



REVIEW

UNITED IMMUNOLOGICAL FORUM: CURRENT TRENDS IN THE DEVELOPMENT OF FUNDAMENTAL AND APPLIED ONCOIMMUNOLOGY (NOVOSIBIRSK, 2019)

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ABSTRACT

The work provides information on the results of the Joint Immunological Forum, which was held from June 24 to 29, 2019 in Novosibirsk. The modern directions of the development of fundamental and applied immunology are analyzed. Particular attention is paid to the discussion of the most issues identified in the section "Immunopathogenetic bases of tumor growth", which also presented the results of studies conducted at the National Medical Research Centre for Oncology of the Ministry of Health of Russia for the study of isolation and study of the biological properties of tumor stem cells. Noteworthy are the new advances in modern immunology, which clarify the hierarchical structure of lymphocyte populations, with the separation of various minor subpopulations based on the phenotypic, molecular genetic and functional properties of cells, whose role in ensuring the integrity of the body has not been fully studied. In addition to theoretical reports, during this Forum the results of using new methodological approaches to study the structural and functional organization of individual links of innate and adaptive immunity both under model conditions and during the development of various human diseases were presented, the most promising ways to improve analytical and technological platforms were identified. In the crayfish of the Forum, several advanced training programs were implemented for employees of various levels of practical health care and fundamental science.

Keywords:

fundamental and applied immunology, oncoimmunology, state and prospects of development of science, innate and adaptive immunity, antitumor immunity, lymphocytes, cytokines

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Information about funding: no funding of this work has been held.

Conflict of interest: authors report no conflict of interest.

For citation:

Sagakyants A.B. United Immunological Forum: current trends in the development of fundamental and applied oncoimmunology (Novosibirsk, 2019). South Russian Journal of Cancer. 2020; 1(2): 36-45. <https://doi.org/10.37748/2687-0533-2020-1-2-5>

Received 11.11.2019, Review (1) 16.01.2020, Review (2) 19.01.2020, Accepted 01.06.2020

ОБЪЕДИНЕННЫЙ ИММУНОЛОГИЧЕСКИЙ ФОРУМ: СОВРЕМЕННЫЕ НАПРАВЛЕНИЯ РАЗВИТИЯ ФУНДАМЕНТАЛЬНОЙ И ПРИКЛАДНОЙ ОНКОИММУНОЛОГИИ (НОВОСИБИРСК, 2019)

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РЕЗЮМЕ

В работе представлена информация об итогах проведения Объединенного иммунологического форума, который проходил с 24 по 29 июня 2019 г. в Новосибирске. Анализируются современные направления развития фундаментальной и прикладной иммунологии. Особое внимание уделено обсуждению вопросов, обозначенных на секции «Иммунопатогенетические основы опухолевого роста», на которой также были представлены результаты проводимых в ФГБУ «НМИЦ онкологии» Минздрава России исследований в области выделения и изучения биологических свойств опухолевых стволовых клеток. Обращают на себя внимание новые достижения современной иммунологии, уточняющие иерархическую структуру популяций лимфоцитов, с выделением на основе фенотипических, молекулярно-генетических и функциональных свойств клеток различных минорных субпопуляций, роль которых в обеспечении целостности организма изучена не полностью. Помимо теоретических докладов, в ходе данного Форума были представлены результаты использования новых методических подходов для изучения особенностей структурной и функциональной организации отдельных звеньев врожденного и адаптивного иммунитета как в модельных условиях, так и при развитии различных заболеваний человека, обозначены наиболее перспективные пути совершенствования аналитических и технологических платформ. В рамках Форума были реализованы несколько программ повышения квалификации для сотрудников различных звеньев практического здравоохранения и фундаментальной науки.

Ключевые слова:

фундаментальная и прикладная иммунология, онкоиммунология, состояние и перспективы развития науки, врожденный и адаптивный иммунитет, противоопухолевый иммунитет, лимфоциты, цитокины

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Researcher ID: M-8378-2019

Информация о финансировании: финансирование данной работы не проводилось.

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:

Сагакянц А.Б. Объединенный иммунологический форум: современные направления развития фундаментальной и прикладной онкоиммунологии (Новосибирск, 2019). Южно-российский онкологический журнал. 2020; 1(2): 36-45. <https://doi.org/10.37748/2687-0533-2020-1-2-5>

Получено 11.11.2019, Рецензия (1) 16.01.2020, Рецензия (2) 19.01.2020, Принята к печати 01.06.2020

INTRODUCTION

The achievements of practical Oncology are largely related to new data obtained using a number of modern methodological approaches that allow us to identify the features of the structural and functional organization of innate and adaptive immunity elements. It is generally accepted that the immune system is involved in the control of antigenic homeostasis of the human body and, as a result, the fundamental importance of this system both in the fight against cancer, and, with a number of defects or its failure, in the occurrence and progression of the tumor.

For the further development of oncoimmunology, it's important to exchange experience with representatives of various scientific and practical teams, discuss new experimental data obtained by them, and involve promising theoretical approaches to explaining the facts observed in practice, what happens at forums and congresses of various levels.

The purpose of this report was to briefly highlight the results of the Joint immunological forum with international participation. The source of information was direct personal participation in the Forum, as well as the study of new theoretical and practical results of oncoimmunology presented in publications.

One of the most important events for immunologists this year was the holding of the "United immunological forum-2019" with international participation in Novosibirsk from 24 to 29 June 2019.

This forum brought together a number of events: VI Congress of the Russian scientific immunological society (RNOI); VIII Conference of the Russian cytokine society (RCO); VIII reproductive immunology conference; VIII Neuroimmunology conference; XV conference of immunologists of the Urals; Conference on targeted and cellular immunotherapy; Oncohematology and oncoimmunology conference; primary immunodeficiency international conference; School of flow cytometry; school of rheumatology; professional development Cycles.

The forum was attended by more than 500 people (12 academicians of the Russian Academy

of Sciences, 12 corresponding members of the Russian Academy of Sciences, 111 doctors of science, 102 candidates of science, more than 190 people-practical health workers, postgraduates and students). The forum participants are representatives of 30 Russian cities, speakers and participants from near and far abroad: the USA, the Netherlands, Japan, the Czech Republic, Hungary, Bangladesh, Uzbekistan, and Kazakhstan.

During the forum 376 oral reports were presented at 43 symposiums, 22 reports were presented at 7 plenary sessions, and two round tables were held (problems of teaching immunology in medical Universities, the state and prospects of immunological journals). More detailed information is available on the official websites of the event (<http://niikim.ru/ru>; <http://rnoi.ru>; <https://bs-sib.ru>).

Analysis of the work of the «United immunological forum-2019»

During the Forum, various specialized sections and plenary sessions discussed the molecular and genetic basis of innate immunity, infectious and inflammatory diseases of the mucous membranes and lymphoid organs: new aspects of diagnosis and therapy of immuno-mediated diseases, the possibilities of modern flow cytometry in solving the problems of fundamental and applied immunology. The relevant sections covered such aspects as: the use of cytokines in the diagnosis, pathogenesis and treatment of human diseases, the state of the problem of autoimmunity, ophthalmology, tuberculosis immunology, immunological aspects of atherosclerosis, tumors of the immune system, and vaccination. The issues of fundamental and clinical psychoneuroimmunology, the state and prospects of hematopoietic stem cell transplantation, gene therapy and cell technologies in immunology, allergology and clinical immunology, etc. were considered.

Undoubtedly, special attention was drawn to the work of the section "Immunopathogenetic foundations of tumor growth" (27.06.2019). Within the framework of this section, reports were presented on both fundamental and applied oncoimmunology.

Would like to focus on the report of I.A.Baldueva (FSBI «N.N.Petrov National Medical Research Center Of Oncology» of The Ministry Of Healthcare of The Russian Federation, Saint Petersburg), which provided information about immuno – mediated adverse events (IAE) that occur in the body of a cancer patient during immunotherapy (IT) with drugs that inhibit the control points (ICT) of the immune response (anti CTLA-4 and anti PD-1/PDL-1). The development of Ionia is associated with excessive activity of effector mechanisms of the immune system against the background of it, which can lead to autoimmune damage to almost any organ and organ system [1].

After considering the main mechanisms of ion exchange, attention was drawn to the cytokine release syndrome as a modulator of cell-mediated reactions. Based on the analysis of a clinical case of a patient with melanoma of the skin, with the progression of the disease after surgical treatment, the mechanism of development of Ionia against the background of it (anti-CTLA therapy) was considered. The features of changes in some cellular parameters of the immune status (IC) are determined. An increase in individual subpopulations of cytotoxic lymphocytes (CD3⁺CD8⁺, CD8⁺HLA-DR⁺, CD3⁺CD38⁺, CD3⁺CD16⁺CD56⁺) was shown after. In the patient's body, elimination of FoxP3⁺Tged, an increase in the number of eosinophils and their activation was noted, which is accompanied by the release of a number of chemokines (CXCL9, CXCL10, CCL5), which cause chemotaxis of cytotoxic CD8⁺T lymphocytes, their migration to the tumor. The speaker noted that "IAE arise from the overall immune response to the tumor and, in most cases, effective treatment of ICTs can temporarily be subjected to immunosuppression with glucocorticosteroids (GCS)". GCS do not inhibit the cytotoxic activity of activated T-lymphocytes, and a number of studies have proven the synergy of their use with certain types of immune therapy.

Summing up, I.A.Baldueva noted: the mechanisms of development of antitumor immune response and IAE are identical; GCS are pathogenetic therapy for IAE, support a specific antitumor CD8⁺ – T cell immune response to therapy with immune synapse modulators.

Novik A. V. (FSBI «N.N.Petrov National Medical Research Center Of Oncology» of The Ministry Of Healthcare of The Russian Federation, Saint Petersburg) in the report "Problems of immunotherapy in clinical practice: the need for immunological research" continued the discussion of issues related to it, noting the urgent need for immunological research. Assessment of quantitative and qualitative (functional) parameters of individual links of innate and adaptive immunity in cancer patients against the background of it, will identify new prognostic factors, the probability of development, the achievement/end of the effect, as well as identify and manage risks.

Savchenko A.A. (Krasnoyarsk scientific center of the Siberian branch of the Russian Academy of Sciences, Krasnoyarsk) in the report "Regulatory mechanisms of the formation of the phenotype and functional activity of dendritic cells", having considered modern ideas about the heterogeneity and mechanisms of maturation of dendritic cells (DC), as well as factors that determine these processes, focused on the features of the phenotype of blood monocytes (CD14⁺CD16⁺) in patients with kidney cancer [2]. The speaker noted that the work revealed a decrease in the number and functional activity of blood monocytes against the background of an increase in the content of Treg lymphocytes, and the phenotypic differences between DC are in the level of expression of CD80 and HLA-DR. An increased content of activated Treg lymphocytes in kidney cancer is accompanied by an increase in the number of Mature DCS with increased expression of CD80-a marker that contributes to the formation of immune suppression in the patient's body. Summing up, Savchenko A.A. he noted that the tumor's tolerogenic effect is realized in the formation of regulatory interactions with the immune system, the phenotype and functional activity of DC depends on the state of the monocytes from which they are formed, and in cancer, an important factor will be the tumor-associated progression factors.

Would like to draw attention to a number of facts presented in the report of N.V.Cherdintseva (research Institute of Oncology, Tomsk National Research Medical Center of the Russian Acade-

my of Sciences, Tomsk) "Macrophages and tumor progression: on the way to macrophage-specific therapy". In particular, there is no doubt that each person is a unique ecosystem, in which the outcome of the disease during the formation of a tumor is determined by the exposure of damaging factors, constitutive genetic parameters of the person, features of systemic and local (microenvironment) regulation, as well as tissue architecture, which guide the development of the somatic cell. In the occurrence of a tumor and the severity of antitumor immunity, a special role is assigned to tumor-associated macrophages (TAM), for which high plasticity is shown, participation in such key processes as the regulation of the proliferative activity of tumor cells, the influence on their invasive properties, angiogenesis, the severity of the epithelial-mesenchymal transition, the ability to metastasize and resistance to radio and chemotherapy. We discussed the ideas that have been accumulated to date about the methods being developed for reprogramming stromal-inflammatory elements to counteract the tumor, while specialized populations of tumor-promoting macrophages can act as a target for cancer therapy.

This section presents the results conducted in the National Medical Research Centre for Oncology of the Ministry of Health of Russia studies aimed at the isolation and study of biological properties of tumor stem cells (report, "Tumor stem cells and their microenvironment: role in tumor development", Sahakyants A.B.), imple-

mented in the framework of public procurement "Study of possibility of using the tumor stem cells to create models of xenogeneic tumors in the experiment". 19 tumor cells with the stem phenotype were isolated from postoperative material of patients by immunomagnetic separation using reagents from MiltenyiBiotec (Germany). The selection was made in accordance with the manufacturer's instructions. For each case, depending on the type of tumor, the necessary set of primary antibodies conjugated with magnetic particles was selected. Also, depending on the number of cells, the concentration of reagents and the type of magnetic column were selected. The cells of the target population were adsorbed (positive separation) on magnetic spheres and separated into a single fraction upon completion of separation. To isolate tumor stem cells (OSC), antibodies to the following antigens were used (table 1).

Among these, glial brain tumors accounted for 9 cases, breast cancer-7 cases and 3 more cases-brain metastases (ovarian cancer, lung cancer).

The cell population isolated as a result of separation (positive fraction) was from 0.2 to 1 million cells. Cells were transferred to a T25 vial in a culture medium without serum with insulin, transferrin and L-glutamine (GMP DC, CellGenix, Germany) in an amount of at least 0.5 million per 5 ml vial. A negative fraction that does not contain the target cell population was used as a control. The composition and volume of the medium, the type of vial, and the number of cells in the negative fraction were similar

Table 1. List of markers and reagent kits used to isolate tumor cells with the stem cell phenotype

№	Antigen OSC	The set of reagents	type of neoplasm
1	CD133	CD133 MicroBeadKit, human (130-097-049)	Glial tumors; metastasis of lung cancer to the brain; ovarian cancer metastasis to the brain; breast cancer (BC)
2	CD90	CD90 MicroBeads, human (130-096-253)	Glial tumors
3	CD44	CD44 MicroBeads, human (130-095-194)	BC, metastasis of lung cancer to the brain
4	CD24	CD24 MicroBeadKit, human (130-095-951)	BC
5	CD117	CD117 MicroBeadKit, human (130-091-332)	Ovarian cancer metastasis to the brain

to the positive fraction. After 1–3 days, the growth of free – floating spherical colonies-oncospheres was observed in the vials, while the number of colonies in vials with an enriched target cell fraction was several times greater than in the corresponding control samples, which is evidence of the presence of stem properties in the isolated subpopulations of tumor cells. It is known that in conditions of low adhesion, differentiated tumor cells and non-malignant cells undergo anoikis-apoptosis as a result of incorrect cell adhesion or its absence [3], while OSCs survive and selectively multiply, forming free-floating in the environment of the oncosphere [4, 5]. In the future, the first experiments were carried out on the experimental creation of a xenogenic model of a human brain tumor on immunodeficient mice. A total of 6 transplants of oncospheres with the phenotype (CD90⁺CD133⁺) obtained from OSC isolated from gliomas were performed [6].

The attempts made to create xenograft models of gliomas by transplanting isolated OSC did not give the expected result – no visible macroscopic growth of the tumor was obtained in the experiment after three months. Taking into account a number of methodological features and practical experience, work in this direction continues.

Summing up the information presented in the reports on this section, it should be noted that much attention was paid to modern ideas about the immunology of tumors, the role of both individual lymphocytic and myeloid representatives in the occurrence, progression and response to treatment of various tumors. Special attention was paid to the consideration of dendritic cells, monocytes, and macrophages in oncological diseases

During the presentations, the mechanisms of tumor occurrence in multicellular organisms were discussed, as well as the recognition of the mutation theory of multistage carcinogenesis, according to which the malignant properties of a cell are the result of the accumulation of genetic disorders (mutations and chromosomal aberrations). Driver disorders are changes in the activity of genes that determine the lifecycle of cells-proto-oncogenes and anti-oncogenes [7].

It is noted that the appearance and develop-

ment of a tumor is not always accompanied by the presence of a pronounced immunodeficiency or signs of immune disorders. Thus, the incidence of most types of solid tumors does not increase with immunosuppression, and the incidence of breast cancer actually decreases. In addition, the incidence of spontaneous tumors in mice bastianich not higher than that of immunocompetent animals. The ambiguous experience of using immune system stimulation in the vast majority of patients with malignant tumors-all this points to the complex, contradictory nature of the interaction between the tumor and the immune system, the ambiguous role of the latter in the progression of the disease, which is reflected in such a concept as the idea of immunoreduction of tumors [8].

The malignant tumor development is the result of exogenous and endogenous nature combination factors that increase the probability of survival, increase the number and spread of tumor cells, which is a consequence of genetic instability, reprogramming of cell metabolism, manifested in changes in the nature of biochemical processes and affecting almost all their aspects. Of particular importance in the occurrence and progression of a tumor is its ability to "escape" from immune surveillance, as well as the impact of tumor-promoting chronic inflammation [7, 9].

Considering the mechanisms of "eluding" the tumor from the immune response, the special role of immune selection of tumor cells (loss of neo-antigens and/or changes in the expression of HLA-I and costimulatory molecules), as well as the formation of an indifferent microenvironment and the induction of immunosuppression, which in turn can be associated with:

with the expression of molecules that induce apoptosis of effector cells (soluble forms of FasL and MICA);

– release of soluble ligands that block T-cell receptors;

– secretion of cytokines that inhibit the activity of lymphocytes and dendritic cells (IL-10, TGF- β , VEGF);

– isolation of cytokines and factors that attract T-reg and macrophages with immunosup-

pressive activity (GM-CSF, G-CSF, IL-6, IL-10, VEGF, PGE2, IL-1).

There is no doubt about the special role of immune control points in inducing immune suppression, the role has been discussed in several reports.

The study of the widest possible range of factors of the tumor microenvironment is the key to a better understanding of the biology of tumors, searching for the most effective ways to diagnose and treat these diseases. It is important to determine the molecular and genetic characteristics of tumors, and to study the system for controlling gene expression: epigenetic, post-transcriptional, and post-translational. In addition, the study of transcription factors and functional specialization of lymphocytes and leukocytes continues [10], the role of heterogeneous micro-RNAs as regulators of inflammatory and immune responses during tumor growth [11].

The information about the classification of tumors depending on the phenotype of transformed cells (PD-L1 expression) and prevailing immunological components (TIL– tumor-infiltrating lymphocytes) in their microenvironment was interesting [12]:

- type 1-acquired resistance to cellular immune responses, which is associated with the expressed expression of PD-L1 tumor cells against the background of the presence of TILs with the phenomenon of inhibition of their activity;

- type 2-immunological ignoring, developing in the absence of PD-L1 simultaneously with a number of features of the antigenic properties of the tumor, without its infiltration of TILs. In this case the ICCS do not identify the transformed cells and do not respond to them;

- type 3-internal PD-L1 induction, a number of factors contribute to the expression of PD-L1 by cancer cells, but there is no penetration of cytolytic lymphocytes into the tumor;

- type 4-immunological tolerance that occurs without the presence of PD-L1 on tumor cells under conditions of its pronounced infiltration of TILs that do not show cytolytic activity. Probably, in this case, additional immunosuppressive pathways are involved.

Despite the fact that the proposed classification scheme of tumors is simplified, it can probably be used to discuss the strategy of immunotherapy, depending on the microenvironment of the tumor.

We should also mention the role of the microbiota in determining the type of immune response, the probability of developing tumors, as well as the nature of the body's response to anti-tumor treatment, including inhibitors of immune response control points, which was reflected in the report of T.A.Karmakova [13, 14].

When discussing the strategic prospects for the development of tumor Immunobiology, it was pointed out that it is necessary to characterize the individual characteristics of the immune response in each patient, as well as to monitor changes in immune indicators during treatment, which is a General trend in Oncology at the moment. The range of defined indicators, as well as the multiplicity of the research is not unified, but is actively discussed at various specialized events. However, General approaches are being developed to develop these standards and determine the most informative indicators that reflect the state of the immune system of the cancer patient.

Considering the methodological aspects of studying the immune response in the development of tumors, it was pointed out the need to reconstruct the network of intercellular signals, which involves the use of new information technologies and accumulated empirical data, the study of the relationship between local and systemic indicators of the immune system, as well as the need to harmonize data obtained with the use of modern technologies.

Without touching on the methodological aspects, which was not the purpose of this work, we should note those modern technologies that, in our opinion, and in the opinion of colleagues, are promising for studying the immune response [15]:

- Multiplex immunohistochemistry;
- Mass cytometry;
- Multiplex analysis methods;
- Omix technologies;
- Cluster analysis.

At the section "New models, research methods and diagnostic systems in immunology"

(28.06.2019), our attention was drawn to the report of Tarasevich A.A. on the topic "from cells to tissues: mass cytometry-the latest method of cell phenotyping in immunology and Oncology".

This report provided information about a new technology – CyTOF[®], used for cell phenotyping and combining traditional approaches in cytometry with mass spectrometry [16].

It is known that standard approaches to phenotyping, such as immunohistochemistry combined with microscopy, flow cytometry, high-content Screening, are based on the analysis of the fluorescence of labeled antibodies interacting with corresponding markers in target cell populations. However, there are a number of known features that must be taken into account when using these technologies: the probability of overlapping dye spectra, different signal intensity from different fluorophores, and background fluorescence, which imposes a number of restrictions for multiparametric analysis. These limitations significantly complicate the design of the experiment and the interpretation of the resulting data.

CyTOF[®] technology eliminates the limitations of fluorescence, since signal separation is based on detecting the mass of labels, not the wavelength of the fluorescent molecule. In this case, special tags are used, consisting of non – radioactive isotopes of rare earth metals (lanthanides) attached to various probes-the same monoclonal antibodies, intercalators, etc. the Main advantages of using rare earth metals are that they are not detected endogenously in biological samples. After performing all the necessary preanalytical procedures, the samples are examined on a mass cytometer (mass spectrometer), in which the material is sprayed in special media into individual drops. Subsequently, the droplets containing the cells are separated, followed by the measurement of metal isotopes on each individual cell in the suspension. Modern devices can analyze more than 40 parameters [16].

However, according to a number of authors, this technology is not without disadvantages: the presence of impurities used in the analysis of metals in accompanying samples; the probability of formation

of metal oxides, which shifts the signals in terms of molecular weight and, as a result, leads to overlap between the probes; incompatibility with living cells; relatively low throughput (5–7 min per sample) [17].

Despite this, mass cytometry is finding more and more applications in various fields of fundamental and applied science and its use allows you to get new data. Thus, Li N. and colleagues, examining biopsies of frozen intestinal tissue of human embryos, showed the presence of memory T-cells in the embryos, which allows us to state the fact that the embryo's immune system is more mature than it was previously thought [18].

The use of these methodological approaches will allow the most effective modeling of tumor growth processes, forecast the response to immunotherapy, and select an adequate personalized treatment.

A promising direction is the development of relevant experimental models [19]:

- a new generation of humanized mouse models (transgenic expression of cytokines, HLA antigens, hormones, human MHC molecules);
- study of the genetics of induced tumors (search for models with high mutation load);
- comparative immunology and immunogenetics of human and laboratory animals;
- *ex vivo* surrogate models (primary organoid cultures: co-culture with lymphocytes and monocytes, selection of personalized treatment regimens, genetic manipulations (CRISP-CAS9; SIRNA), research of stem tumor cells).

Separately, it should be noted that the forum held a full-time part of the professional development program "Flow cytometry in clinical practice". The following issues were raised during the program (some of them were discussed):

- Multicolored analysis-basic principles and approaches (Kudryavtsev I.V., Saint Petersburg);
- Application of standardized technology of leukocyte immunophenotyping in the clinic. Role of assessment of small subpopulations of lymphocytes (Zurochka A.V., Chelyabinsk);
- Assessment of the cellular component of the "immune status" for monitoring the state of the immune system (S.V.Khaydukov, Moscow);

– Features of assessment of cellular immunity in newborns and young children (Semykina E.L., Moscow);

– Study of markers of lymphocyte activation in the clinic of various pathological conditions (Kalinina N.M., Saint Petersburg);

– Immunograms. Diagnostic possibilities of assessing the cellular level of immunity (Nikitin Yu V., Saint Petersburg);

– The role of flow cytometry in Oncohematology (Lugovskaya S.A., Moscow);

– Flow cytometry in clinical oncoimmunology (Zabotina T.N., Moscow);

– Multicolored flow cytometry. Advantages and methodological approaches (Savitsky V.P., Moscow).

Course participants and forum participants had the opportunity to get new information about modern developments in the creation of the most effective fluorochromes used for the identification of phenotypic markers of immunocompetent cells, which, in turn, allows improving multiparametric flow cytofluorimetry. Undoubtedly, new issues and problems related to the need to improve the software used in the analysis of the obtained data were also discussed, as well as the discussion of the rules for creating working panels of monoclonal antibodies and the most appropriate strategies for gating.

During the practical classes, there was an opportunity to get acquainted with the work and capabilities of the new cytometer, to review and analyze the results of the analysis of the immune status (flow cytometry) for primary and secondary immunodeficiency, allergic diseases, and various oncohematological diseases. A General strategy for processing and analyzing the results of determining the parameters of cellular immunity using flow cytometry was presented.

CONCLUSION

Based on the results of the visit and work of a number of sections and plenary sessions of the forum, the Following General trends can be iden-

tified in the study of the mechanisms of the functional organization of the immune system in various human diseases:

1) identification and assessment of the contribution of heterogeneous subpopulations of (minor) white blood cells and lymphocytes to the immune system and immunopathogenesis of diseases;

2) special emphasis on the study of effector leukocytes (monocytes, macrophages, dendritic cells, neutrophils) and lymphocytes (T -, B -, NK), the mechanisms of their functional activity and interaction with each other in the development of the pathological process;

3) study of heterogeneity and functional activity of regulatory subpopulations of leukocytes and lymphocytes with the allocation of 3–4 separate functional types of cells with regulatory function in each population;

4) assessment of the expression level of PD-1/PD-L1, -L2 on various somatic cells and study of their contribution to the implementation of the immune system function in a particular individual (norm and pathology);

5) relevance of screening studies using modern methodological approaches (e.g. multiplex analysis), which allows us to identify new patterns of the immune system both in normal and in various pathological conditions;

6) certain prospects for the development of immunology are associated with the further improvement and implementation of mathematical modeling of immunological reactions, the work of individual organs of the immune system in normal and pathological conditions.

Thus, the result of the work of the "United immunological forum-2019" with international participation was the accumulation and systematization of information about the immunology of tumors, current views on the immunological mechanisms of infectious and inflammatory, allergic diseases, trends in approaches to the diagnosis and treatment of these pathologies, as well as the designation of a number of promising areas in the organization and conduct of research in the field of fundamental and applied immunology.

Author contribution:

Sagakyants A.B – the concept and study design, writing text, processing of the material.

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