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Interaction of engineered nanomaterials with the immune system: health-related safety and possible benefits

Diana Boraschi, Benjamin J. Swartzwelter, Paola Italiani

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Dear Prof. Pallardy,

thank you for the constructive comments to our review in nanomaterials and immunity.

We have revised the text following the reviewers' suggestions. Hereafter please find the answers to the reviewers' queries and comments, in italics below each comment. We have succeeded in uploading only this file, with the clean version of the manuscript, as the system did not allow to upload multiple text files. Therefore, we are sending you by email the files with the track changes, to show where the corrections were made. Figures were not corrected. Despite our efforts, the modified text is longer than the original one: we couldn't satisfy all the requests made by the reviewers and at the same time keep the original length, we hope you will understand.

Thanking you again for your attention, we are looking forward to your final decision

Best regards

Diana Boraschi

Reviewer 1

This review of Boraschi deals with engineered nanomaterials and their interaction with the immune system with consideration about their safety or benefits in nanomedicine. It is a concise review giving a clear idea of the different potential threats of ENM with the immune system but also their potential benefits. It also focuses on difficulties to evaluate the immune effects of ENM, a problem not restricted to this outcome.

1. As this paper concerns mainly the use of **nanomedicine: this word should be present either in the title or at least in the keywords.**

Answer: The term "nanomedicine" has been included among the keywords. We have not added it to the title, as the title already implies it. Page 2

2. **Stating that the contact of our immune system with ENM is new is somewhat exaggerated.** Human exposure to particles is frequent as airborne particles contain an ultrafine fraction that is in the same range as ENM and it can contain particles of similar composition as ENM such as metal oxides.

Answer: The sentence at the beginning of the introduction has been changed, to mention the exposure to non-engineered airborne particles. Page 3

3. Other statement that **"ENM do not persist in the organism for long" should be modulated as it is dependent on the route of exposure.** By inhalation for instance even if a translocation through the air-blood barrier has been shown, there is biopersistence of ENM in the lung.

Answer: The statement that ENM do not persist in the organism for long (Introduction) has been modulated. Indeed, ENM can actually persist for very long, but taken up by phagocytes and secluded, so that they are not in direct contact with the rest of the tissue. When phagocytes do not succeed in degrading particles, they just store them away. And if the material is toxic and phagocytes die, other phagocytes come and take up the dead cells and their content. Thus, even if the particles are still there, very rarely they are "dangerous". It is the same that happens with tattoos, lots of macrophages eating up the ink and keeping it away from the rest of the skin. We hope that the new sentence conveys the sense better than the previous one, despite the need to be brief. Page 3

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