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Antibacterial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections

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Handling editor:
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1st editorial decision:

Date: 22-Nov-2015

Ref.: Ms. No. JCTRes-D-15-00011
Antimicrobial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections
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Dear Ms. Liu,

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 resubmit your work.

Your revision is due by Dec 22, 2015.

To submit a revision, go to http://jctres.edmgr.com/ 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

Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research

*****Reviewer comments*****

Reviewer #2: This review reads very well and seems to present a concise overview of the subject.

Reviewer #3: This is a review of antibacterial photodynamic inactivation.
In the abstract it claims to be "comprehensive" but this is of course impossible in the present day as the number of papers has grown dramatically in recent years.
They have chosen (probably wisely) to limit themselves to Gram-positive, Gram-negative and mycobacteria and to omit various fungal cells and parasites such as Leishmania. However this does mean that they are reviewing 'antibacterial PDI" and not "antimicrobial PDI". All references to "antimicrobial" must be changed.
The biggest problem is probably Figure 2. The caption reads "generic structures of the photosensitizers addressed in the review." I think this is a mistake. They should have given the structures of selected members of individual classes of compounds. Then they could have made it clear what were the important structural features in each molecule in particular the importance of cationic charges. This message is not clear in inspecting the structures. The chlorin structure (Fig 2.10) is puzzling. The flavin (Fig 2.9) is riboflavin not FLAIR. The C70 fullerene (Fig 2.6) is completely generic, but the C60 fullerene (Fig 2.5) is not and would be insoluble. Rose Bengal should be included in figure.
There is a big difference between "phenothiazine" and "phenothiazinium". The first is yellow and is not a photosensitizer while the latter is dark blue and is a photosensitizer.
I think it is misleading to call the ruthenium chelates "phenanthrolines". "Ruthenium-bipyridyl complexes" is a better generic term.
The big problem in endodontic infection is Enterococcus faecalis and not Streptococcus mutans which principally causes caries.
I realize they cannot include everything, but I think they should include the following.
An entire book devoted to this subject (Photodynamic Inactivation of Microbial Pathogens: Medical and Environmental Applications, edited by Hamblin MR and Jori G. RSC Publishing, Cambridge, UK: 2011. ISBN-13: 978-1-84973-144-7)
The idea of conjugates between anionic photosensitizers and cationic polymers.
Photosensitizers conjugated to particles, surfaces and fibers for textiles.
SAPYR (Photodynamic biofilm inactivation by SAPYR--an exclusive singlet oxygen photosensitizer. Cieplik F, Späth A, Regensburger J, Gollmer A, Tabenski L, Hiller KA, Bäumler W, Maisch T, Schmalz G. Free Radic Biol Med. 2013 Dec;65:477-87.)
Induction of immune response against a bacterial infection (Photodynamic therapy induces an immune response against a bacterial pathogen. Huang YY, Tanaka M, Vecchio D, Garcia-Diaz M, Chang J, Morimoto Y, Hamblin MR. Expert Rev Clin Immunol. 2012 Jul;8(5):479-94.)

Authors' rebuttal:

To Reviewer #3

In the abstract it claims to be "comprehensive" but this is of course impossible in the present day as the number of papers has grown dramatically in recent years.
They have chosen (probably wisely) to limit themselves to Gram-positive, Gram-negative and mycobacteria and to omit various fungal cells and parasites such as Leishmania. However this does mean that they are reviewing 'antibacterial PDI" and not "antimicrobial PDI". All references to "antimicrobial" must be changed.

Reply: Excellent point. We changed the phrasing accordingly throughout the text.
The biggest problem is probably Figure 2. The caption reads "generic structures of the photosensitizers addressed in the review." I think this is a mistake. They should have given the structures of selected members of individual classes of compounds. Then they could have made it clear what were the important structural features in each molecule in particular the importance of cationic charges. This message is not clear in inspecting the structures. The chlorin structure (Fig 2.10) is puzzling. The flavin (Fig 2.9) is riboflavin not FLAIR. The C70 fullerene (Fig 2.6) is completely generic, but the C60 fullerene (Fig 2.5) is not and would be insoluble. Rose Bengal should be included in figure.

Reply: We changed Figure 2 to show some of the representative structures. Rose Bengal was already listed in Table 2.
There is a big difference between "phenothiazine" and "phenothiazinium". The first is yellow and is not a photosensitizer while the latter is dark blue and is a photosensitizer.

Reply: We changed phenothiazine to phenothiazinium throughout the text.
I think it is misleading to call the ruthenium chelates "phenanthrolines". "ruthenium-bipyridyl complexess" is a better generic term.

Reply: We changed the term accordingly.
The big problem in endodontic infection is Enterococcus faecalis and not Streptococcus mutans which principally causes caries.

Reply: We added an entire section about *E. faecalis*.
I realize they cannot include everything, but I think they should include the following.
An entire book devoted to this subject (Photodynamic Inactivation of Microbial Pathogens: Medical and Environmental Applications, edited by Hamblin MR and Jori G. RSC Publishing, Cambridge, UK: 2011. ISBN-13: 978-1-84973-144-7)

Reply: We added this reference to Introduction and addressed the limitations of the present review.

The idea of conjugates between anionic photosensitizers and cationic polymers.

Reply: There is one section (section 6.2) on conjugation of cationic peptides to anionic photosensitizer. We added some more text in the introductory part of section 6 and added references.

Photosensitizers conjugated to particles, surfaces and fibers for textiles.

Reply: We added text in introductory part of section 6. In order not to expand the review or increase the complexity, the limitations of the review are addressed in the introductory part of section 6 and readers are referred to the book by Hamblin et al. as the reviewer suggested.

SAPYR (Photodynamic biofilm inactivation by SAPYR--an exclusive singlet oxygen photosensitizer. Cieplik F, Späth A, Regensburger J, Gollmer A, Tabenski L, Hiller KA, Bäumler W, Maisch T, Schmalz G. Free Radic Biol Med. 2013 Dec;65:477-87.)

Reply: We added this reference in the section on *E. faecalis*.

Induction of immune response against a bacterial infection (Photodynamic therapy induces an immune response against a bacterial pathogen. Huang YY, Tanaka M, Vecchio D, Garcia-Diaz M, Chang J, Morimoto Y, Hamblin MR. Expert Rev Clin Immunol. 2012 Jul;8(5):479-94.)

Reply: We added text to the in vivo and clinical development section and added the reference.

2nd editorial decision:

Date: 28-Nov-2015

Ref.: Ms. No. JCTRes-D-15-00011R1
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Journal of Clinical and Translational Research

Dear Ms. Liu,

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

Comments from the editor and reviewers can be found below.

Thank you for submitting your work to JCTR.

Kindest regards,

Rowan van Golen

Associate Editor
Journal of Clinical and Translational Research

Comments from the editors and reviewers: