Reviewer's report

Title: Effect of 5-fluorouracil/PEG-hydrogel on the pharmacokinetic properties and antitumor efficacy

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Reviewer: Yukio Kato

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The authors developed PEG-hydrogel containing 5-FU as a controlled release system. The 5-FU-loaded PEG-hydrogel slowly releases 5-FU in vitro. Subcutaneous administration of this hydrogel resulted in plasma 5-FU concentration much longer prolonged, compared with 5-FU alone, leading to obvious anti-tumor effect. This hydrogel system would be a useful tool for development of cancer chemotherapy using 5-FU with more efficient pharmacodynamic effect.

Major Compulsory Revisions

(i) The authors also examined “side effect” of the hydrogel (Fig. 7, page 6, page 8), but the objective of these experiments was vague: First, they used adenocarcinoma cell line A549. However, the side effect of anticancer drugs should be examined in normal cells. Second, they said “no cytotoxicity” for A549 cells (page 8, line 16), but this was incompatible with the antitumor effect of the 5-FU-hydrogel for A549 cells inoculated (Figs 4, 6). The sustained release profile of 5-FU at relatively lower plasma concentration (Fig. 3) may decrease the side effect of 5-FU, so the authors should examine more detailed information regarding the side effect exerted by 5-FU-loaded PEG-hydrogel or 5-FU alone. Overall, this reviewer wonders the significance of the data shown in Fig. 7.

(ii) There would be redundant description in Figures and table. First, Fig. 6 was just the repetition of Fig. 4 and can be deleted. The authors would be able to simply described IR values in text, as already written in page 8, lines 12-14. Second, Fig 5 simply represents the morphology of tumor tissues and can also be deleted because this is out of the scope of the present study. Third, in table 1, AUMC was not used in details in text and can be deleted. Both ka and kel are simply proportional to reciprocals of their corresponding half-lives (t1/2a and t1/2), and either can be deleted.

(iii) The more general discussion regarding the novelty of the authors’ hydrogel system would help the understanding by the readers. For example, they introduced much more advantage of their system compared with that previously reported by Blanco et al [28], but did not discuss the possible reason for such discrepancy.

(iv) Were the injection sites separated between A549 cancer cells and 5-FU hydrogel? If these were inoculated/injected in close proximity to each other, is
there any possibility that 5-FU released from hydrogel can directly react against the cancer cells?

(v) The authors mentioned that 5-FU-loaded PEG-hydrogel was injected at 85 mg/kg, but how did they adjust the dose of 5-FU? Did they measure the content of 5-FU in the hydrogel injected? In addition, they may need to clearly describe the solvent used for the injection of hydrogel and 5-FU alone.

(vi) The description of exact values for each parameter (page 7, lines 1-8 from the bottom) would also be redundant because those are described in Table 1. The authors may alternatively need to discuss the difference between 5-FU-loaded PEG-hydrogel and 5-FU alone.

Minor Essential Revisions

(vii) The release of NHS from the reaction can be written in Fig 1, and this may help the understanding by the readers.

(viii) The meanings of symbols and inlet should be described for Fig 3.

(ix) The authors may need to correct the following description if needed: “In the clinic,” (page 2, line 3 from the bottom); “5-FU is not dose-dependent” (Page 3, line 1); “5-FU found on the surface” (page 4, line 11); “changed into a solid gel (PEG-“ (page 9, line 5 from the bottom)

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.