Medical nanorobotics: Biotechnology or nanoengeneering?

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Nanomedicine: Does this term more than pseudo-scientific “pink of fashion”, at least potentially? From a "classical" point of view, the goal of nanomedicine is the creation of nanoscale autonomous technical devices (nanorobots), programmed to perform diagnostic and/or therapeutic manipulation in a living organism: the destruction of malignant cells, destruction of atherosclerotic plaques, and so on. The main advocate is a point of view (technocratic) on the subject of nanomedicine which is controversial, and its feasibility is questionable. Furthermore, most importantly, the question arises - WHY develop and create wonders of engineering - technical nanoscale devices for correction of the condition of the body, if they have already devised and are effectively being used by biological systems? Does it make sense to reinvent the wheel if it has already been invented and produced by nature, even if called differently? Is it not better, instead of inventing another bike, to focus efforts and resources on understanding the principles of functioning of the natural nanodevices, as well as practicing ways to improve efficiency (optimization) of their functioning in vivo?

Keywords: Nanomedicine; Biomolecules; Technic devices; Auto-antibodies; Health state; Diagnostic; Correction

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Introduction

From the point of view of technocrats, promoted in today’s media and on the internet, the goal of nanomedicine is the creation of nanoscale autonomous technical devices (nanorobots), programmed to perform the diagnostic and/or therapeutic manipulation in a living organism (destruction of malignant cells, destruction of atherosclerotic plaques, and so on) [1]. The inventors of such technocratic fantasies do not consider the complex issues that inevitably arise when considering the relationship between biological and technical systems. For example, how reliable is it for technical devices to recognize, and differentially respond to "useful" and "harmful" components of a biological system in terms of high numbers of transitional forms? How is the harmful effects of failures in many of the nanorobots that are running in the expanse of the body avoided? How to remove (deactivate) the set of nanorobots in the body, in case they malfunction? Given the current level of development of engineering, we are forced to refer to nanomedicine as "the main glamour" or (at best) as to the tasks, the feasibility of which is belonging to the distant future. Besides being heavily promoted by the technocratic point of view, the subject of nanomedicine is highly debatable, there is another (main) question: WHY? Why develop and create technical nano-devices (nanorobots), intended for the correction of pathological conditions of the organism, if such a device has already been invented, constructed and used effectively by Nature?

Molecular nanorobots of the living systems

It is known that any biological function is ordered based on interactions of specialized molecules. The result of the natural interactions of nanoscale devices, may lead to the production
of energy (chemical, mechanical, electrical, thermal), used for the needs of organism and the manufacture of polymeric "building materials" (polypeptides, structural components of cell membranes, etc.), going to the constructing of new cells and other specialized biological structures. Natural nano-effector device provides playback of complex biological structures (replication of DNA, cells reproduction, etc.), and perform many other functions that ensure the functioning of the organism throughout the life span. Ordered intermolecular interactions of DNA, proteins, receptors, and other macromolecular complexes are based on the physiological functions of the human body, they include, reproductive functions, integrative activity of the nervous system, digestion, pressure regulation in the circulatory system, clearance, protection from the damaging effects of the environment, etc. [2]. Endogenous molecules nanorobots function as "builders", "engineers", "couriers", "managers", "soldier", "scouts", "energy", etc. The conversion of photon energy into electrical energy of nerve impulses was provided by rhodopsin. Chlorophyll helps provide the transformation of photon energy in various endergonic reactions, including photosynthesis (the conversion of carbon dioxide into organic matter by green plants). Molecules-trophines induce the growth and reproduction of some particular types of cells, etc. For remote control of cells of different organs and harmonization of the functional activity of very different cell types of a multicellular organism, in the course of evolution, were selected from thousands of the molecular nanorobots-messengers (of molecules-messengers, signaling molecules, transport molecules, etc.). The control and matching of molecular nanorobots are programmable, autonomous and have the ability to move directionally through the body in given biological addresses. Delivery messages are perceived in a different type of endogenous nanorobots (specialized receptor molecules), transforming the information received in the extracellular, intracellular and intranuclear processes. A good example of the co-ordinated (co-tuned) functioning of one system of biological nanorobots, is the system involved in the inhibition of aging, dying and damaging of cells of organisms. In accordance with a given (genetically determined) program, any aging (or damaged) cell is nearing the end of its functional resource, expressed on its surface is the peculiar molecular signals "eat me" [3] - "signaling molecules-flags", band-three type [4]. Specialized molecules of the immune system - antibodies-controllers, contact with such molecules' flags designed and labeled for disposal cells (stamped "for processing"). After that, the cells or subcellular particles labeled by antibodies are easily recognized by membrane receptors of phagocytes-macrophages -they are miniature "waste-utilizing factories". Inside phagocytes occurs the disassembling of the utilizable cells and their fragments and sorting their components occurs in the phagocytes, most of which are recycled as raw materials for the production of new biological structures or enzymatic "combustion" and energy production. Similarly, marked specialized antibodies are then disposed off by phagocytes "defective" (modified, mutated) cells, and hazardous microorganisms. We emphasize that all components of these complex "slurry" process, programmed for certain effector operation, and are characterized by autonomy, the nano range and surprisingly high degree of reliability, while unattainable for technical devices. Every second in the body goes through a number of such parallel automated processes using natural molecular nanorobots (synthesis of polymer molecules of proteins from amino acids-the monomers on molecular programmable "conveyors" - the ribosomes, molecular self-assembly of intracellular "pipelines" - the microtubules, etc.).

These examples show that nature has already decided, and decided very effectively, many of the issues are put on the agenda of the engineering as future medical nanotechnology devices. Obviously, if the experts in the field of medical nanotechnology will take into account developments of nature - it can significantly speed up and improve the effectiveness of ongoing and planned developments. We mean the following: (1) Before proceeding to costly technical designs of artificial nanoscale devices, it is desirable to provide to experts of technical profile to get acquainted with existing "Nanomolecular development" of nature; to assess their capabilities, merits and demerits from a technological point of view. (2) Weighted expert analysis of the situation in many cases will refuse the designing of artificial nanorobots in favor of existing effective practices of wildlife. Note that advances in molecular biology allows create de novo and directed to modify (to "improve"), to give new properties, specialized molecular nanorobots produced by living cells. Moreover, if the timing modification (optimization, fitting the task) natural nanorobots in the course of evolution took thousands of years, today, similar modifications can be executed within weeks. (3) The most probable and rational future medical nanotechnology/biotechnology seems to us not so much in the form of formation of a new autonomous industry, but in the form of a development of a kind of synthetic (border) area of activity of specialists in different fields, which will be based on engineering design (process) understanding of "natural developments" and the use of ready-made or modified biological signaling and effector molecules. (4) It is important to consider that the specialists, immunologists, biochemists, molecular biologists, are usually poorly trained in matters of technological comprehension of the subject and as well as technical specialists who are unable to understand the advantages and the possibility of using nanoscale molecular-biological structures of natural origin. Without the awareness and elimination of such "gaps in education", it will
be difficult to expect effective cooperation of representatives of the Life Science and technical specialists.

Below, is a closer look at the functions of one of the many types of natural molecular nanorobots, namely molecules of autoantibodies (auto-AB) produced by cells of the immune system.

### Introduction to the immunophysiology

Historically, immunology emerged as the direction of applied Microbiology. Therefore it is clear that the immune system was viewed solely as a tool to protect the body from microbial predators. This view was cultivated by microbiologists who taught immunology for many years. But what if initially immunology evolved as one of the areas of general physiology, if founders were not microbiologists L. Pasteur and P. Ehrlich, and physiology, I. P. Pavlov and Walter Cannon? If immunology initially developed as part of General physiology, probably today we would treat the immune system, as the main system for maintaining antigenic and molecular homeostasis of the organism. In this case, instead of the habitual idea of permanent war waged by the immune system against "Aliens" (microbes-aggressors), we would have had much more peaceful views. For example, the idea that the activity of the immune system is not so much the search for and destruction of "Alien", but with the elimination of potentially harmful homeostasis factors - endogenous, and to a lesser extent, exogenous. In other words, the immune system would be associated more with a housewife, constantly and meticulously providing the established order, rather than with watchful policeman. The lonely voice of I. I. Mechnikov, interpreted its role exactly (1896), was not heard [5]. Modern "reincarnation" of ideas Mechnikov is the concept of danger by Polly Matzinger [6]. According to her the idea of the immune system, it is not concerned with the identification and destruction of “Alien”. It focuses on identifying and processing or blocking potentially "Dangerous" endogenous and exogenous in origin. This concept allows for the explanation of such essentially unexplained present day phenomena, as no appreciable reaction of the immune system to a huge number of microbial bodies, permanently present in every healthy body (normal microflora of the skin and mucous membranes of gastrointestinal and urogenital tracts). Or the ability of any healthy woman's bearing half-alien to her fetus. Or no rejection of the breast with the beginning of lactation, despite the fact that the cells begin to express new proteins (e.g. casein). Taking the concept Matzinger, it is natural to wonder how the immune system distinguishes between "Dangerous" and "Harmless"? According to Matzinger the basis of distinction is the detection of excessive production of the signals of tissue injury (“danger signals”, molecular factors tissue stress) such as heat shock proteins, extracellular DNA, inflammatory cytokines, etc. [6]. These signals triggers complex immune reactions aimed at eliminating the source of “danger signals” and activate the mechanisms of tissue reparation.

The shift of emphasis on homeostatic function, as the fundamental for the immune system, entails a revision of certain propositions relating to the biological role of natural autoimmunity and such specific products of the immune system, as auto-AB of IgG class. The last are the most important molecules responsible for clearance of the organism from potentially harmful factors. Note that the clearance is the archetype of the functioning of the immune system. It is the most basic, primary evolutionary manifestation of homeostatic functions of the immune system [3]. It includes elimination of such versatile stimuli as harmful viruses, fungi and bacteria, but primarily it is aimed at the permanent utilization of billions of dying cells, worn out and replace with new ones as required.

Previously it was thought that the clearance is carried out mainly by macrophages. This is true, only if it stipulates that: On the surface of macrophages are present a TL-receptors, and a number of others interacting with typical antigens walls of bacteria [7]. But, when it comes to most endogenous products that are to be disposed, it turns out that their macrophages "can't see". No macrophage cannot distinguish between "old" red blood cells (or hepatocytes, thyrocytes, or other cells) that exhaust their resources and can be recycled, from the new ones. Despite this, the question of what the macrophage to destroy, and which should not touch, effectively solved by using the specialized molecular signatures, "labels", attached to any product that should be utilized. Such signatures (molecules-informers) serve a natural auto-AB of IgG class [3]. Macrophages have on their surface a large number of Fc-receptors, specific binding of IgG antibodies at the Fc-portion, if their Fab-sites associated with the respective antigens [7]. Engulfing antigen-binding antibody, macrophage engulfs also labelled antigens. In the process of clearance the auto-AB doing much the same that guides the blind: they seem to take on the function of the missing "eyes" and positioned the macrophages over the target, which must be destroyed. As a result, the macrophages effectively engulf and utilize the endogenous products of catabolism, provided that the latter are marked by the relevant auto-AB. Without one, the products of apoptosis and other catabolites not swallowed up or are swallowed inefficiently [3].

### Autoantibodies as diagnostic nanorobots

Production of auto-AB IgG is regulated by the quantity of relevant antigens in intercellular compartments of the body [8].
Therefore, the more products that are to be disposed are formed in the body, the more specific auto-AB are producing for specifically binding to respective antigens, marking them, and initiating the utilization of the latter by macrophages. In healthy adults, the intensity of the programmed death (apoptosis) and substitution (regeneration) of differentiated cells of any organ approximately the same. This leads to approximately the same levels of generation of organ-specific antigenic products are recyclable and, therefore, approximately the same levels of production of respective auto-AB. The similarity in the serum content of different auto-AB IgG in healthy individuals, it was noted long ago [9], but for a long time received no explanation.

Approximately equal levels of individual products "cardiotropic", "hepatotropic", "neurotropic", etc. auto-AB IgG in adults is vital, because the development of almost any pathological process in any organ induce noticeably changes in production of auto-AB corresponding specificity. The reason for this is a local increase in the activity of apoptosis (necrosis) of specialized cells and changes in the expression of many enzymes, membrane receptors and other molecules. Such natural autoimmune reactions are secondary and adaptive (sanogenic), because they aimed to maintain and restore the disturbed homeostasis by optimizing the clearance of the affected organ and the activation of regenerative processes [3, 5].

Ergo:

• The development of various diseases is based on continuous impairment of the synthesis and/or decay of those or other molecular components in certain populations of cells in our body and is accompanied by activation of apoptosis of cells of an organ.

• These deviations usually begin long before clinical manifestation of diseases, reflected changes in the secondary production of auto-AB IgG specific for each form of pathology.

• Such changes in production and serum content of auto-AB, these natural and universal diagnostic nanorobots, can be considered as a versatile marker sign, accompanying the development of any chronic disease.

Important properties of auto-AB of IgG class

A distinctive feature of auto-AB IgG is their permanent and ubiquitous presence in the body. No placental or blood-brain or other tissue barriers, or even cell membranes are not for them insurmountable obstacles [10, 11, 12]. Content auto-at the same antigenic specificity of an individual differs very little from the sampling of blood from different blood vessels [10, 12]. In other words, whole-organismic network auto-AB IgG ("Immunculus"[13]) arranged on the holographic principle [3]. The main feature of a hologram is that any small portion of a holographic image contains information about holistic three-dimensional picture. Due to the fact that a holistic representation of any piece of the hologram, the smaller the fragment will be used, the less clear it will be, however, in any case, provided his "holism" without loss of parts. "Mirror" autoimmune the image of the body (Immunculus) is a non-localized (unlike Wilder Penfield’s topically organized "neurological Homunculus"[14]). Loss of some portion of individual Immunculus, for example, after massive blood loss, as in the case of a hologram, it is not accompanied by selective gaps in the reflection of some organs.

Detection and analysis of abnormalities in the serum content of a plurality of auto-AB IgG, as a natural diagnostic nanorobots, can and should become an effective tool for preclinical diagnosis of future multiple disorders from atherosclerotic changes of cerebral vessels, to malignant tumors [3]. Successful development of this approach may lead to a revision of the basic paradigm of modern medicine and turn the practice of medicine from treatment to prevention of disease (PROGNOSIS OF THE DISEASE - THE DISEASE PREVENTION; instead of the modern: DIAGNOSIS OF THE DISEASE - DISEASE TREATMENT).

The question arises: whether to rely on the possibility of technical invention "of nanoagents" introduced into the body for the purpose of receiving reports about the anticipated problems? Or would it be wiser to use it for any human body biological (molecular) "nanosensors" reflecting any form of trouble starting?

Autoantibodies as natural nanorobots for self-reparation

Prospects of application of auto-AB of IgG class as endogenous "treatment" nanorobots originate from the works of the student of I. I. Mechnikov - A. A. Bogomolets. He discovered [15] that low doses of antibodies to corticosteroid antigens induced in the target organ activates the secretion of specific hormones i.e. antibodies could act as modulators of the activities of the endocrine cells. Later these observations were confirmed by L. R. Perelman [16], and then by A. S. Zaichik and his staff [2, 11, 12]. They, in particular, showed that antibodies of class IgG antibodies to tissue-specific antigens chromatin of target cells (adrenal cortex, anterior pituitary, thyroid gland), can stimulate production of hormones in specialized cells, induce mitogenic effects, and prolonged exposure may lead to hyperplasia of target organs.
Immune net, anti-idiotypic antibodies, and Immune Panacea

Antibodies are recognizing molecules. On the basis of specific recognitions are being built all of the information processes in the body. Creating specific auto-AB to any self-antigens, including membrane surface and intra-nuclear (chromatin) receptors, the immune system may regulate cell proliferation, maturation and differentiation, secretory activity, etc. genetically deterministic functions of all types of cells in vivo [3, 11]. It is assumed that bioregulators and their nuclear and membrane receptors, together with auto-AB to them are included in a single system idotype-antiidiotypic interactions, in order to obtain a precise coordinated implementation of genetic programs in different cells and in the organism as a whole [11, 12]. Moreover, idotype-antiidiotypic mechanism can lead to the emergence of auto-AB - a kind of "secondary" anti-antibodies, supporting the specificity of the complementary sites of the antigen-binding center of primary antibodies. Obviously, some of specific anti-antibodies (anti-idiotypic antibodies) will be structural (steric), and sometimes functional analogues of the antigen that triggered the immune response. If it was a hormone, neurotransmitter, autacoid, enzyme or drug, some of the anti-idiotypic antibodies will represent immunologically the biologically active sites of antigen and, accordingly, will be able to at least partially reproduce the biological effects of the primary antigen. Accumulation of a considerable amount of experimental, clinical and pathophysiological data proving the reality of this situation [5, 10, 11]. If you ponder about this idea, we can come to a paradoxical conclusion: the immune system is able to create copies of any existing biologically active molecules! To some extent this may be true incarnation of the ancient myth about Panacea [12].

Abzymes

Another important property of natural auto-AB is the ability to modulate the functional activity their antigens target, but with biological activity, primarily catalytic, molecules of auto-AB themselves, depending on the structure of their active sites, i.e. their hypervariable Fab-fragments. Found that some of the antibodies, as such, have their own enzymatic activity (so-called "abzymes"). Described antibodies exhibiting the activity of superoxide dismutase, stimulating the hydrolysis of phosphoinositides, catalyzing transferring of acyl groups, catalyzing stereospecific aminolysis, hydrolysis of aromatic amides and ring cyclization, and possessing proteolytic and nuclease activity [5, 10]. A huge number of possible active site antibodies, theoretically may provide to them ALL forms of enzyme activity. It is important that abzymes is not some virtual substance, representing a purely theoretical interest. It is assumed that the molecules at possessing enzymatic activity, can find clinical use. For example, in model experiments it was shown that in mice, drug addicts receiving cocaine, can induce the production of antibodies-abzymes, effectively destroying the drug molecules. It is assumed that such abzymes can find application in the treatment of cocaine addiction and other forms of addiction [10]. It is also possible that specific abzyme can be used to treat an enzymatic deficiency caused by genetic defects (including cystic fibrosis, phenylketonuria, etc.) and possibly in the treatment or prevention of Alzheimer's disease (abzymes, whose able to hydrolyze beta-amyloid) [10].

The question arises: whether to rely on the potential future of invention technical "nanorobots", introduced in the body to correct those or other pathological changes or reasonable force and means to invest in the study and subsequent use of natural pervasive and Autonomous "robots-correctors" produced by the organism itself?

One can cite many examples to illustrate the perfection of molecular nanorobots biological origin. It is the elegance and precision of the work of tiny mitochondria, with a surprisingly high efficiency producing energy, or work ribosomes - these multifunctional programmable stations biosynthesis of macromolecules. And so on and so forth. They all illustrate one thing: Living Nature (Evolution, the Creator... it's not the terms) ahead of today's capabilities of our engineering technology something like floating over the Aegean sea gull ahead of aeronautic capabilities of Icarus glued to his wax feathers. Although, it is worth noting that two and a half thousand years later, the feathers of Icarus turn into aircrafts and space shuttles.

Conflict of Interest

The authors declare that they have no Conflicting interests.

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List of abbreviations used

auto-AB: autoantibody.

Authors’ contributions: equal

¹Auto-AB is biologically active molecules. Therefore, their abnormally increased synthesis, unconditioned by the needs of the organism (primary), may cause many disorders, including allergic and autoimmune diseases [12].
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