

# Some heuristic problems of the modern oncology



## Abstract

Some heuristic discussion problems of modern oncology are presented, some of which are under development, and some are only in the future. But in any case, they are extremely important not only for oncologists, but also for specialists in related disciplines.

There is a fairly steady trend: the aim of anti-cancer therapy are mainly tumor targets, which is confirmed in this way by the use of LAK-cells, NK-cells, CD8-T-Lph (lymphocytes), Mø (macrophages) armed, stem cells (hematopoietic in the treatment of malignant blood diseases), vaccine therapy, etc.

Special words can be said about monAb (monoclonal Ab), with the help of which the targeted therapy is carried out, when they are not aimed at killing a cancerous tumor, as in CT, but at inhibiting its specific receptors—"targets." In the past year, antibodies have been obtained against cells of the human immune system, which "cancel" inhibitory processes in it, making it difficult to fight a tumor, blocking cancer neutralizers of the immune system. It is very good; the targeted therapy is our future; however, at the later stages of cancer, the targeted therapy often does not work; besides, it is very expensive and effective in a limited group of patients.

Now, monAb have been obtained which, using Fab-fragments, bind to tumor AG (antigen), CD3-AG of T-Lph, and by the Fc-fragment, to a NK-cell or Mø-i.e., 3 killers at once kill one target. This is another scientific breakthrough.

## Introduction

Inhibitors of "immune control points" as a rule, monoclonal antibodies of nivolumab and pembrolizumab against the immune control point - PD1 receptor ("Programmed cell Death pathway") on the cytotoxic T-lymphocytes membrane (or its PD-L1 ligand - atezolizumab), which provides cells with protection against autoimmune aggression and damage to own tissues. Activation of these receptors by PD-L1 ligands, often due to their overexpression in tumors, allows tumors to "hide" from the immune system, by triggering T-lymphocytes apoptosis and turning them off from antitumor protection. LAK cells - lymphokine-activated killers, are generated from blood mononuclears when incubated with interleukin-2. Macrophages reinforced - activated macrophages with specific antitumor antibodies fixed on the membrane through Fcγ-receptors.

We see tremendous clinical and scientific

success; nevertheless, as it has already become clear, many controversial issues remain in oncology.

1. Insufficient attention is paid to the immune system itself, whose role in protecting against and fighting tumors is equally important at all stages of the tumor process—from its emergence to termination. This is the antitumor surveillance, aimed not only at the tumor target, but also at the preservation and restoration of immune homeostasis, about which we have only purely general information and which is significantly impaired in a tumor process, and its ultimate role in defense is still not clear. This is confirmed by the fact that, often, immune cells not only do not "see" cancer cells, but help them develop.

2. The most important factor is the presence of many non-tumor cells (fibroblasts, T-Lph, Mø, NK-cells, etc.) in a tumor, complicating tumor treatment, which create a micro-environment that often contributes to malignant growth,

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because it provides local immunosuppression helping the tumor escape the body's immune control. Furthermore, often T-Lph does not kill tumor cells, as they recognize the latter as normal. Therefore, today there is already a revolutionary way of suppressing T-cell special receptors erroneously perceiving a tumor as normal tissue.

3. The next discovery is inhibitors of immune checkpoints which remain one of the most successful methods to fight metastatic cancer. Checkpoint inhibitors crack tumor protection against the immune system; T-lymphocytes find defective cells, recognize proteins of only healthy cells, and if it is cancer cell proteins, T-cells kill it. At the same time, the immune system itself forms molecules-immune checkpoints that prevent destructing by Lph of healthy cells. Therefore, the therapeutic effect on the micro-environment is no less significant than cytostatic therapy.

4. The most important area is CHEMOTHERAPY (CT), which, unfortunately, is far from being effective in all patients: except for the target effect, it has a toxic effect on the body and its immune system, and there is almost no work to prevent such influence-only sporadic attempts. This toxic effect works also in favor of the tumor, exacerbating the process, whereas, in fact, neutralization or reduction of the CT toxic effect is a large share of success, but this problem is still unresolved. In 2004, our scientific discovery No. 257 was approved for neutralizing low molecular weight RNA the toxic effect of cytostatics, antibiotics, heavy antihistamines, bacterial exo-and endotoxins. However, we have done very little in this field, although success and effectiveness were evident.

5. Extremely important is the analysis of the immune system, definition of its integrality, since it is already disturbed before surgical removal of tumors-and this occurs before the surgery, when the immune system is already compromised, and not in terms of changes in specific tumor markers, but in terms of its main protective function. And what happens next, what is decisive in the selective direction of the tumor process development, what determines or directs it, and what is the reason for often reliably described cases of self-healing from the most severe oncological diseases? We should pay the most attention to these facts, rather than avoid them.

It seems that a separate field of study-effects on immune disorders in the presence of a tumor in the pre-surgery period and especially after removing it-is almost unknown to us; however, it is one of the most important keys of successful treatment of cancer in general.

6. Another interesting problem is dormant, i.e. "sleeping", tumor cells, which we could see surrounded by normal tissues using the latest technology. Why do they "sleep"? What does "awaken" them and how to prevent it? Over time, we will surely find out it.

7. Directed cell transport. We developed this problem theoretically and experimentally many years ago. Its essence is to create in the body a "guard" pool of primed, moreover, reinforced cells (we performed it on mobile macrophages), which further migrate to the focus for structural destruction using a special vector delivered to a specific target (including a tumor) using the "ligand-receptor" mechanism and additionally enhanced directional activation of the cell migration ability.

8. The whole line of research proposed in the 70s by Dr. Niu from the USA, is already completely forgotten-although it is about genetic reprogramming of a cancer cell, which he successfully showed in model experiments when introducing RNA of a healthy cell. There have been successes in this area, many reports, but it is also forgotten, so that we should return to it after many years: to discover the already discovered.

9. For many reasons, we start talking about the personalization of cancer treatment. Therefore, I want to say that personalized, predictive medicine is just the ark of our future, which must take into account the above areas, and along this way, surely, we are waiting for big wins. The patient must receive individual treatment-determination of molecular genetic markers of the tumor and choice of a drug depending on them. However, today this applies to only 10% of tumors.

10. At the same time, we need to slightly deviate from traditional orthodox approaches in the cancer treatment; despite many revolutionary breakthroughs in scientific research, it is necessary to pay attention to the issues some of which I already explained, developing them without forgetting about completely new physical aspects of oncology science and other very interesting issues.