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REVIEW

of a member of the dissertation council for the dissertation Korolev Dmitry Vladimirovich on the title: "Development of drugs for theranostics and targeted delivery of cardioprotective substances based on silica and magnetic nanoparticles", submitted for the degree of Doctor of Chemical Sciences in the specializations of 02.00.21 - Solid State Chemistry, 02.00. 16 - Medical chemistry.

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As it follows from its title, "Development of drugs for theranostics and targeted delivery of cardioprotective substances based on silica and magnetic nanoparticles", the doctoral thesis by D.V.Korolev aims, as a big goal, to prepare and investigate a novel family of theranostic agents. More specifically, it aims the delivery of cardioprotective agents and, subsequently, the diagnostics of the related pathologies. As a delivery system for this purpose, the system was selected based on silica and magnetic nanoparticles.

The general idea of the research is well within the current trends, which concentrate on combination and patient-specific preparations allowing for the simultaneous diagnostic imaging and therapy of various pathologies, cancer and cardio-vascular diseases being among them. The choice of specific directions in this study is well justified. First, while the major attention in the area of targeted drug delivery and theranostics is given to cancer, the use of these approaches in cardio-vascular medicine could also be highly beneficial and certainly deserves more attention. The selection of silica/magnetic nanoparticles platform is also quite reasonable, since this platform has already shown its broad versatility and ability to be easily adjusted to meet variable biomedical requirements.

The thesis itself is built in a traditional way: it includes the analytical review of the field aimed to prove the choice of the system and its high promise; experimental part describing all used materials and methods; results and discussion section specifically presenting the outcomes of the research and the author's comments on those; and conclusions and summary.

In general, the work leaves nice impression. This is a big, multifaceted, thorough, and important research closing a clear gap existing in the area of theranostics and drug delivery. The result are clearly presented, well discussed and support the conclusions made. If one would be asked what are the main outcomes of the presented study, the following could be named/listed:

1. Several routes for the preparation of magnetic nanoparticles with the required properties have been developed and implemented, which resulted in the preparation and characterization of the materials required for the subsequent studies. The process of the biodegradation of the prepared nanoimaterials was also investigated because of its importance for clinical administration of such materials. The important conclusion was made regarding the relative biodegradation rate of silica and magnetic nanoparticles;

2. A thorough study has been performed on the synthesis of various spacers for the

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immobilization of various substances including imaging moieties. A set of synthetic approaches to the preparation of different spacers has been suggested. Several different spaces have been investigated, tested, and used for the immobilization of various biologically-active substances (of cardioprotective nature) including adenosine, bradykinin, and fluorescent dyes;

3. The conjugates have been synthesized capable of accumulation in required sites under the action of the external magnetic field, which allowed for good visualization of the accumulation zone and could be important for the subsequent preparation of the theranostic agents;

4. Spontaneous (passive) accumulation of drugs in the ischemic zone of the myocardium was shown (or, more exactly, confirmed), which can facilitate the therapeutic effect;

5. An interesting use of the iodine-containing X-ray contrast agent, iodixanol, was suggested and demonstrating using an original coupling method via the water-soluble carbodiimide. This approach has a general significance, since it could be spread over many other relating systems;

6. An original approach of quinacrine immobilization via the glycidine spacer was suggested and developed, which resulted in a product simultaneously performing both targeted functions – diagnostic as well as therapeutic;

7. The approach has been developed allowing for the simultaneous targeted delivery of therapeutics into the target zone and the visualization of the delivery process itself, which could be of crucial importance for controlling the delivery extent and rate;

8. Multilayered nanoparticles have been engineered for the real theranostic application in ischemic areas, in particular in ischemic myocardium, which could represent the basis for novel scalable therapies in cardiovascular diseases.

Thus, one can firmly claim that we have here a strong, consistent, important,and promising research with a significant basic/fundamental and practical outcome.

Naturally, like any other large-scale research, this study also has certain insufficiencies, the major of which could be summarized as follows (in random order):

1. Figures 1 and 2 do not show any errors, which does not allow to draw any conclusions and makes the given p values senseless.

2. The author is not very clear regarding the differences between active and passive targeting. It is currently well understood and generally accepted that passive targeting (EPR effect in cancerous and ischemic tissues) is also the first step (bottle-neck) for active targeting, since the active targeting may be performed in the required area only after the accumulation there of targeting ligand-carrying nanopreparations via the passive targeting. As was clearly shown in the studies by Kirpotin, Papahajopoulos, and others, targeting ligand does not increase the accumulation of the system in the target, but only facilitates the intracellular delivery when already in the target. In other words, active targeting could be useful only in cases when an increased intracellular uptake (internalization) of the active matter is desirable (see for example Kirpotin et al, Cancer Res 2006).

3. The author is completely incorrect claiming that the first publication on targeting the ischemic myocardium appeared in 2009. The approach began to develop long before that. It started with the seminal publication of Caride and Zaret (Science, 1977) on the liposome accumulation in regions of experimental myocardial infarction. The idea was further developed in several following publications from the same group. Khaw et al described targeted healing of hypoxic cardiocytes with antibody-modified liposomes in

1995 (Nature Medicine). Xu et al described myocardial accumulation of ATP-loaded liposomes in 1990 (Pharm Res). My group has extensively published on this topic (FASEB J 1992; BBA 1996) including the papers directly describing the use of cardioprotectors (ATP, CoQ10) for minimizing the ischemic damage in animal experiments (Pharm Res 2005; 2007). None of these publications is mentioned or cited.

4. In connection with this, one has to notice that in general, the list of references looks very arbitrary. Many insignificant publications from mediocre journals are cited, while key publication in leading scientific journals are not mentioned.

5. None of protocols used for the determination of reactive groups on the surface of nanocarriers is characterized in terms of precision and experimental errors.

6. The author claims the size of nanoparticles to be 8+2 for NChK and 15+5 for MNCh. How was it determined? If by the analysis of EM images, it clearly cannot be true (much broader distribution can be seen by the naked eye).

7. The title of the thesis claims the development of the preparations for theranostics and targeted delivery of cardioprotectors, however very little data on any in vivo therapy or diagnostics are provided in the study. More correct title would be "The development of the preparation, which can be used for etc…)

Still, the positive outcome of this research well overweights the noticed drawbacks, and the author of this study deserves the degree he is looking for.

Summing up, Korolev Dmitriy Vladimirovich's dissertation on the title: "Development of drugs for theranostics and targeted delivery of cardioprotective substances based on silica and magnetic nanoparticles" meets the requirements for dissertations for the doctor of chemical sciences, and the applicant Korolev Dmitry Vladimirovich deserves the degree of doctor of chemical sciences in specialties 02.00.21 - Solid state chemistry / 02.00.16 - Medical chemistry.

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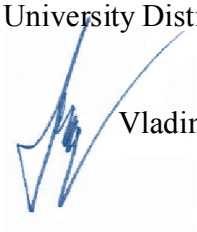
January 20, 2020  Vladimir Torchilin