Journal of Clinical and Translational Research
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Current role of nanoparticles in the treatment of lung cancer

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Handling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

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1st Editorial decision
22-Oct-2020

Ref.: Ms. No. JCTRes-D-20-00099
Current role of nanoparticles in the treatment of lung cancer
Journal of Clinical and Translational Research

Dear Dr. Lopez Campos,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Nov 21, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Overall, this is a very well-written, informative review article. Thanks for your contribution to the field! I don't have any major recommendation or changes that need to be made.

Reviewer #2: In this paper, the authors reviewed different types of nanoparticles and platforms for the treatment of lung cancer. However, the authors failed to review the most important works for each type of nanoparticle, with very few examples reviewed under each category and inadequate references to the most recent works. This may severely affect the quality of a review article. Thus, I strongly suggest the authors expand the length of each section and add more examples to each category. Below are my comments:

1. The goal of this review is to summarize different nanoparticle platforms for lung cancer treatment. However, in section 2.1 when reviewing the MNPs, the MRI is for imaging and diagnosis purpose. The most important applications of MNPs for disease treatment such as magnetic hyperthermia therapy, drug delivery are not reviewed.
2. In section 2.1, the authors should add one paragraph commenting on the cytotoxicity and biocompatibility of MNPs.
3. In section 2.1, there is also FDA approved iron oxide MNPs for clinical applications, please also mention that with proper references.
4. Section 2.4, this section reviewing virus nanoparticles is too short. Please consider expanding this section with more work referenced.
5. Overall, each nanoparticle-based applications discussion in Section 2 is too short and lacks adequate references. I would suggest to expand each section reviewing more works.
6. No references to this sentence? 'In the treatment of lung cancer, nanoparticles have been used for the selective delivery of gene molecules such as DNA, plasmid DNA (pDNA), messenger RNA (mRNA), small interference RNA (siRNA), microRNA (miRNA), RNA precursors, etc.'
7. The authors should consider combining the discussions on Au and platinum-based methods for tumor treatment (in section 2.3 and section 3.2). These platforms should be categorized as a new sub-section titled 'metal nanoparticles' under section 2.
8. Since MNPs and metal nanoparticles are not degradable in the nature. The authors should also add one paragraph of discussion on the proper disposal of these kind of nanoparticles after clinical use.
9. Tables 1 and 2 are only mentioned at the end of Introduction section once, no further discussion are given to describe these tables. Please consider adding several sentences describing what information are listed in these tables and comment on the clinical progresses of these works.

In addition, the quality of English should be improved throughout the manuscript. I just list some of them here:
1. Typo, Introduction section, 'PET-TC scan' —> 'PET-CT scan'.
2. Typo, Section 2.1, 'glycocopolymer' —> 'glycopolymer'.
3. 'Camptothecin display cytotoxic effect against A549 cells line when is conjugate with nickel' —> 'Camptothecin shows cytotoxic effect against A549 cells line when conjugated with nickel'
4. 'Both natural and synthetized polymers of different structures' —> 'Both natural and synthetic polymers of different structures'
5. 'They have a globular shape with a central core with multiple extensions (dendrimers) and have useful groups on the surface for encapsulation or conjugation of antineoplastic drugs.'—> 'They are spherical with multiple extensions and chemical groups on the surface for encapsulation or conjugation of antineoplastic drugs.'

Reviewer #3: Lung cancer is one of the prevalent malignancies and the leading causes for death worldwide. Recent progress in nanomedicine has encouraged the development and application of nanotechnology in the detection, diagnosis, and therapy of lung cancer. In this literature, the authors have summarized the progress in therapeutic nanomedicine in lung cancer, especially focus on future studies and ongoing clinical trials in this field. This review can provide some references and information for those interested in the field, and the topic of this review is matched with the scope of Journal of Clinical and Translational Research. However, the manuscript also remains some insufficient points, which need to be adjusted and supplemented. Therefore, I recommend a revision of this manuscript.
Several issues should be addressed before the acceptance of this manuscript, as list below.

1. In recent years, various nanosystems were employed as co-delivery systems for lung cancer diagnosis and treatment. These nanoparticle compositions include polymers, lipids, dendrimers, proteins, virus, metals, carbonaceous, mesoporous silica and hybrid etc. In the manuscript, the author reviewed therapeutic nanomedicine in lung cancer with examples from magnetic, lipid and polymer nanoparticles. The author should appropriately expand the types and scope of nanoparticles in lung cancer treatment.
2. Polymeric nanosystems play an important role in cancer diagnosis and treatment because of their various advantages including molecule protection against degradation, sustained release, convenient functionalization and selectively targeted delivery. Numerous polymeric nano-delivery systems are reported to have diverse physiochemical properties to deliver anticancer drugs, other therapeutic molecules and diagnostic reagents together. The author should review more broadly these works in the article. For example, JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 2014,136(20):7317-7326; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA2015,112(25):7779-7784; JOURNAL OF CONTROLLED RELEASE,2018,269:374-392; BIOMACROMOLECULES,2014, 15, 2896−2906; JOURNAL OF CONTROLLED RELEASE2018,275:117-128 ,etc.
3. Most of the references cited in this article are not new enough, especially in the part of "2.2 Polymer nanoparticles" and "3. Future perspectives". It is recommended that the authors pay more attention to the research of the past two years and summarize them into the article.

Authors' response

Thank you very much for all your comments, we have proceeded to review the draft in depth, incorporating all your suggestions.

Reviewer #2: In this paper, the authors reviewed different types of nanoparticles and platforms for the treatment of lung cancer. However, the authors failed to review the most important works for each type of nanoparticle, with very few examples reviewed under each category and inadequate references to the most recent works. This may severely affect the quality of a review article. Thus, I strongly suggest the authors expand the length of each section and add more examples to each category. Below are my comments:

1. The goal of this review is to summarize different nanoparticle platforms for lung cancer treatment. However, in section 2.1 when reviewing the MNPs, the MRI is for imaging and diagnosis purpose. The most important applications of MNPs for disease treatment such as magnetic hyperthermia therapy, drug delivery are not reviewed.
We would like to thank the referee for his comments and suggestion, this data has been included in the new text.

2. In section 2.1, the authors should add one paragraph commenting on the cytotoxicity and biocompatibility of MNPs. *Done*

3. In section 2.1, there is also FDA approved iron oxide MNPs for clinical applications, please also mention that with proper references.
We would like to thank the referee for his comment, this data has been included in the text.

4. Section 2.4, this section reviewing virus nanoparticles is too short. Please consider expanding this section with more work referenced.
Thank you, this section has been expanded.

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Thank you for the suggestion, this information has been included

6. No references to this sentence? 'In the treatment of lung cancer, nanoparticles have been used for the selective delivery of gene molecules such as DNA, plasmid DNA (pDNA), messenger RNA (mRNA), small interference RNA (siRNA), microRNA (miRNA), RNA precursors, etc.' *References added*

7. The authors should consider combining the discussions on Au and platinum-based methods for tumor treatment (in section 2.3 and section 3.2). These platforms should be categorized as a new sub-section titled 'metal nanoparticles' under section 2.
New section created 2.4 merging the previous two sections and adding new information
8. Since MNPs and metal nanoparticles are not degradable in the nature. The authors should also add one paragraph of discussion on the proper disposal of these kind of nanoparticles after clinical use.
We would like to thank the referee for his comment, this data has been included in the new text.

9. Tables 1 and 2 are only mentioned at the end of Introduction section once, no further discussion are given to describe these tables. Please consider adding several sentences describing what information are listed in these tables and comment on the clinical progresses of these works.
We have added a new section called clinical status, developing the clinical trial in progress, indicated in the table.

In addition, the quality of English should be improved throughout the manuscript. I just list some of them here:

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2. Typo, Section 2.1, 'glycocopolymer' —> 'glycopolymer'.

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Thank you very much for the corrections made, we have proceeded to review the grammar and the vocabulary.

Reviewer #3: Lung cancer is one of the prevalent malignancies and the leading causes for death worldwide. Recent progress in nanomedicine has encouraged the development and application of nanotechnology in the detection, diagnosis, and therapy of lung cancer. In this literature, the authors have summarized the progress in therapeutic nanomedicine in lung cancer, especially focus on future studies and ongoing clinical trials in this field. This review can provide some references and information for those interested in the field, and the topic of this review is matched with the scope of Journal of Clinical and Translational Research. However, the manuscript also remains some insufficient points, which need to be adjusted and supplemented. Therefore, I recommend a revision of this manuscript.
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Thank you for your comments, we have proceeded to expand the types and scope of nanoparticles in lung cancer treatment.

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Thank you, we have considered, developed and added these references

3. Most of the references cited in this article are not new enough, especially in the part of "2.2 Polymer nanoparticles" and "3. Future perspectives". It is recommended that the authors pay more attention to the research of the past two years and summarize them into the article.
Thank you, we have added new references.

2nd Editorial decision
09-Dec-2020

Ref.: Ms. No. JCTRes-D-20-00099R1
Current role of nanoparticles in the treatment of lung cancer
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jan 08, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #2: The authors have taken care of my previous comments in great detail. Some small issues need to be solved before its acceptance for publication:

1. There are several typos and grammar mistakes throughout this manuscript. The authors should proofread this manuscript again. I just list some of them here:
they can enter into the body cavities —> they can enter the body cavities
the potential uses of NPs for the treatment of lung cancer —> he potential use of NPs for the treatment of lung cancer.
Its high surface to volume ratio and the fact that can be detected and manipulated by remote magnetic fields —> Its high surface to volume ratio and the fact that it can be detected and manipulated by remote magnetic fields
must be small enough (<200 nm) to prolong the time of free circulation in the blood and avoid filtration of the spleen and liver —> must be small enough (<200 nm) to extend the free circulation time in the blood and avoid filtering by the spleen and liver
MNPs may disrupt cell metabolism causing undesirable effects —> MNPs may disrupt cell metabolism and cause adverse effects.
Another form of cytotoxicity is produced by the increased concentration —> Another form of cytotoxicity is caused by the increased concentration
that stars various forms of cellular damages that lead to cell death —> that causes various forms of cellular damages and finally leads to apoptosis
It was also studied the heating efficacy of polyacrylic acid coated MNP clusters under an alternating magnetic field—> The heating efficacy of polyacrylic acid coated MNP clusters under an alternating magnetic field was also studied
2. Please consider to revise this sentence: 'Among the materials used for the creation of MNPs we find pure metals, alloys and oxides'
3. Put the full name of ROS.
4. Section 2.6 Carbon nanotubes should not be included in this review. It's not categorized under NPs.
5. The conclusion section is too short. Please elaborate the future developing trends in NPs for lung cancer treatment, the advantages and disadvantages of NPs, the unmet needs in this area, etc. And insist on the importance of this review paper for researchers in this area.

Reviewer #3: Such being the case, some concerns raised in previous review have been addressed in the revised manuscript. The current manuscript may be published.

Authors’ response

Reviewers' comments:

Reviewer #2: The authors have taken care of my previous comments in great detail. Some

small issues need to be solved before its acceptance for publication:

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Thank you very much for the corrections made, we have proceeded to review the grammar.

The authors should proofread this manuscript again. I just list some of them here:

they can enter into the body cavities —> they can enter the body cavities
the potential uses of NPs for the treatment of lung cancer —> he potential use of NPs for the treatment of lung cancer.
Its high surface to volume ratio and the fact that can be detected and manipulated by remote magnetic fields —> Its high surface to volume ratio and the fact that it can be detected and manipulated by remote magnetic fields
must be small enough (<200 nm) to prolong the time of free circulation in the blood and avoid filtration of the spleen and liver —> must be small enough (<200 nm) to extend the free circulation time in the blood and avoid filtering by the spleen and liver
MNPs may disrupt cell metabolism causing undesirable effects —> MNPs may disrupt cell metabolism and cause adverse effects. Another form of cytotoxicity is produced by the increased concentration —> Another form of cytotoxicity is caused by the increased concentration that stars various forms of cellular damages that lead to cell death —> that causes various forms of cellular damages and finally leads to apoptosis
It was also studied the heating efficacy of polyacrylic acid coated MNP clusters under an alternating magnetic field—> The heating efficacy of polyacrylic acid coated MNP clusters under an alternating magnetic field was also studied

2. Please consider to revise this sentence: 'Among the materials used for the creation of MNPs we find pure metals, alloys and oxides'
Thank you for your comment, we have proceeded to omit this sentence.

3. Put the full name of ROS. *Done*

4. Section 2.6 Carbon nanotubes should not be included in this review. It's not categorized under NPs.
Thank you for your comment, we have proceeded to omit this section.

5. The conclusion section is too short. Please elaborate the future developing trends in NPs for lung cancer treatment, the advantages and disadvantages of NPs, the unmet needs in this area, etc. And insist on the importance of this review paper for researchers in this area.
Thank you, this section has been expanded.

3rd Editorial decision
29-Dec-2020

Ref.: Ms. No. JCTRes-D-20-00099R2
Current role of nanoparticles in the treatment of lung cancer
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jan 28, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for revising the manuscript, which has now been deemed suitable for publication on the condition that the text is further improved in line with the journal's explicit guidelines. We cannot publish papers that do not conform to academic level English. This is certainly not intended to harass the authors. Instead, the high linguistic bar we set serves to help the credibility of the journal, facilitate easy indexing, and exude respect for the published work.

May I kindly ask you to engage a native speaker, a third-party service provider, or a staff member at JCTR who can provide language editing for a fee.

Thank you and the best of luck with the last revision.

Michal Heger
Editor

Authors’ response

Reviewers' comments:

Dear authors,

Thank you for revising the manuscript, which has now been deemed suitable for publication on the condition that the text is further improved in line with the journal's explicit guidelines. We cannot publish papers that do not conform to academic level English. This is certainly not

intended to harass the authors. Instead, the high linguistic bar we set serves to help the credibility of the journal, facilitate easy indexing, and exude respect for the published work.

Thank you very much for your comments, a thorough revision of the grammar of the manuscript has been carried out by an oncologist English native speaker.

4th Editorial decision
27-Jan-2021

Ref.: Ms. No. JCTRes-D-20-00099R3
Current role of nanoparticles in the treatment of lung cancer
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: