Conceptual approaches to development of highly effective
Erbisol drugs of new generation

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Erbisol preparations are characterized by the original mechanism of action. This mechanism allows these preparations to affect not so much a disease as the body activating body’s control systems responsible for the search and elimination of pathological changes. The immune system is one of such control systems. The preparations targetly activate the immune system which effectiveness manifests itself through macrophages which promote the repair of damaged cells and restoration of functional activity of organs and tissues as well as through N- and T-killers responsible for the elimination of abnormal cells and tissues. Erbisol preparations contain non-proteines complex of the natural organic compounds of non-hormonal origin. They are extracted from the embryonic tissue of chicken or duck germs. The preparations contain the specific “signal” low-weight molecules extracted from “markers of cell physiological state”. The latter activate natural, evolutionally formed mechanisms of search and elimination of pathological changes in organs and tissues and promote the body to implement its genetic potential. The rights to develop and produce Erbisol preparations are reserved in 20 countries of the world.

The development of new highly effective medicinal preparations was always a zone of the intent attention for the leading pharmacological firms of the world. Despite an enormous variety of the medicinal preparations a search of universal mechanism influencing on the human body becomes especially actual on the border of new century.

One of such directions in the field of highly effective medicinal preparations of the new generation are Erbisol preparations, developed by the Scientific Production Center “ERBIS”.

Erbisol preparations are characterized by the original mechanism of the action. This mechanism allows them to affect not so much a disease as the whole body activating the body’s control systems responsible for the search and elimination of pathological changes. The immune system is one of such main control systems.

The preparations targetly activate the immune system which effectiveness is first of all manifested through the effect of macrophage link promoting the repair of damaged cell and restoration of functional activity of organs and tissues as well as through N- and T-killers responsible for the elimination of abnormal cells and tissues.

The fundamental examinations of regenerative processes in animal organs and tissues with different kind of damages were a basis for the development of principally new methods influencing the restoration of organ and tissue functional activity under the pathologic changes. The regenerative process, as is generally known, is broadly developed in lower organized animals. For example, if the worm is cutted in half the two new ones will grow (restore) from two parts. The claws grow in a crab, the pads – in a triton, the tail – in a lizard but the birds and mammals are devoided of such
possibility. Did they lose such ability really or is it blocked or in somnolence state in the course of evolution and is only manifested at the level of wound healing, restoration of dermal and hairy integument, epidermis of intestine and other cells that are constantly repaired in the process of body vital activity? But the search of a key for starting the organ and tissue regenerative processes can approach the treatment problems of pathological foci in a principally new fashion. No strive for curability such foci as many as the substitution for the healthy tissue by accelerating the regenerative processes of damaged cells and the elimination of abnormal cells and tissues inflexible for the regeneration and also the activation of hypertrophy processes and proliferation of healthy neighboured cells substituting for the necrotic foci. Furthermore, activating the regenerative processes in the elderly the functional insufficiently of organs, modulating the process of “rejuvenation” of the tissue and the different approach to the problem solution of active longevity can be restored in that way.

A dream is excellent but how get it near? But now the nature itself gives us a prompting.

It appears if the 2/3 part of the rat liver is almost cut, the new liver is nearly grown in full volume from the part remained next day. Notice, this is occurred in higher organized animals and such increased regenerative speed there is not accessible even to the lower organized animals as a worm cut, the crab claws, the triton pads, a lizard tail are recovered during some months. Certainly, the rat liver regeneration is different from that of organ regeneration in these animals but nevertheless it indicates that higher animals did not lose this property.

Studying the rat liver regenerative process, an appearance of “new” antigens such as the protein molecules, absent in norm, changing immunogenicity of regenerative tissue on the surface of remained liver hepatocytes (basic functional cells of the liver) in 4-5 hours after hepatoectomy of 2/3 parts was revealed by us. This has in its turn induced a response of the body immune system. However under existing conditions the classical immune reaction has no time to react to quick-changed phases of organ regenerative process. As is generally known the classical specific immune response is formed in 5-8 days but the principal phases of the rat liver regeneration after partial hepatoectomy – in 4-32 hours.

A first phase of the liver regeneration is accompanied by the increase in the autoantibody titer and activation of nonspecific immunity initiating the regenerative process. The cells of macrophage series play a key role in this situation. In the liver they are presented by the Kupffer cells. If at that instant they are neutralized by the injection of Indian ink, colloid iron or gold into circulatory bed the regeneration will be absent.

Many of these autoantibodies are the immunoglobulins characteristic for the growth processes with specific structure of Fc-fragment that has probably no small importance in their fixation to the immunocompetent cells taking part in nonspecific immunity and playing the role of their receptors while contact with typical antigens.
It is interesting to note that macrophages were for the first time discovered by I.I. Mechnikov who tried to resolve the problem of human longevity with their help. Indeed he was on the way to this resolution. However it becomes clear just now but at that time this was considered as an imagination of the old man. His experiments were carried out on the monkeys. This is very interesting history: he had meeting with a millionaire advanced in age who wanted to be included into the experiment and to be rejuvenated in the spirit of science fiction of that time.

The scientist was subsidized by that man: all the monkeys were purchased by him. The trouble was that I.I. Mechnikov started to carry out his experiments in France at 1st world war. The soldiers of Germany came up to Paris, the capital of France, the projectiles began to fall into the town. The authorities of Paris were afraid if the projectiles will hit into the breeding nursery with infected monkeys (scientist attempted to force the macrophages to work whipping up them with infection) they will scatter along Paris and will cause the epidemic. The people of France made in the spirit of war-time: a detail of soldiers arrived and the precious monkeys were shot in sight of the investigator. I.I. Mechnikov could not bear it and he was soon died, and the idea was for some time forgotten – so it was not at that time comprehended by nobody. But we could have such medicine already at that time.

Something was not enough in all that. Really infecting body I.I. Mechnikov “whipped up” the macrophages but started the very strong additional side-processes. It was obviously necessary to go by other way – many of these things became clear while it was detected that our “repairing” system includes no a link but two ones at least. Firstly the macrophages attempt to “repair” the damaged cell and if it is not succeeded an another line is going up – “killers”, the special cell-killers destroying the hopeless ill cells.

It is particularly necessary to underline that millions of cancer cells are daily born in everybody of us. It is unimportant what is a cause of their appearance: are there a result of the cancerogenic substances or radiation, or virus. Probably, every of these causes is collected its part of the sacrifices which ration is dependent on the oecological peculiarity of the given medium. All these cancers, mutant cells, virus carries and other irreversibly pathologically changed (anomalous) cells have to be destroyed by the immune system without mercy. Namely the principal task is in this but not in the fight against an external infection as it was early considered over a long period of time. The cell-killers (killers) that are present in the body by two lines are responsible for this function:

a) natural killers accomplishing the function of a police and destroying any anomalous cell;

b) T- killers that are ordered killer-terminators, selectively destroying only programmed sacrifice by the command of immune response. Such sacrifice is more often the tumor cell or cells of virus carriers.

Thus, the immune system is in a norm obliged to destroy all this negative but the part of tumor cells steal away from punishment in a case of losing the step in it
and the accumulation of their critical mass is resulted in a tragedy. Oncologic diseases are consequence of the immune system disease. The prevention and successful fight against tumor diseases can be reached in a case of the timely directed correction of the immune system.

But, let us come back to the regenerative liver. There are the cancer cells in the remained part of organ that have to realize more quick reproduction during its intensive growth in comparison with the healthy cells, and the regenerative liver has to reduce into cancer theoretically.

Fortunately it does not happen like it in the nature. No such case was fixed in the literary data and own practice (more than 4 000 rats were operated by us). Sometimes we were met with spontaneous tumors in the liver of the experimental animals, but they were disappeared next day after the operation. It appears that the “new” antigens revealed by us activate killers controlling “cleanness” of the regenerative process and destroy the tumor cells.

Thus, we discovered an appearance of the “new” antigens which are in a norm absent during the damage of organs and tissues and are called for the immune system helping. Just these “new” antigens discovered by us became an object of our intent study.

It has been shown that these antigens were glycoproteins of hepatocyte plasmatic membrane. During the comparative immunochemical analysis of membrane glycoproteins extracted from the plasmatic membranes of hepatocytes: the intact, embryonic and regenerative liver or hepatoma 27 (experimental malignant tumor) it was shown that the protein part of the revealed antigens was found on all the hepatocytes independently on the liver state. Furthermore this part is tissue nonspecific and universal for majority of tissues examined. But a carbohydrate part of the antigens found in the hepatocytes of the regenerative liver is different from that of analogous glyco-proteins in hepatocytes of the intact, embryonic liver and hepatoma 27 that determines the tissue immunogenicity. In this case a degree of molecular immunogenicity is largely determined by the modification degree of its carbohydrate part which is in its turn dependent on the degree of patholo-gical process. In particular, the glycoproteins of hepatoma 27 had the greatest immunogenicity comparing to the intact tissue than that of the regenerative liver and that of the rat embryonic liver at last.

This is associated with a short term of life of the membrane glycoproteins exposed by us and continually repaired molecules. Their protein part is synthesized on the ribosomes inside of the cell and is incorporated into the membrane and the carbohydrate chains are completed on the extracellular terminal section of protein part with the help of enzymes – glycosyltransferases that are in the intercellular matrix. The speed of synthesis in the carbohydrate chains has to be sufficiently high that is provided with an enormous assortment of glycosyltransferases each of them is specific to definite monosaccharide and is provided with the parameter complex of the working medium in these enzymes – the intercellular matrix. These parameters are in the norm optimum and all the glycosyltransferases work with high rate. During
pathological processes the parameters of intercellular medium are changed and some transferases begin to work under unused conditions and could not in time incorporate their monosaccharides. The subsequent synthesis of the chain is stopped suddenly in such case. The stronger pathology, the stronger changes in the parameters of intercellular medium and the glycosyltransferases are more incapable to complete necessary monosaccharides that results in the greater stopping of the carbohydrate chains and a change in the molecular conformation and in significant increase of its immunogenicity. Just so, for example, an acidity of the intercellular medium can reach up to pH 4.0 in malignant tumor that provokes an inactivation in majority of the glycosyltransferases. In this case our membrane glycoproteins are absolutely “bare” and are practically present by a protein part that leads to high immunogenicity of such molecule.

The membrane glycoproteins exposed by us were named “markers of cell physiologic state”6. Under the standard physiologic state such cell markers are full value synthesized and have minimum immunogenicity as well as their normal molecule and that is “imperceptible” for the body immune system. Under pathological processes the conformation of carbohydrate component of such marker and corresponding immunogenicity of molecule with a size proportional to degree of disease heaviness giving the signal (alarm) with immediate reaction of the immune system were changed in that way.

Such markers are present on all the cells (they were not found by us only in erythrocytes that as is generally known didn’t react and perish at any damage) and help to reveal the pathological processes by the immune system.

In addition the protein of such “markers of cell physiologic state” is immunologically conservative for many animal species that evolutionally have a little in common.

The cells of macrophagal series that initiate the reparation of damaged cells and start the regenerative processes of organ tissue are the first immunocompetent cells reacting on the immunogenicity change of such “markers of cell physiologic state”. Slightly later N-(natural) killers destroying the irreversible, damaged cells that are defying the reparation or anomalous cells arised as a result of mutations, anomalies in the genetic code, neoplasia and cells of virus carrier and so on are activated. Therefore, it is no coincidence to discover the malignant and mutant cells in the regenerative organ despite the high degree of risk This is practically difficult to realize. Later the immunocompetent cells responsible for the realization of specific immunity are activating.

If such “markers of cell physiologic state” are isolated from tissue with proceeded processes not peculiar for normal state and “signal” glycopeptide section is chosen after corresponding treatment necessary for the elimination of side effects, so inserting it into other body we insert the trouble signal (alarm) provoking the immune system to the search of pathological processes. Under pathology the complicated chain of mechanism for its elimination is started by the above said activated immunocompetent cells.
Besides the activation of unspecific immunity as macrophages and N-(natural) killers, “signal” molecules isolated from “markers of cell physiologic state” stimulate specific immunity and in accordance with the expression analysis of leukocyte specific antigens activate T-helpers and T-killers of the cell immunity predominantly. Moreover T-suppressors are simultaneously activated that is accompanying with the inhibition of B-lymphocyte humoral immunity.

At that time in patients with deficiency of humoral immunity T-helpers and B-lymphocytes are activated and the state of immune system is corrected in that way depending on patients status. The subsequent influence of the specific stimulus (antigen, infection, vaccine and so on) allows to develop the more effective specific immunity and consolidate the immunologic memory.

Especially it is necessary to emphasize that preparations on the basis of such “signal” molecules manifest their action in full measure only in the presence of pathologic process and in a case of its absence the activity of stimulated immunocompetent cells is already normalized in 2-3 days after preparation administration without any negative consequences for the body.

Thus, after a preliminary treatment for the purpose of preventing some side-effects, “markers of cell physiologic state” became the main functioning source of Erbisol drugs6. Erbisol drugs contain non-protein complex of natural organic compounds of non-hormonal origin isolated from embryonic tissue of chicken germs.

They contain the specific “signal” low-weight molecules isolated from “markers of cell physiologic state” which activate natural evolutionally formed mechanisms of a search and elimination of pathological changes in body and tissues and promote more full realization of body genetical potential. The drugs induce the synthesis of interferon and factor of tumor necrosis.

In this connection unlike other remedies that are widely used in the medical practice a peculiarity of the preparations developed in SPC “ERBIS” is their ability:

1) exert influence not so much on a disease as the activation of whole body internal reserves and systems controlling the internal body constancy. One of them is the immune system that more exactly finds a hearth of affection without an external intervention and eliminates not only pathological process but concomitant diseases too;

2) exert influence on all the complex of different pathologies that are under control of the competent immune system and first of all on the cells of macrophage series, N-, T-killers and also T-suppressors, providing their work;

3) only exert influence on a sore organ and left practically inert for healthy people and animals without provoking the side-effects that is that the preparations are innocuous, did not provoke the drug poisoning at over dosage or prolonged use. The complex usage of this preparation with other agents is possible.

The results of scientific researches obtained by SPC “ERBIS” found their technical realization in the developed drugs that were patented with 2 patent as
“Biologically active substance, method of its production and preparations on its basis” in the Ukraine (Patent N 2163, N 2164) and in Russia (N 2041715, N2041717) and also in 18 countries of the world with international claims (PCT/UA93/00003 and PCT/UA 93/00004).

At present SPC “ERBIS” are developed series of the given class drugs where Erbisol registered by Pharmacological Committee of the Ministry of Public Health of the Ukraine in 1994 is the first of them that confirmed the competence of conception. Showing its high efficiency in accordance with many parameters exceeding that of the import analogues Erbisol became one of the first native preparations registered in the Ukraine as the life necessary remedy. Erbisol had been shown an excellent effect in the treatment of:

hepatitis of various aetiology, including medicamentous hepatitis (for example, provoked by the usage of antibiotic agents or chemotherapy), and virus hepatitis, hepatocirrhosis, hepatosis, erosive ulcerous diseases of gastrointestinal tract, paradontium, in therapy of diabetes mellitus, bronchial asthma, oncologic neoplasms.

In virus hepatitis Erbisol inducing the interferon synthesis and activating T-helpers promotes the elimination of virus itself as well as the cells of virus carrier where virions are developed. The titer of virus antigens was significantly decreased and patients with critically degree of disease were already passed into the mild form in 10-15 day. According to this index Erbisol is more effective than commercial Interferons. Our drug is also more effective than Essenciale in the next phase of the liver regeneration.

Erbisol increases sufficiently the effectiveness of the treatment of hepatocirrhosis including the ascitic forms of “hopeless” patients.

In diabetes mellitus Erbisol inhibits the development of autoimmune process of pancreatic lesions, decreases the insulin used dose and treats for concomitant diseases such as angiopathies in particular preventing the development of diabetic gangrene which results in amputation of the lower extremities.

At the same time, the clinic of oncologic diseases is one of the special directions developed in our Center.

The results of preclinical examinations carrying out at the Institute of Pharmacology and Toxicology of AS of Ukraine shown that Erbisol inhibited the growth of 5 types of experimental malignant tumors up 70-90% and suppressed metastatic spreading completely.

Erbisol activates T-killers (basic acting chain in oncologic diseases) directly and inhibits humoral immunity (that is promoting the target cell screening from the elimination by T-killers that determined the principal cause of unsuccessful usage of so-called “total” immunomodulators in Oncology).

An effectiveness of Erbisol and that of new preparations on its basis is explained by its ability for increase an interior potential of the immune system during prophylaxis and treatment of malignant neoplasms but when the tumor development goes to far the immune system can not independently resolve a given problem the necessity in combined chemo-, radiotherapy and oncosurgery with classical methods of treatment is appeared.
It is known that the tumor as well as the liver and the immune system are affected during chemotherapy that excites the apprehension of the use of intensive, effective treatment course. In this plan Erbisol is excellent hepato- and immunoprotector. Indices of the state of the liver and the immune system were even improved after chemotherapy against a background of Erbisol usage without a decrease in the efficiency of course itself. At radiotherapy the non-healing suppurating wounds could be appeared in the site of treated tumor for some months. Usage of standard reparants promotes their healing and also the growth of malignant cell which were remained. Erbisol has more quick influence on the wound healing and activating T-killers promotes the elimination of tumor cells remained. Here as well as in oncosurgery Erbisol is used as reparant and immunomodulator.

Erbisol is used in the treatment of stomach and duodenum ulcers, erosive ulcerous damages of gastrointestinal tract, traumata, pyo-ceptic wounds and fractures, trophic ulcers and paradontosis. It is planning to start the clinical trials regarding the therapy of bronchial asthma, cardiovascular diseases, rehabilitation of postmyocardial infarction state, radiation injury and also in gerontology, sexual pathology and in the other directions, a list of which is continually added.

References