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Magnetic Field-inducible Drug-eluting Nanoparticles for Image-Guided Thermo-Chemotherapy, Magnetic field-inducible drug-eluting nanoparticles for image-guided thermo-chemotherapy

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Reviewer #1: In this work, the authors developed magnetic field-inducible drug-eluting nanoparticles by embedding superparamagnetic iron oxide nanoparticles and cancer therapeutic drugs (doxorubicin; DOX) in a temperature-responsive PLGA nanomatrix, which is very innovative and informative for the readership of Biomaterials. The manuscript is well written and organized with a clear structure. And the results are sound to take in. I think this work is suitable for publication in this journal. However, there are some formative issues in the draft. Therefore, I think minor revision is needed.

We thank the reviewer for the comment. We have corrected the following formative issues in the manuscript.

- We have changed the format of in vivo and in vitro in the manuscript to *in vivo* and *in vitro*
- In 3.1. Synthesis and Characterization of MIDENs (PLGA/SPIONs/DOX) under Results Discussion, Line 20, we changed FT-IR to FTIR.
- In Figure 2 caption, we changed F3O4 to Fe_3O_4.
- The format of reference 17, 36 and 37 was changed according to the other references.

Reviewer #2: In this work, the superparamagnetic iron oxide nanoparticles and DOX were embedded into temperature-responsive PLGA as a magnetic field-inducible drug-eluting nanoparticles (MIDENs) for cancer theranostic, using CT26 cell line, *in vitro* and *in vivo*. Many similar works have been reported by other groups [J Nanosci Nanotechnol. 2014 Jun;14(6):4082-9; Nanoscale. 2015 Oct 21;7(39):16470-80; Theranostics. 2018 Jan 1;8(3):693-709; J Control Release. 2018 Feb 28; 272:145-158]. Other comments and suggestions are listed below.

We thank the reviewer for the comment.

Recently, AMF based treatment with magnetic nanoparticles incorporated thermosensitive polymers has been recognized as a promising approach for cancer therapy as the reviewer indicated them with some recent articles. Yet, there are fundamental differences between our approach and other published works.

In our work, we have designed an effective drug release platform based on FDA approved PLGA as thermoresponsive matrix possessing a glass transition temperature (T_g) around hyperthermic temperature (42-45℃). The hyperthermic temperature obtained by AMF application changes the MIDENs from solid to rubbery state, thereby allowing us to achieve the on-demand drug release in a controllable manner. Importantly, the developed T_g based MIDENs would not undergo abrupt structural or solubility changes, which further enables us to perform multiple AMF treatments. Moreover, our strategy overcomes the burst drug release phenomenon commonly