1. The firm's project

The formation of coatings on the surfaces of implants which improves their functionality.

2. Scope & Effect

The designs used in world implantology do not meet the set of the modern requirements imposed to them. We propose the solution on forming on surfaces of the implanted medical designs of coatings based on nanocarbon film with the maximum content of diamond Sp^3 phase and organic bioactive layer which have a number of the physical and chemical properties, significantly increasing efficiency of operation and the implanted products resource.

2.1 Cardiovascular Surgery – Coronary and Peripheral Stents, Nodes and Details of the Implanted Heart Pump, Prostheses of Rings and Heart Valves

Coatings advantages

The main problem is a stent thrombosis (blockage). Patients have to take anticoagulants for a long term.

The Solution for the Stent – from an external part of the stent we apply the material strengthening walls of vessels, inside the stent - the material influencing maintenance of blood liquid state and preventing the thromboses.

For Nodes and Details of the Implanted Heart Pump, Prostheses of Rings and Heart Valves.

A. Mechanical prosthesis.

Thrombogenicity is the main disadvantage of the mechanical prostheses. The risk of anticoagulant therapy. Patients with mechanical prostheses have the risk of complications and lethality, considerably due to continuous anticoagulant therapy.

Our films on the prosthesis will obviate the need for anticoagulant therapy.

B. Bioprostheses. Pork heart valves, allotransplants (human valves).

Thrombogenicity. The risk of thromboembolism is significantly lower, than after implantation of mechanical prostheses, but to avoid anticoagulant therapy at all is not possible. Durability. The main disadvantage is fragility. Fibrosis and calcification develops over time, initially along commissure (the place of greatest tension), then the process extends to the cusp.

Our films used on the bioprosthesis will not only obviate the thrombogenicity, but also considerably raises their resource and durability.

2.2 Stomatology and Maxillofacial Surgery – Dental Implantation.

Today the implantation is uncontrolled, and the result becomes clear after a while and depends on many factors.

Our implant with a multilayered coating ‘manages’ the implantation through the following:

- formations of blood clot*;
- suppression of infections in the wound;
- microcirculation improvements (where blood stagnation is, there is inflammation);
- optimizes the regeneration of the peri-implant tissues, accelerating the beginning and reducing the overall time of osteointegrative connection formation between the implant and the surrounding bone tissue

*Modern ideas about the blood clot role in the sphere of surgical trauma gives it a primary role in the healing processes. Biochemical reactions and physiological changes that occur during the stages of clot formation, retraction and its subsequent modification are the catalyst for the process of the bone remodeling.

All this allows the fastest achievement of cosmetic and functional results, reducing the long process of wound healing and final rehabilitation of patients.

2.3 Orthopedics - Total Hip, Knee and Elbow Joints Endoprostheses, Dynamic Intervertebral Disc Endoprostheses.

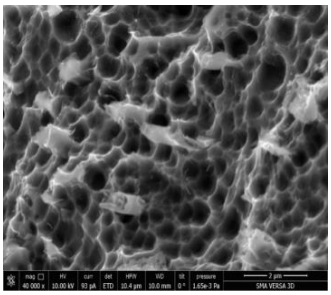
Despite the very long service life in case of installation at a young age, orthopedic implants may require replacement after 20-30 years. The implant can be replaced also earlier in case of severe wear, or in the development of body reaction to the material of the prosthesis and particles of the mechanical and biological destruction.
Today the main elements of the frictional units in the construction of endoprostheses used a combination having number of disadvantages (**Annex 1**).
Application in the elements of the endoprosthesis of nano -structured diamond-like carbon coatings enhance the functionality and resource of prostheses due to the increase of the coefficient of friction and the surfaces micro-hardness.

3. Documented Evidence (Tests or Articles)

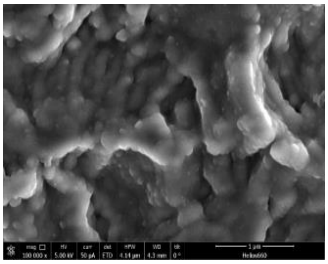
Currently, the technology of a nanostructured diamond-like carbon coatings' formation is implemented for dental implants.
Protective film based on carbon (amorphous film with a thickness of about 200 nm with 90% Sp^3 carbon phase), which prevents titanium bio-degradation and the ingress of metal particles into the surrounding tissue.
The tests and the results are shown in the **Annexes 2 and 3**

4. Development Readiness Level

The proposed solution on coatings' formation based on nano-carbon films with a maximum content of diamond Sp^3 phase and organic bioactive layer with specific properties is fully implemented in dental implants. The pilot batch of products is issued (ready to transfer samples and additional materials of researches).



Initial surface of the dental implant.



Surface of the dental implant with a coating.

Annex 1.

1) Metal - high-molecular polyethylene, particles of polyethylene wear during operation of the endoprosthesis provoke bone destruction around the prosthesis that demands new operative intervention.
2) Metal - the metal is potentially dangerous because of the metal dust which is formed in the course of friction. The use of metal implants is always complicated by the galvanic-electric phenomena, leading to metallize of the surrounding tissues and corrosion of the same metals tend to cause bone resorption.

3) In the metal-ceramics pair under the influence of the impact loadings the microcracks in ceramics are formed, which increase in use and cause destruction of the hinged element.
4) The ceramic-ceramic, the main problem with these designs is that during their use, the elements of the prosthesis can crack even with minor impact of micro-cracks, leading to their destruction.

According to the Global Data Analytics Company, by 2019, the global market volume for total hip endoprosthesis replacement will reach $7.1 billion, while in 2014 the amount of legal claims against the three leading manufacturers of implants for this operation has reached a comparable value of $6 billion. Over the past 20 years endoprostheses selling has been suspended by the manufacturers, as a rule, at the expense of patient complaints and lawsuits.According to the FDA data since 2002 to 2012, the six leading manufacturers recalled 578 varieties of hip endoprostheses and their components. In June 2012, having received an official warning from the FDA, Stryker company has voluntarily withdrawn from sale Rejuvenate and ABG II, having told the surgeons that the products can harm the tissues of the hip and lead to more serious consequences.
More than 300 thousand people worldwide (from them 200 thousand in the USA) received defective articulate endoprostheses of the Stryker company – Rejuvenate and ABG II. Patients were promised that the device would serve decades, but some problems began only after two or three years.

Annex 2.

TEST for Titanium Particles Separation

Testing of dental implants without coating and implants coated by method of dynamic light scattering (DLS).
The tests of dental implants for the release of nano particles from their surface, namely the investigated supernatants after incubation of the implant by dynamic light scattering (DLS).
The implants were incubated in water for injections of 1 ml within 5 days, after that supernatants were selected, added 1 ml of water (total volume of test - 2 ml) and took measurements. Experiments were made on the device of 90 Plus Partical Size Analyzer Brookhaven instruments corporation (USA) in the multimodal mode. The measurements were registered at a temperature of 250C, the fixed angle of light dispersion of the 900 laser is 661 nm. For determination of the size of particles were used automatic function 90Plus/BI-MAS.

DLS results

Sample	The molecular-mass parameters of the supernatants after incubation of dental implants		
Implants	D, nm	ACR, kcps	PD, %
Without coating	221	5.3	0.005
With Sp3carbon phase coating	0	0	0

Where, D – average diameter of particles
ACR – signal intensity(average count rate, kilo counts per second)
PD – sample poly-dispersion, %

Conclusion: as a result of incubation within 5 days in water for injection of dental implants samples without the mechanical and physical effects in the supernatant of the sample WITH COATED particles were not detected (ACR and PD = 0), while in the supernatant of the sample WITHOUT COATING (BARE TITANIUM), there are particles with an average diameter of 221 nm (ACR=5.3 kcps).

Annex 3.

Experimental study of regularities of response formation of tissues during implantation with nano-sized diamond-like carbon coating. The nature of the tissue response upon implantation of the samples without coating was estimated.

The set of observable responses reflect the typical sequence of changes in the introduction area of the foreign body. At the same time, the inflammatory changes persisted long enough - on the 21st day granulation tissue with signs of incomplete maturity, the site of inflammatory response was present even after 6 months. On the early stages, gigantocellular reaction of macrophages to foreign body-implant was revealed, which has been growing in the range of 7 to 21 days. After 6 months, the implant was fully encapsulated. However, the formed connective-tissue capsule was heterogeneous: areas of predominant fibrosis (even with the sites of hyalinosis) were combined with areas of inflammatory infiltration. Epithelioid histiocytes cells were determined on the inner surface. The full integration of the capsule structures into the surrounding connective-tissue was not observed, between them the border was clearly visible.

Further, we have estimated the nature of the tissue reaction upon implantation of experimental samples **with nano-sized diamond like carbon coating**. The uniform zone of granulation tissue with a visually lower density of the cellular structure, in comparison with the control, was determined on the 7th day of the experiment around the sample. The outer border of the infiltration was also obscure, but defined width was significantly smaller and amounted to 100-150 μm ($p < 0.05$). The cellular structure also differed significantly, there was dominated immature fibroblasts, amounting to 55-70 % ($p < 0.05$), and leukocytes and histiocytic elements amounted to 30-45 % ($p < 0.05$).

Infiltrate had a loose structure, did not contain capillary structures, typical for granulation tissue. Huge cells of foreign bodies were absent. The surface of the experimental sample implants in histological specimens contained a continuous gray-brown coat with a thickness of 1,5-2 μm. The contact of the covered outer surface with the surrounding reactive tissue was dense, no penetration of the elements of the infiltrate into the thickness of the implant (Fig. 1).

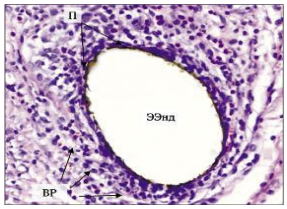


Fig. 1. Reaction of connective tissue for the experimental sample with nanosized diamond-like carbon coating (EEnd) on the 7th day of the experiment: there was the continuous coating layer of gray-brown color (L), narrow area of inflammatory response (IR), diffusion character with a moderate density of cell structure, the visible number of young fibroblasts on the implant surface.

The continuous layer of granulation tissue with width of 100-160 μm ($p < 0.05$) was formed around the material on the 21st days after implementation. The, single radially focused capillaries were defined, the fibroblasts were dominated in cellular structure which made 60-70% ($p < 0.05$), leucocytes in equal proportion (10-15%, $p < 0.05$) are presented by polymorphonuclear elements and small lymphocytes, in different sites histiocytes consist 5-10% ($p < 0.05$). On this term has been notable processes of granulation tissue maturation in the fibrous, which was manifested by the presence of clearly distinguishable evenly distributed sites of fine fibred structure and zones of homogeneous oxyphilic extracellular matrix. Huge cells of foreign bodies were absent (Fig. 2).

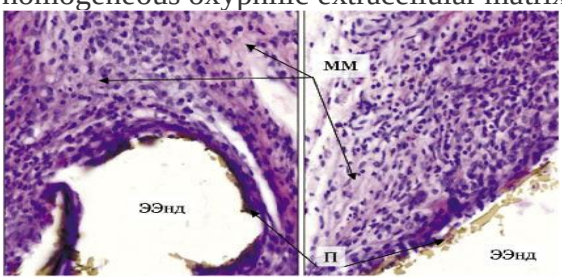


Fig. 2. Morphological changes in the implantation area of the experimental sample with nanosized diamond-like carbon coating (EEnd) on the 21-th day: fibroblastic elements (F) dominated in the

cellular structure, the leukocyte component is expressed moderately, clearly defined area of the formation of the intercellular matrix (IM), implant coating (C) are fragmented at sites, but is determined throughout. The significant features in comparison with the control group were revealed after 180 days after implantation. The overall picture was of the full encapsulation of the prosthesis with the capsule structurally completely integrated into the surrounding connective tissue.The capsule structure was presented by 5-10 compact layers of collagen fibers, the sites having hyalinized view, between which are evenly distributed a small number of fibroblasts. Elements of the inflammatory infiltrate, epithelioid histiocytes on the inner surface of the capsule, huge cells of foreign bodies were absent. The blood vessels were almost absent. The inner layers of the capsule had a concentric orientation around the mesh structures of the implant, outside slipped into the bundles of collagen fibers of the connective tissue. The thickness of the capsule was smaller and made up 60-70 μm ($p < 0.05$) (Fig. 3).

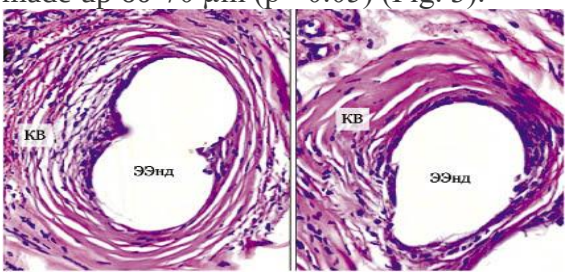


Fig. 3. The structure of the connective tissue capsule around the experimental sample: concentric low-cellular layers of collagen fibers (CF) with a smooth transition to the surrounding connective tissue, no inflammatory changes and huge cell reaction to the implant. Thus, the visible differences in the nature of tissue reaction at the implantation of experimental samples with nanosized carbon coating was determined already by the 7th day of the experiment. There was earlier formation of the fibroblastic component in the granulation tissue, that reflected the results of counting the relative number of cellular elements in the infiltrates composition.The fibroblasts with morphological featuresof functionally active forms amounted to 60-70 % on the 21st day, on this term was clearly defined formation zones of amorphous and fibrous component of intercellular substance. The complete biointegration of the implant in the subcutaneous connective tissue in the form of, and the jet of encapsulation by connective tissue, directly connected with the surrounding structures were revealed on the long-term (180 days). Inflammatory and other reactive changes were found. One of the most significant differences from the control group was the absence of the experiment huge cell transformation of macrophages at all stages, and formation of cells of foreign bodies.

Conclusion

The obtained data demonstrate that the experimental samples with nanosized diamond-like carbon coating, in comparison with a similar uncoated sample, have higher biocompatibility and better biointegration in the surrounding connective tissue in the course of encapsulation in long-term period. There is an apparent lack of fibrous tissue formation leading to implant failure.