggregate in solutions.

The authors developed a technique that helps obtain a stabilized solution of magnetite nanoparticles for targeted delivery of antitumor drugs by way of dispergation of magnetite nanoparticles and bilayer coating with dextran-90 or sodium oleate and a mixture of natural phospholipids during sonification of the solution. The resulting stable solution of nanoparticles does not form agglomerates and sediment for a long period of time.


УКРАЇНА UKRAINE

ПАТЕНТ

НА КОРИСНУ МОДЕЛЬ

№ 47930

СПОСІБ ОТРИМАННЯ СТАБІЛІЗОВАНОГО РОЗЧИНУ НАНОЧАСТИНОК МАГНЕТИТУ ДЛЯ АДРЕСНОЇ ДОСТАВКИ ПРОТИПУХЛИННИХ ПРЕПАРАТІВ

Видано відповідно до Закону України "Про охорону прав на винаходи і корисні моделі".

Зареєстровано в Державному реєстрі патентів України на корисні моделі 25.02.2010.

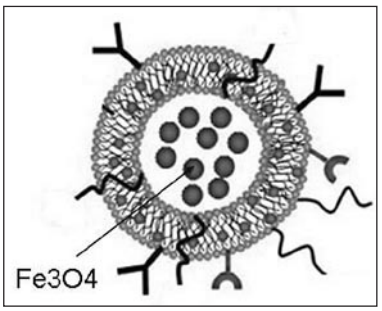
Голова Державного департаменту інтелектуальної власності М.В. Паладій

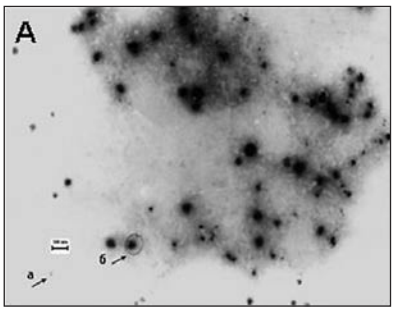
The process of producing the stabilized solution of magnetite nanoparticles for the targeted delivery of antitumor drugs includes the use of magnetite nanoparticles in polymer coating.

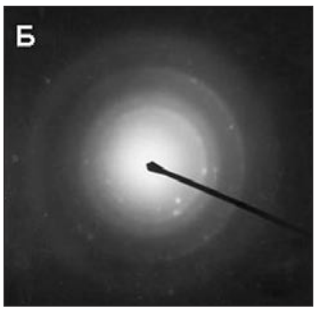
In the course of this process, the first coating layer of nanoparticles containing dextran-90 or sodium oleate is applied with the help of ultrasound in 4-5 steps with 5-minute intervals at a temperature of 90-100°C to the final concentration of 0,25-0,5%.

The second layer containing phospholipids is made in 5 steps at a temperature of 40-50°C; the final concentration of phosphatydylcholine is brought to 1,5% weight in the water phase.

The nanoparticles synthesized by this method can be used for purposes of production of magnetic field-controlled forms of drugs and can help improve the results of chemotherapy and reduce toxic side effects of cytostatics with respect to normal cells.







Electronographic phase analysis (a) and transmission microscopy (b) of stabilized magnetoliposomes

Content of the innovation:

METHOD FOR LIGHT-OPTICAL VISUALIZATION OF IRON-CONTAINING NANOPARTICLES IN CELLS *IN VITRO*

One priority tasks for experimental and clinical oncology is the creation of modern anticancer drugs designed for targeted delivery to tumors. To this end, latest achievements of nanotechnology are used. Recently, research efforts have been focused on creating targeted transport systems using iron nanoparticles as vectors. Due to their size, nanoparticals gain some unusual features, in particular, magnetic properties.

One way to control whether iron-containing nanocomposites have been successfully delivered to the target site is visualizing their presence in tumor cells.

Established methods for visualization of iron in tissue samples, which are based on histochemical techiques or electron microscopy, have drawbacks. For instance, use of paraffin sections of the tissue impedes visualization of a ferromagnet when working with cell cultures in an *in-vitro* system.

The authors propose an informative, not time-consuming and fairly simple method of light-optical visualization of iron oxide, which is part of anticancer nanomedicines in cytological preparations of tumor cells in an *in-vitro* system.

The method is based on a cytochemical reaction with potassium ferro- and ferricyanide to detect Fe^{3+} and Fe^{2+} in cytological preparations.

The method proposed is an objective marker of the presence of a ferromagnet in cells that were cultured *in vitro*, as well as in ascite cells. It helps obtain information about the pattern of influx, accumulation and localization of iron in the cells. This method helps visualize iron nanoparticles by light microscopy in the cytological preparations of cells that were cultured with iron nanosystems.

Content of the innovation:

METHOD FOR QUALITATIVE ANALYSIS OF LIPIDS FOR PRODUCING LIPOSOMES AND ASSESSMENT OF THE STABILITY OF MAGNITOLIPOSOM

Liposomal formulations help overcome obstacles in the application of chemotherapy of tumors due to reduced side effects, improved selectivity of target cells destruction, as well as optimized circulation time of the drug in the bloodstream.

A necessary condition for preserving the functions of liposomes over a certain period of time is their stability, which is determined by the degree of oxidation of fatty acids that make up the phospholipid membranes. One of the main indicators that characterize the degree of oxidation of fatty acids is the peroxide, or iodine, index (number of milliequivalents of oxygen, which corresponds to the amount of peroxide per 1000 g of tested substance).

Stability of lipids and liposomes is also extremely important in the production of liposomal nanocomposites containing nanosized particles of ferromagnetic materials and in targeted delivery of drug to the tumor site in case it is resistant to existing chemotherapeutic agents. The authors propose a method for measuring the iodine index of lipids by means of differential voltammetry.

The method is instrumental in measuring this index in optically opaque solutions, which serve as raw materials for the synthesis of liposomes. Moreover, this method is useful for rapid analysis, regardless of the optical density of the solution of liposomes.

This improved method removes the restrictions that exist in traditional methods of measuring the lipid peroxidation index.

Content of the innovation:

STUDY OF CARCINOGENIC PROPERTIES OF NEW COMPOUNDS AND MEDICINAL AGENTS

At the stage of experimental approbation of new medicinal agents (MA), the detection and prevention of their possible hazardous action as carcinogenic compounds is of special importance. The testing of medicinal agents for carcinogenic activity has a lot in common with the methodical principles used in studies of mutagenic action of chemical compounds, biological products, and dietary supplements. However, MAs are administered for long periods of time in some therapies; and this should be specifically taken into account in the interpretation of findings and evaluation of the potential danger of MAs for humans. Therefore, a well-managed system should be in place to test MAs for potential carcinogenicity.

The authors have developed guidelines for testing MAs and compounds for carcinogenicity and evaluating their potential danger for humans. The first chapter entitled «The main principles for selection and characteristics of medicinal agents for experimental carcinogenicity studies» substantiates the necessity of analytical and information support at the initial stages of a preclinical study of a new MA; lists the MA classes that must be assessed for carcinogenic danger for humans and the agents whose testing for carcinogenic properties is not obligatory. The following MAs are classified as those that must be tested for carcinogenic risk: the MAs indicated as therapeutic, curative-cosmetics, or repellent agents and contraceptives, especially those that are recommended for life-long use with prolonged repeated courses; over-the-counter MAs; MAs for pediatric practice; MAs for treatment of pregnant women and during lactation in therapeutic pathologies. The testing for carcinogenicity is not obligatory for MAs indicated for treatment of malignant neoplasm in adults; for treatment of life-threatening diseases; and analogs of foreign MAs, if there is substantive evidence in the literature that they are not carcinogenic.

The chapter «Requirements to experimental carcinogenicity studies» describes the criteria that should be considered when planning a study, such as selection of experimental animals; determination of the dosage; routes of administration (oral, parenteral, subcutaneous, intradermal, epicutaneous, intramuscular, intraperitoneal, etc.; epicutaneous testing, intratracheal, transplacental method); pathomorphological study of the experimental material; basic records of the study and requirements to the documentation of findings.

The chapter «Evaluation of the findings of a carcinogenicity study» looks into requirements for the documentation of histological assays, data on the average latent period of cancer, metastases, changes in the animal's weight, and survival. Methodical approaches are specified that should be used in selecting the methods for statistical analysis with account for concrete objectives, conditions of the tests, and data obtained at various stages. The procedure for determination of main parameters of carcinogenic activity is described in details, including the presence (and the rate) of MA-induced tumors; increased rate of spontaneous tumors; reduced latent period; increased average number of tumors per animal (multiplicity coefficient); shifts in the benign to malignant tumor ratio.

The principles are described based on which the State Pharmacological Center of MH of Ukraine (on the basis of IARC guidelines) recommends to evaluate the findings of carcinogenicity studies of an MA.

The paper contains guidelines on the preparation of a scientific report about the results of a study in compliance with the applicable national standard.

A final decision on the sufficiency of findings of MA testing for carcinogenicity and its approval for clinical trials is made by the State Pharmacological Center of MH of Ukraine.

Content of the innovation:

A CYTOGENETIC METHOD TO EVALUATE INDIVIDUAL RADIATION SENSITIVITY FOR PRIMARY PREVENTION OF RADIOGENIC CANCER

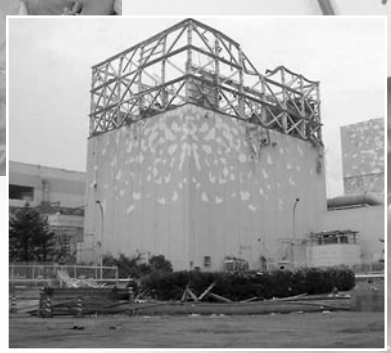
The World Health Organization had declared the 21st century a century of preventive medicine and individualization of health care. Therefore, the world tendencies in cancer prevention have shifted towards a focus on primary prevention of cancer, including radiogenic cancer.

Radiation-induced chromosome destabilization in somatic cells is known to have a prognostic potential and predict increased risk of radiogenic cancer. To assess this parameter, the Department of Radiobiology and Ecology of the Institute developed a test system which measures the individual radiosensitivity based on cytogenetic parameters. The system registers and analyzes chromosome aberrations in peripheral blood lymphocytes (PBLs) induced by test exposure of G2 phase PBLs to radiation and quantitative assessment of ionizing radiation effects on the human body taking into account the efficiency of DNA reparation. This information allows predicting objectively possible acute and remote consequences of radiation exposure, including exposure in a low-dose range. The measurement of individual radiation sensitivity has a practical value in developing and introducing measures for primary prevention of radiation-induced diseases in the following cohorts of the Ukrainian population:

- nuclear power plant workers;
- inhabitants of radioactively polluted regions, in particular after the Chernobyl catastrophe;
- medical staff exposed to ionizing radiation;
- cancer patients treated with radiotherapy, chronic patients with weakened immunity who are frequently exposed to irradiation during X-ray examinations, and others.

The application of the developed cytogenetic method of human individual radiation sensitivity evaluation will contribute to the effectiveness of primary prevention of radiogenic cancer.





Content of the innovation:

A METHOD TO TEST NON-CYTOTOXIC DRUGS FOR ANTITUMOR ACTIVITY

The authors developed a new method for testing non-cytotoxic drugs (NCDs) for antitumor activity that is suitable for rapid screening of a wide range of NCDs and administration modes. The novelty of the proposed method lies in the fact that the NCD is administered to healthy animals and the results of the test are assessed using a previously patented method (O.A. Orlov, V.F. Chekhun. Method for Integral Evaluation of Nonspecific Resistance to Malignant Tumors with the Help of Carcinolysis Reaction. — Pat. Ukraine No. 45210 dated 26.10.2009. — Bull. No. 20/2009).

The classical method of testing drugs for antitumor activity has drawbacks, which greatly complicate preclinical studies of NCDs in oncology. The traditional method does not differentiate between the testing of cytotoxic drugs and NCDs. It requires a full-scale long-term oncological experiment using a sufficiently large number of animals with transplanted or induced tumors. Moreover, only a small number of different drugs or different doses and administration modes can be tested in one experiment.

The proposed method is free from all these drawbacks. The first drawback is overcome by definition (name) of the method. Due to the fact that healthy animals are used instead of animals with tumors, there is no need to conduct a full-scale oncologic experiment. Thus, there is no need to wait for a long time to see the result. Also, there is no need in a large numbers of animals, which, in the case of the classical method of testing, is due to the fact that any animal population is heterogeneous in terms of antitumor resistance. Because of this, the proposed method is also free from the last drawback, i.e. it allows expanding several times the range of the drugs tested or doses and administration modes of the same drug.

Content of the innovation:

A METHOD TO TEST NUTRITION PRODUCTS FOR ANTITUMOR ACTIVITY

In the classical method of testing foods for anti-tumor activity, the following parameters are used as endpoints: tumor rate (i.e., the percentage of animals showing tumor growth); average weight of a tumor at the standard time point when animals are sacrificed; growth rate, which is determined by periodic measuring the geometric dimensions of the tumor in living animals; and average life span of animals in the control and main groups.

This method requires many months of experiments on chemical and radiation carcinogenesis (where the influence of the diet on the occurrence of induced tumors is studied) or experiments with transplantable tumors, which take about a month or more for some commonly used tumors. In these experiments, the number of animals per group is usually around 10, if the resulting effect is to be determined reliably. If it is necessary to measure the tumor weight on the day of sacrificing the animals and the life expectancy, each group should be doubled. In addition, in order to develop sound recommendations on the use of any product for clinical nutrition, at least three nutrition regimens should be tested. According to existing standards, such experiments should be conducted using not less than two transplanted tumors for each of at least two species of test animals (usually mice and rats).

Thus, the total number of animals used to test a nutrition product is about 160, if only the growth rate and weight of tumors is evaluated. If the life expectancy is also evaluated, the number of animals should be doubled. Such a study is very material- and labor-intensive, so it is usually difficult to study several nutrition products simultaneously.

Such experiments are necessary in order to reasonably determine the antitumor activity of the tested product and develop guidelines for its use

Content of the innovation:

DISPERSED FIBROUS CARBON ADSORBENTS

Dispersed fibrous carbon adsorbents are finely dispersed activated carbon fibrous materials in 70% ethyl alcohol or 0.2% zinc sulfate solution. Dispersion of the fibrous material to individual fibers improves its sorption-kinetic properties, ensures a more complete contact with the wound area of any configurations and decreases the traumatism and soreness during bandaging. The quantity of sorbent per ligation decreases too. Ethyl alcohol or zinc sulfate as the components of dispersed fibrous sorbents, bring in an additional antibacterial or anti-inflammatory effect. Dispersed fibrous carbon adsorbents ensure a 1.5–1.8 fold reduction of the disability period caused by occupational or domestic microinjury.

Dispersed fibrous carbon adsorbents do not cause allergic reactions and skin irritation.

Dispersed fibrous carbon adsorbents in 70% ethyl alcohol or 0.2% zinc sulfate solution are used in surgery and combustiology (in hospital settings and at home), and are designed for local therapy of microinjury and surface burns, trophic ulcers, decubitus ulcers and erosive lesions of the mucous of the nasal cavity, mouth, vagina.



Available in hermetically sealed bottles or containers.

Content of the innovation:

ADSORPTIVE CARBON DRESSING

Adsorptive carbon dressing represents an activated carbon fiber material with expanded (1500 cm^2/g) sorption surface and unique sorption-kinetic characteristics, which provides rapid adsorption of a large quantity (up to 1.5 g per 1 g of weight of the carbon material) of various biologically active components from the wound content, including the products of protein catabolism and proteolysis, bacterial endotoxins, biogenic amines and mediators of inflammation. This leads to the attenuation of the intensity of local vascular and inflammatory reactions. Haemostatic properties of carbon fiber materials due to their specific surface chemistry help reduce the duration of bleeding 2–4 times, and the volume of blood loss 1.5–2 times. Adsorptive carbon dressing blocks local sources of intoxication and prevents the reinfection of wounds. It does not cause allergic reactions and skin irritation.

Adsorptive carbon dressing is used in surgery and combustiology (in hospital settings and at home). It is designed for application-sorption therapy of wounds and burns, trophic ulcers, decubitus ulcers and erosive lesions of mucous of the nasal cavity, mouth, vagina, as well as for the prevention and treatment of wound infection and for ex tempore immobilization of biologically active compounds, such as proteolytic enzymes and antiseptics.


ДЕРЖАВНА ІНСПЕКЦІЯ
З КОНТРОЛЮ ЯКОСТІ ЛІКАРСЬКИХ ЗАСОБІВ
МІНІСТЕРСТВА ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
СВІДОЦТВО ПРО ДЕРЖАВНУ РЕЄСТРАЦІЮ
№ 9608/2010
Засоби перев'язувальні на основі волокнистих вуглецевих матеріалів
ТУ У 24.4-05416946-001:2010
3005 90 99 00
Виробник: Інститут експериментальної патології, онкології і радіобіології ім. Р.Є. Кавецького Національної академії наук України
03022, м. Київ, вул. Васильківська, 45, Україна
Свідоцтво дійсне до 03 вересня 2015 р.
Голова комісії з проведення реорганізації Держлікінспекції МОЗ А.Д.Захараш
№020340

Available in double sealed packages, in pieces of the following sizes: (5x10), (10x10), (10x20) cm. Other sizes are available on a by-order basis.

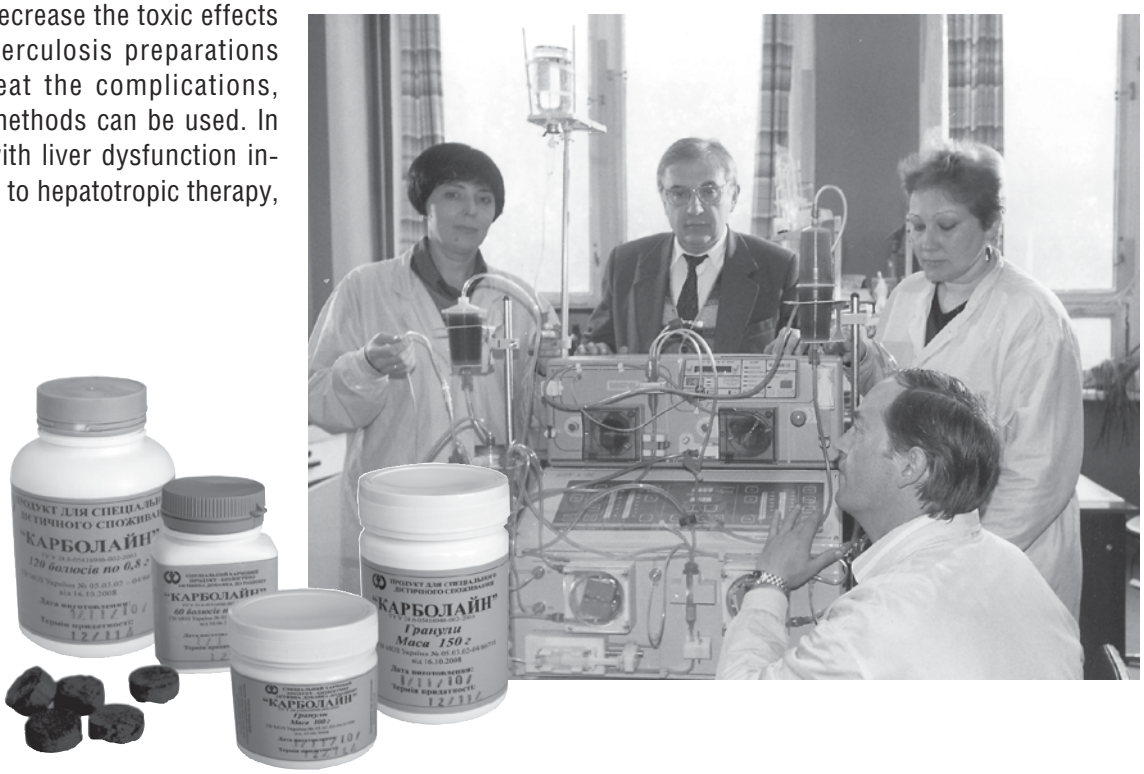
Content of the innovation:

CARBONIC ENTEROSORBENTS

Pharmacotherapy and prevention of tuberculosis warrant timely and active use of the most effective and safe curative means. Also, modern therapy of tuberculosis includes a combined use of specific antibacterial preparations and medicines of various pharmacologic groups. Combined chemotherapy allows increasing the overall efficacy of treatment. However, antituberculosis drugs have side effects, which can aggravate when applied in a combined therapy or in supportive treatment.

Acute and chronic hepatitis is one of the most common complications of antituberculosis therapy. Despite significant progress in the treatment of tuberculosis, the problem of detoxification during prolonged administration of antituberculosis drugs remains to be solved.

To decrease the toxic effects of antituberculosis preparations and to treat the complications, sorption methods can be used. In patients with liver dysfunction insuspective to hepatotropic therapy, hemosorption on carbon sorbents helps normalize biochemical indices of the blood and improve the tolerability of tuberculostatic therapy in the patients with toxico-allergic reactions to antituberculosis drugs. Carbon enterosorbents can be used as reliable detoxification agents to treat overdosing or poisoning caused by antituberculosis drugs or to decrease the toxic effects of medicines.









RE Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology of the National Academy of Sciences of Ukraine employs highly qualified researchers with profound expertise in the areas of physiopathology and oncology as well as material and technical resources needed to provide high-quality novel services, such as:

1. — REFERENCE LABORATORY FOR DIAGNOSTICS OF ONCOHEMATOLOGIC DISORDERS:

diagnostic testing of hemoblastoses: acute and chronic leukemia, myelodysplastic syndromes, various forms of myeloproliferative disorders (morphological, cytochemical, molecular genetic studies and identification of malignant immune cells).

Differential diagnostic testing includes:

- identification of morphocytochemical variants of acute leukemia according to the French-American-British (FAB) classification (ALL L1 L3, HML M0 M7);
- identification of immunological variants of acute and chronic lymphocytic leukemia of B and T cell origin according to the classification of the European Group for the Immunological Classification of Leukemias (EGIL) and according to the WHO classification;
- identification of the nosologic forms of B and T cell non-Hodgkin's malignant lymphomas (NHML) in the leukemic phase of development using immunocytochemical and morphocytochemical methods according to the 2008 WHO classification.

Regular scientific workshops for hematologists, oncologists and clinical laboratory technicians on topical issues of diagnostics of hemoblastoses, discussion of new WHO classifications, strategy for diagnostics and treatment of certain nosological forms of diseases.

2. — MONOCLONAL ANTIBODIES (MABS) FOR BIOMEDICAL RESEARCH:

Murine monoclonal antibodies against human antigens:

CD3, CD4, CD5, CD7, CD8, CD10, CD13, CD15, CD16, CD19, CD20, CD22, CD25, CD27, CD34, CD37, CD38, CD43, CD45, CD45RA, CD48, CD54, CD56, CD66e, CD95, CD150, CD227/MUC1, CD326/EpCAM, κ and λ light chains Ig, HLA-ABC, HLA-DR, pan-keratin keratin-18, p53, nuclear antigen of proliferating cells IPO-38.
(Marketing Authorization No. 11072/2011 for «Monoclonal Antibodies, Standard Specification U24.4-05416946-002:2011 »)

Contents of a vial: 200 μg of purified antibodies in PBS with 0.2% BSA and 0.1% of sodium azide. For laboratory use *in vitro*. Storage: at a temperature of 4-8oC.

Applications:

- visualization of subcellular localization of proteins;
- immunophenotyping of cells of various histogenesis;
- immunophenotyping of subpopulations of cells involved in immune response;
- identification of tissue-specific antigens;
- functional studies, ways of signal transduction;
- specific isolation of cells and proteins;
- immunophenotyping of cells in leukemia and lymphoma;
- differential diagnosis of tumors of various histogenesis;
- assessment of immune status.

3. — VACCINE THERAPY FOR CANCER:

- production of individual anti-tumor vaccines based on the patient's tumor antigens and an adjuvant of microbial origin (Certificate of Ukraine Health Ministry No. 411/03-300200000 dated December 9, 2003); production of individual anti-tumor vaccines based on glycoproteins isolated from the patient's tumor cell (Patent No. 57608 A. Ukraine. 16.06.2003);
- long-lasting prevention of relapses and metastases with the help of anti-tumor vaccines based on very-low-dose tumor antigens;

- assessment of the levels of tumor growth markers (cancer-embryonic antigen, α-fetoprotein, etc.); circulating immune complexes; delayed-type hypersensitivity test for assessment of the efficacy of vaccinotherapy

4. — DETERMINATION OF INDIVIDUAL RADIATION SENSITIVITY (IRS):

quantitative assessment, including by cytogenetic methods, of the impact of ionizing radiation on the human body with account for its specific features, especially those caused by the cells' ability to repair radiation-induced DNA damages.

IRS determination is relevant for the following populations and applications:

- cancer patients before a radiation therapy to minimize post-radiation complications for healthy tissues surrounding the tumor;
- health workers exposed to ionizing radiation (radiation oncologists, radiologists and others);
- repeated x-ray examinations of persons with hereditary cancer burden and patients with chronic diseases, immunocompromised, exposed to multiple examinations, including contrast-enhanced examinations, etc.;
- population exposed to the radiation factor of the Chernobyl accident to improve the efficiency of primary prevention of radiogenic pathologies;
- selection and examination of workers for nuclear power plants;
- residents of settlements located near enterprises producing nuclear wastes.

5. — BANK OF CELL LINES OF HUMAN AND ANIMAL TISSUES PROVIDES HIGH-QUALITY SERVICES:

Deposition of biological research materials in liquid nitrogen (-196°C):

- long-term storage in the cryobank of cell lines and strains of viruses, bacteria, DNA samples of tumors and others study-related materials from research and educational institutions. Deposition services are available to both individual customers and organizations;
- cryopreservation and subsequent long-term storage of samples of cord blood, bone marrow and pure populations of stem cells of humans and other living creatures in the cryobank in liquid nitrogen. Deposition services are available to both individual customers and organizations.

Deposition of biological materials from cancer patients:

- storage of tumor fragments obtained during surgery in liquid nitrogen.
- preparation of sterile suspensions of fragmented cell tumors and their programmable cryopreservation and storage (in conditions that maintain them viable).
- obtaining suspensions of mononuclear cells of blood, bone marrow from patients with leukemia and their programmable cryopreservation and long-term storage (in conditions that maintain them viable).
- storage of samples of plasma or serum or other biological fluids in liquid nitrogen.

Providing researchers with strains and tumor cell lines.

6. — IDENTIFICATION OF HEREDITARY PREDISPOSITION TO CANCER:

- Clinical and genealogical examination of patients and assessment of the risk of malignant disease in their families and descendants;
- Genetic-mathematical analysis of pedigrees to determine the type of inheritance and evaluate the possible risk of this oncological pathology in their descendants;
- Evaluation of the genome instability of peripheral blood lymphocytes (DNA comet assay, cytogenetic analysis of chromosomes, including quantitative and qualitative analysis of aberrations and sites of increased fragility);
- Providing recommendations on cancer prevention.

7. — PRE-CLINICAL STUDIES OF SPECIFIC AND TOXICOLOGIC ACTIVITIES OF NATURAL AND CHEMICAL SUBSTANCES:

- primary screening of antitumor drugs; screening of substances for anti-tumor effect *in vitro* using a panel of cell lines from various tumors;
- preclinical studies of anticancer and antimetastatic activity of cytotoxic/cytostatic agents *in vitro*;

- study of acute toxicity of drugs; study of cumulative toxicity of drugs; study of chronic toxicity of drugs;
- pharmacokinetic and pharmacodynamic studies of drugs;
- determination of the levels of tumor markers, cytokines and growth factors in biological fluids and tissues (enzyme-linked immunoassay);
- culturing and cloning of cells, transfection and transduction of cells, preparative accumulation and programmable cryopreservation of cells;
- cytogenetic assessment of cells, species identification, determination of the authenticity of strains;
- assessment of antiviral, particularly anti-retroviral, activity of investigational products;
- determination of the cytotoxic activity of lymphocytes, natural killer cells, and macrophages;
- determination of the angiogenic and anti-angiogenic activity of substances on cells *in vitro* and *in ovo*;
- microscopic assessment and photography of cytological preparations of living and stained cells;
- assessment of individual sensitivity of tumors to chemotherapy and hormone therapy: expression of Pgp, GST, etc. and steroid hormone receptors, estrogens and progesterone;
- assessment of the photosensibilizing activity of substances that can be used as photosensitizers for photodynamic therapy of tumors;
- molecular/genetic screening in cytological and surgical material of human highly oncogenic papillomavirus, herpes virus, cytomegalovirus, etc.;
- assessment of the immune status (immunogram, phagocytic activity);
- determination of specific proteins of the inflammatory process (alpha-2 macroglobulin, alpha-1-antytrypsin, alpha-fetoprotein, anti-thrombin III, fibrinogen, C-reactive protein, etc.) in blood plasma of patients with malignant tumors and other diseases (enzyme-linked immunoassay);
- complete blood analysis with differential and erythrocyte sedimentation rate (ESR) tests using automatic blood analyzer;
- determination of parameters of methionine turnover (methionine, glutathione, homocysteine, cysteine, S-adenosylhomocysteine, S-adenosylmethionine, etc.) in tissues and blood plasma of healthy subjects and patients with various pathologies, including cancer, with the view to correct abnormalities (ELISA, biochemical methods, HPLC).

8. — NMR SPECTROMETRY

An analytical method used to establish the structure of chemicals as well as for qualitative and quantitative determination of chemical compounds in mixtures (food, drugs and psychotropic substances) and for identification of the molecular structure of chemical compounds. NMR spectrometer «Mercury-300» (VARIAN, USA), operates on a frequency of 300 MHz (1H), is used to record NMR spectra of 1H, 13C, 31P, 29Si, 15N nuclei. The device allows for a wide range of methods in one- and two-dimensional high-resolution spectroscopy, is equipped with a computer-aided signal processing system and data presentation system.

Registration and interpretation of 1H, 13C, 31P, 29Si, 15N NMR spectra for quantitative and qualitative determination of chemical compounds and biomedical studies.

9. – DEVELOPMENT AND PRECLINICAL EVALUATION OF NEW HEMOSORBENTS, enterosorbents, and application sorbents.

- *in vitro* assesement of sorbents' physical and chemical properties;
- study of key mechanisms of sorbents' action;
- study of clinical effectiveness of sorbents in a variety of human diseases using animal model experiments.

10. – PREPARATION AND ISSUE OF REPORTS ON PATENT RESEARCH IN LINE WITH THE NATIONAL STANDARD OF UKRAINE 3575-97 for planning and completion of R&D and planning of thesis works:

- information retrieval in line with the National Standard of Ukraine 3575-97 for planning and completion of R&D and planning of thesis works;
- ensuring protection of intellectual rights and record-keeping in the commercialization of intangible assets created in medico-biological research institutions of various departmental subordination.

11. — PERFORMANCE EVALUATION OF RESEARCH with the help of the Automated Data Processing System entitled «Researcher's Questionnaire» using a rating technology based on differentiated performance indicators developed in the Institute:

- Performance evaluation of individual research and innovation work of researchers and equated persons in the institutions of the natural science domain of various departmental subordination (National Academy of Sciences, Health Ministry, National Academy of Medical Sciences, Education and Science Ministry, Ministry of Education, Science, Youth and Sports, National Academy of Agrarian Sciences of Ukraine);
- Evaluation of the innovative capacity of R&D results of biomedical orientation in institutions of different departmental subordination (National Academy of Sciences, Health Ministry, National Academy of Medical Sciences, Education and Science Ministry, National Academy of Agrarian Sciences of Ukraine).

12. — A SERIES OF LECTURES FOR STUDENTS OF EDUCATIONAL INSTITUTIONS, parents and teachers delivered as part of the socio-educational project «Scientific and Educational Lectures of Specialists in Oncology Care to Protect the Youth of Ukraine» dealing with the primary prevention of cancer:

- Oncology: Key Concepts ,
- Environmental Factors and Cancer,
- Role of Hereditary Factors in Cancer,
- Hormones and Cancer,
- Specifics of the Structure of Tumor Cells,
- Modern Experimental Methods and Models in Cancer Research,
- Modern Diagnostic and Treatment Methods in Oncology
- Modern Diagnostic Methods in Oncohematology,
- Modern Approaches to the Treatment of Cancer Patients,
- Prevention of Cancer,
- Healthy Lifestyle as a Factor of Cancer Prevention.

1. DEVELOPMENT OF A MULTI-ORGAN SYSTEM TO ASSESS *IN VITRO* TOXICITY OF CHEMICAL COMPOUNDS FROM THE EXTERNAL ENVIRONMENTAL *(project manager — Yu.Yo. Kudryavets, Doctor of Biology, IEPOR).*

The system is based on transgenic immortalized cell lines from different normal human tissues.

These lines, being co-cultured in a special container, which provides for the intercellular exchange of soluble components of the microenvironment, form an *in vitro* system that reflects the expected real multiorgan toxicity of xenobiotics *in vivo* (in humans).

Our experiments have shown that, by using cells from various human organs which are co-cultured *in vitro*, we can get a picture of the toxicity of substances, which is sufficiently realistic and can be extrapolated to the expected toxic manifestations in humans *in vivo*. An important feature of this system is that conditions are created where the cells do not contact with each other directly, but only through soluble components thus giving rise to inter-organ interactions. The cells are cultured in separate wells which are modified to allow humoral intercellular contacts.

Proposal 1 The Multiorgan Toxicity System consists of two components: special plastics for culturing cells and a panel of cell lines and strains as targets for xenobiotics.

In Proposal 1, the panel of test cells includes human cells of various tissue origins:

1. Connective tissue cells (fibroblasts)
2. Epithelial cells (keratinocytes, upper respiratory epithelium)
4. Liver cells (hepatocytes)
5. Kidney cells
6. Blood cells (mononuclear cells of spleen or tonsils)
7. Nerve cells (microglial cells, astrocytes, neuronal cells)
8. Endothelial cells

These cellular models will be subjected to genetic modification to form normal, but immortalized cells of various organs to ensure the standardization of results and the regular use of the test system.

The Multiorgan Toxicity System may be applied as a test-system to determine the selective toxicity for human tissues of medicines, perfumes, cosmetics, detergents, as well as chemical compounds of industrial origin, and other harmful environmental factors.

Project duration: 3 years

Annual budget: UAH 1 million

Total budget: UAH 3 million.

Expected results: A new technology for the determination *in vitro* of toxicity of different compounds to the body. A panel of new unique cell systems.

2. DESIGN OF A MULTI-ORGAN SYSTEM FOR *IN VITRO* DETECTION OF ANTICANCER DRUGS ACTIVITY WITH DIFFERENT MECHANISMS OF ACTION *(project manager — Yu.Yo. Kudryavets, Doctor of Biology, IEPOR).*

Development of the system provides for the creation of sub-lines (clones), on the basis of a panel of human tumor lines of different histogenesis, which are resistant to chemotherapeutic drugs with different mechanisms of action. The sub-lines will be developed by way of selection and/or transgenesis of multidrug resistance genes in tumor cells. Prototypes of normal cells will serve as a multi-organ panel of immortalized normal human cells. When cells are co-cultured in conditions that allow for humoral intercellular contact, we can determine *in vitro* the simultaneous selective toxicity of the drug for human normal, cancer and chemotherapy-resistant tumor cells.

Development of a multi-organ system for *in vitro* detection of the activity of antitumor drugs to treat human tumors with various degrees of drug resistance.

The technology for the development of this system is similar to that of the Multi-organ Toxicity System, but the panel of test cells additionally includes tumor cells of various tissue origin and various sensitivity levels to chemotherapeutic drugs.

Due to intercellular contact, the system will help determine *in vitro* simultaneous selective toxicity of the antitumor drug for normal, tumor and chemotherapy-resistant human tumor cells.

Project duration: 3 years

Annual budget: UAH 3,5 million.

Total budget: UAH 10,5 million.

Expected results: A new technology of fast and selective *in vitro* selection of active anticancer drugs with simultaneous control of the overall toxicity for the body. A panel of new unique cell systems.

3. USE OF NANOTECHNOLOGIES TO IMPROVE THE SELECTIVITY OF ANTICANCER DRUGS
(Member of the National Academy of Science of Ukraine, V.F. Chekhun, IEPOR).

Given the existing knowledge about molecular-biological nature of changes in neoplastic cells, a modern strategy should address the problem based on the use of new diagnostics technologies and targeted therapies. Innovative nanotechnologies may be useful in this context. Currently, a technology has been developed in the IEPOR to produce a nanocomposite containing iron oxide (III) nanoparticles, produced by chemical synthesis and quantum-beam technologies. Methods have been selected to control physical and chemical properties of nanocomposite components at each production stage. Various methods have been tested to produce liposomal complexes of anticancer drugs with iron oxides. A series of studies have been performed and proved that the resulting nanocomposite possesses a high cytotoxic activity against malignant transformed cells compared with the freeform of the chemotherapeutic drug. It has been shown that the accumulated mass of magnetite particles in the capillary is dependent on the flow speed of the magnetic fluid and the duration of action of the permanent magnetic field on it. The time has been determined required for the concentration of magnetic nanoparticles in the capillary of the model system at a constant flow speed of the liquid.

Expected result: As a result of the project, a new pharmaceutical form will be developed based on nanocomposites and preclinical studies of its efficiency will be completed. Also, and apparatus complex will be developed to concentrate magnet-guided ferrous particles.

Practical application: for targeted binary therapy of patients with tumors of various genesis and localizations.

Project duration: 4 years.

Total budget: UAH 75 million

Investment may return as the study proceeds due to obtaining joint patents and vending of licenses for the technology under development.

4. ENHANCEMENT OF PHOTODYNAMIC THERAPY OF TUMORS BY THE APPLICATION OF QUANTAL NANO-BIOLOGY
(Prof. M.F. Gamaleya, Doctor of Medicine, IEPOR)

The project is designed to develop a new method for photodynamic therapy of tumors, which is expected to surpass the existing world analogues in terms of effectiveness, due to application of original nanocomposite preparations.

Photodynamic therapy (PDT) is a modern promising treatment for tumors, which has recently been introduced in the ontological practice of leading Western countries. The principle of the method is that the patient is injected a non-toxic dye, which selectively accumulates in the tumor. This is followed by irradiation with a bright laser light (directly if the tumor is located on the surface of the body or through the endoscope if it is located in the esophagus, stomach, bronchi, bladder, etc.). The stain accumulated in the tumor is thus activated and initiates a series of processes in tumor cells that lead to a cell death.

The method PDT features an exclusive selectiveness of the antitumor action, because even occasional exposure to light of normal tissues does not damage them due to the absence of the dye in normal tissues. PDT is a minimally traumatic method. For certain types of tumors it helps avoid surgery. Moreover, there

are almost no side effects. Unfortunately, the light penetrates into the tissue only a little, and therefore PDT provides a complete cure only at the initial stages of cancer, for small and flat tumors.

An original nanocomposite dye for PDT with colloidal gold has been synthesized and studied in the IEPOR Quantal Nano-Biology Laboratory. Experiments on tumor-bearing animals showed that gold nanoparticles not only increase the drug accumulation in tumors, but also considerably enhance the light-mediated damage of tumor cells due to unique optical properties of gold, even in the depth of the tumor, where little light penetrates. Consequently, larger tumors can be treated successfully.

Thus, the implementation of this technology in the public health practice will make it possible for national oncology to use the PDT method (which is currently not available in Ukraine) in its original version. It is worth noting that its projected efficiency is greater than such of well-known analogues.

Practical application of the method. In today's Ukraine, this method will be applied, in the first place, in the appropriate divisions of the institutes of the Health Ministry and the Academy of Medical Sciences of Ukraine, in 5 state medical diagnostic centers, 73 regional cancer clinics, in several central hospitals plus in private clinics.

Estimated Budget. Estimated budget totals UAH 10–15 million for the 2-year period.

Projected duration. The above budget is estimated for two years.

End-result. As already mentioned in the descriptive part of the project, it will result in the implementation in the medical practice of a new for Ukraine promising method for treating cancer patients. It is expected that, in case of successful implementation, the original version of the method will be at least as effective as foreign analogues.