Review of: "The effect of spacers in dual drug-polymer conjugates toward combination therapeutic efficacy"

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This is a study of tumor synergistic therapy using dual drug-polymer conjugates, in which amide bond were used for MMC and DOX to conjugate dual drugs onto single XG carrier and synergistic chemotherapeutic effects of two drugs have been investigated. The principal finding was meaningful and polymer-drug spacers present diverse therapeutic efficacy that consistent with other studies.[1-3]. The article has some innovative issues and the experimental results can support the conclusion. However, this study had some incomplete experimental design for control variables that may limit their further applications.

There are some of concerns with this study which include the following:

1. Technically, peptide bonds and amide bonds are essentially the same meaning. They have the same chemical structure with different names. In the field of chemistry, CONH bonds is called amide bond while it is called peptide bond in protein structure. In current study, it should be use the same name of CONH bonds as amide bonds and peptide bond is not appropriate to describe them. If there needs a difference between two bonds, author should reasonably explain that nanoparticles linked with peptide bonds have similar properties with a kind of protein and different from amide bonds.

2. Different grafting methods, drug loading content and physical characteristics of nanoparticles would affect the drug release process.[4] At the same time, the degree of drug release will also affect the drug effect. [5] There is a significant difference in the drug release at 48 hours, indicates that the difference in treatment effect may be affected by the actual drug release, not by different chemical bonds. I realize these contents are required in this study.

3. Drug carriers (XG) have an impact on the delivery of drugs, for example, different particle size sizes can affect the time that nanoparticles reach the tumor, [6] thus indirectly affecting drug efficacy. Therefore, the influence of drug carrier(XG) for tumor synergistic therapy should be discussed.

4. In terms of therapeutic effect, this study is still within the scope of chemotherapy. Although there are significant differences in the therapeutic effect of cell experiments, in vivo efficacy experiments did not

show more significant difference, which limits their clinical application in the future.

5. Although the method of statistical analysis is written in the method section, there are no statistical test results and labels in the chart. Moreover, the ANOVA analysis of significant differences should be divided into more details (e.g. $P < 0.001$).[7]

6. After the drugs connected with drug carrier (XG) by chemical bonds, what kind of state do the two released drugs in vivo experiments and whether they will affect the therapeutic effect should be indicated.

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