To
Ms. Shuang Zhao
Assistant Editor
Pharmaceuticals

Manuscript ID: pharmaceuticals-624980
Manuscript title: “Thermosensitive nanosystems associated with hyperthermia for cancer treatment: a systematic review”.

Dear editor

The manuscript was revised according to the reviewers’ comments. The authors would like to express their gratitude for their time to review the manuscript, and for their contributions, which much improved the final version of the manuscript. Please find enclosed the revised manuscript containing the changes (highlighted in yellow). Below, please find a point-by-point response to the reviewer’s comments.

- **Reviewer 3**
This review paper deals with thermoresponsive or thermosensitive nanosystems for cancer treatment, particularly on hyperthermia. The topic is very interesting and relevant. I have few suggestions and comments to the authors:
In chapter 2 ”Hyperthermia” please briefly mention the effects of hypothermia and other possible variations in tumor environment (e.g. hypoxia, pH, neovasculature, etc.) and their use in cancer treatment.

  - **Answer**: A paragraph has been added to the chapter 2, with characteristics of the tumor environment and how it can be used to treat cancer through the EPR effect, and their association with hyperthermia (lines 80-85).

I am missing here further classes of thermosensitive polymers, exploiting the thermal sensitivity (~37°C) labelled with radionuclides for internal radionuclide therapy and radiolabelled magnetic NPs for multimodal treatment protocols. Particularly the works of Hruby group focused on the radionuclide and chemo/radiotherapy delivery and immobilization based on thermosensitive polymers (at various LCST) should be
mentioned. E.g.: New Binary Thermoresponsive Polymeric System for Local Chemoradiotherapy DOI:10.1002/app.29237, New bioerodable thermoresponsive polymers for possible radiotherapeutic applications DOI:10.1016/j.jconrel.2007.02.009, Thermoresponsive polymers as promising new materials for local radiotherapy DOI:10.1016/j.apradiso.2005.05.043, review DOI:10.1021/acs.langmuir.6b01527, etc.

- **Answer:** Two paragraphs were added to the section “4.1 Polymeric nanocarriers” (lines 352-374) in order to meet the reviewer’s suggestion.

Magnetic NPs labelled with radionuclides are also worth to include in this review within the magnetic field induced hyperthermia, since it may open novel multimodal treatment of tumors. Several papers appeared with various combinations of radionuclides, including alpha particle emitters.

E.g.: Pospisilova et al.: 59Fe-labelled SPIONs, DOI:10.1007/s11051-016-3719-0
Wang et al.: 111In-labelled SPIONs, DOI:10.1016/j.nucmedbio.2014.08.014
Mokhodoeva et al.: 223Ra labelled SPIONs, DOI: 10.1007/s11051-016-3615-7
Ognjanovic et al.: 99mTc, 90Y, and 177Lu-labelled Iron Oxide NPs, DOI:10.1021/acsami.9b16428
Possible targeting of magnetic NPs with external magnetic field could be also mentioned (e.g. the work of De Simone et al.: DOI: 10.1002/cmmi.1718).

- **Answer:** A paragraph was added to the section “3. Heating modalities used to induce hyperthermia” (lines 281-304) in order to meet the reviewer’s suggestion.

Please extend the chapter 7 "Conclusion". Please add an outlook to possible future developments in this field.

- **Answer:** A paragraph has been added to the chapter 7 (lines 717-721).

Spell check:

Lines 31-32: Please reformulate "nanosystem systems"

- **Answer:** The term was reformulated.

Lines 64/82/126/143/144/196: Please correct "37.5 °C" to "37.5°C"
- **Answer:** space between temperature and degree Celsius has been removed

Line 451: Please check the nomenclature.
Lines 462 / 588: correct "thermos-sensitive"

- **Answer:** The nomenclature 'thermos-sensitive' has been replaced by thermosensitive.