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REFLECTIONS

A Brief History of Progress on Nanotechnology: When Will the 'Magic' Nanobullet Shoot?

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About a hundred years ago, chemist and biologist Paul Ehrlich introduced the concept of the "magic bullet". So he denoted his dream - a drug that when injected into the body of the patient itself will find and kill the pathogen of the disease, without causing damage to the patient. He suggested that it is possible to find a molecule that would affect a given biological object, for example, kill pathogenic microbes or cancer cells, but did not affect the human body. Such hypothetical molecules he called then "magic bullets"[1].

In the mid-sixties, the English scientist Alec Douglas Bangham, assessing the role of phospholipids in blood coagulation, studied the structure of dispersions formed by the swelling of phospholipids under condition of water excess. On electron micrographs he saw layered particles, similar to the membrane structures of a cell. The following study showed that the substances present in the solution at the time of swelling of the phospholipids are incorporated inside these particles and are retained there for a long time, exchanging with the outer solution at a very low rate. So for the first time it was established that phospholipids, which are the main components of cell membranes, are able spontaneously to form closed shells in water [2].

These structures capture a part of the surrounding aqueous solution, and forming phospholipid membrane has the properties of a semipermeable barrier that prevents the penetration of substances dissolved in the liquid phase. So there were liposomes, used today as the drug carriers. A few years later, Gregory Gregorias created medicines containing liposomal systems for living systems [3]. However, it turned out that the reticuloendothelial system (RES; primarily the liver, spleen, lungs) is a barrier for the delivery of liposomes to organs. One could talk about targeted transport to the cells of RES, but this was not the main task of the researchers. To improve the transporting ability of liposomal delivery, sterically stabilized liposomes were used. The hydrophobic polymer, polyethylene glycol (PEG), made it possible to prolong the circulation time of the liposomes in the body, making them invisible for RES (stealth technology). This phenomenon revealed a real possibility for the implementation of a liposomal drug forms into medical practice [4]. In 1995, the FDA registered the first nano- and liposomal drug form of doxorubicin - Doxil. The first experience was extremely successful. What were the main reasons for its high efficiency? Three main factors can be emphasized: (i) a high degree of "loading" of liposomes with a drug; (ii) modification of the liposome surface, PEGylation allowed a prolonged circulation of the liposomal drug form in the patient's body. (iii) enhanced permeability and retention (EPR) effect, increased penetration of nanoscale particles into the tumor or inflamed tissues due to increased vascular permeability and active endocytosis by surrounding tissues.

At the end of the 1960s Peter Speizer investigated the possibilities of immobilizing medicinal preparations on microparticles at the Swiss Federal Institute of Technology. Improving these technologies, he managed to obtain nanoscale particles. He appreciated this discovery and suggested the unique possibilities of drug forms based on nanoparticles [5]. His PhD students Patrick Couvreur and Jorg Kreiter later created scientific schools that have made an invaluable contribution to the development of medical nanotechnology. P. Speizer promoted forward ideas that seemed fantastic even for his students. I quote the memoirs of J. Kreuter:

"Already around 1980 Peter Speiser had the idea to use i.v. injected nanoparticles for brain delivery. I remember telling him that this was not a good idea– actually I said "stupid idea" – because of the tight junctions between the brain capillary endothelial cells and the powerful biochemical barrier properties of these cells that would make the BBB impermeable for the particles. About twelve years later, a friendly academic guest from Moscow, Renad Alyautdin visited me and suggested the same idea as Speiser…So Renad Alyautdin manufactured poly(butyl cyanoacrylate) nanoparticles in my lab, and I advised him to coat these particles with polysorbate 80. After his return to Moscow, he could indeed observe very significant CNS effects in animals treated with the hexapeptide dalargin, loperamide, or tubocurarine bound to the nanoparticles coated with polysorbate 80" [6, 7].

An interesting chapter in the history of medical nanotechnology is the targeted delivery of medicines, the branch of which is the magnetically responsive transport of nanoscale carriers. The basis for the development of this idea was an extremely interesting property of a ferromagnetic liquid, representing a colloid system consisting of nanoscale ferromagnetic particles, suspended in a liquid phase, usually water. To ensure the stability of such a fluid, ferromagnetic particles bind to a surfactant, which forms a protective shell around the particles and prevents their adherence due to van der Waals forces. The pioneers who realized such idea in experimental medicine were considered to be K.Widder and K.Sugibayashi. The idea was to assemble, in an external magnetic field, albumin microparticles containing a magnetically responsive iron oxide in a given region of the body. In experiments with mice transplanted onto the tail with a tumor, the high efficacy of antitumor substances contained in magnetic microparticles was demonstrated [8, 9]. However, one must bear in mind that the tail is an ideal object for such experiments because easily placed in a magnetic field and does not require a high magnetic field strength. Critics of this method said that this model is not actually for humans. Deeper located tumors required a significantly more powerful magnetic field. In addition, the drugs released from the particles have propagated outside the magnetic field. However, these ideas served as the foundation for the development of nanoscale transport of drugs. Albumin nanoparticles became the basis for an effective antitumor agent. So, in 2005, nanoscale albumin particles containing paclitaxel (Abraxan) were recorded by the FDA, and later by EMA for the treatment of breast, lung and pancreatic tumors.

The ability of magnetite particles to heat in an alternating electromagnetic field led to the development of so-called hyperthermic oncology. The method is based on the fact that in vivo selective death of tumor cells is observed at a temperature of 40-44 ° C. This is due to the characteristic features of the physiology of tumors, in particular the presence of hypoxia sites and low extracellular pH. It is also necessary to take into account the peculiarities of intratumoral blood flow, which contributes to the slow removal of heat from the tumor in comparison with healthy tissues. This allows the tumor to be heated to the required cytotoxic temperature without damaging the normal tissues [10]. A significant treasure in the development of this direction was made by Nikolai Brusentsov from the Russian Scientific Oncology Center, who was at the origin of the formation of this idea [11]. Further development of this idea was the creation of heat-sensitive nanoscale carriers containing antitumor drugs. The first clinically significant nanodrug became ThermoDox®, thermosensitive liposomes loaded with doxorubicin. Drug release from thermosensitive liposomes relied entirely on an increase in lipid bilayer permeability that results from heating to temperatures above the average transition temperature of the lipid mixture. The key feature of ThermoDox® is the inclusion of a lysolipid that is said to result in pores within the lipid bilayer upon heating to the lipid transition temperature, resulting in more efficient drug release (i.e. 80% of drug release within 20 s at 42 °C) [12]. Currently, the heating method of radiofrequency ablation (RFA) is used to treat solid tumors. Its effectiveness can be enhanced by simultaneous local exposure to an antitumor drug. In a clinical trial HEAT were compared the results of treatment of solid liver tumors with RFA and RFA + ThermoDox®. The HEAT clinical trial failed to demonstrate a significantly superior efficacy for the combination of ThermoDox® and RFA [13]. Currently, a new study is being carried out, taking into account the errors of the previous one.

Over the past 50 years since the discovery of liposomes, researchers in the field have obtained convincing results confirming the high efficiency of nanoscale carriers and possibility to enhance and improve drug therapy. New types of nanocarriers such as nanotubes and dendrimers have been developed with

advanced technology for targeting as antibody, heat, and pH-adjustable methods were designed. However, in the realm of the introduction of nanotechnology into medical practice the pace of discovery is very slow. What is the reason? In my opinion, there are several of them: the delicacy of medicinal nanodrugs technology, the complexity of monitoring of their quality, often low stability, the lack of principles for determining nano-similarity and the use of already existing medicines as an active substance (second life of known drugs).

It may seem that the researchers in the field of targeted drug delivery at the present time are between the Scylla and Charybdis and face difficult choice; creating a new low molecular compound, ligands of receptors in targeting organs or using known drugs, placing them in some containers for targeted delivery. This choice is not simple. On the one hand, using new, highly selective medicinal substances lead to the appearance of new, rare, severe adverse reactions, which is often the reason for withdrawal of the drug from the market or cancelling of clinical trials. Furthermore, for nanoscale drugs, the required careful and multilateral toxicological studies lead to a failure of attempts to use certain traditional materials (cyanocrylates) in clinical trials.

Finally, the analysis of the results of modern research in the field of medical nanotechnologies makes it possible to define the current stage as a period of quantitative accumulation of knowledge, which, according to Georg Hegel, will subsequently enhance the quality and prepare for the discovery of the magic nanobullet.

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