Dear Dr. Wahyu Widowati,

We have received your article "Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJ-MSCs)proliferation" for consideration for publication in Biomarkers and Genomic Medicine.

Your manuscript will be given a reference number once an editor has been assigned.

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Dear Dr. Wahyu Widowati,

I like to notify you in advance that the handling editor suggests that your manuscript can be accepted after language proofreading. Before sending the final decision letter to you, we request you to address the following issue.

Comments:

1. The revised manuscript is still with typos and grammar errors in the text. The authors need to check the content carefully before acceptance.
2. Figures:
    a. Please provide clear images for Figure 1.
    b. In Figure 3 & 4, please indicate the item name for X-axis on image and the description for asterisks in the legend.

While you complete the revision, please directly send me the manuscript via email and then I will proceed further for a faster process. If you have any question, please do not hesitate to contact me. Looking forward to hearing from you. Thank you.

Best regards,

LiChen Yen
Managing Editor
Biomarkers and Genomic Medicine

Dear Dr. Wahyu Widowati,

Thank you very much for your detailed explanation, which greatly helps us ensure the conformation of publication ethics. I will send the decision letter to you soon.

If you have any question, please do not hesitate to contact me. Thank you.

Best regards,
LiChen Yen

Dear Dr. Wahyu Widowati,

Your above paper has been reviewed. The reviewers' comments are included below, please carefully address the issues raised in the comments and resubmit the revised manuscript within 14 days.

While you submit a revised manuscript, please outline each change made as raised in the reviewer comments, and/or provide a suitable explanation to the comment that you not addressed.

To submit your revision, please do the following:

1. Go to: http://ees.elsevier.com/bgm/

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This takes you to the Author Main Menu.

4. Click [Submissions Needing Revision]

I look forward to receiving your revised manuscript.

Yours sincerely,

Li-Chen Yen, Ph.D.
Managing Editor
Biomarkers and Genomic Medicine

Reviewers' comments:

Reviewer #1:
The manuscript, BGM-D-15-00002, entitled "Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJMSCs) proliferation" reports a protocol for propagation of human WJ-MSCs as an alternative to xeno-free medium. This finding is important in identifying a potential translational application for stem cell research. However, multiple grammatical errors and ambiguous statements are throughout the manuscript, and some methods and experimental results require further clarification. The comments are listed below.

ABSTRACT
Lines 7-8: "…under two different conditions: 10% FBS (as the standard control medium), 20% FBS, 0.250; 0.125; 0.063 and 0.031 mg/ml huPL." 10% FBS is not mentioned in the paper; there are more than two conditions.

Line 10: No data about "stemness genes expression."

Lines 16-17: "The optimum concentration of huPLABO in culture medium was 0.250 mg/ml…" This concentration is different from what is mentioned in Discussion.

Lines 16-19: "The optimum concentration of huPLABO in culture medium was 0.250 mg/ml was the lowest population doubling time (PDT) of WJ-MSCs with the PDT value 1.117." Incorrect grammar.

Lines 21-23: "HuPL-ABO produced by this method was able to enhance the WJ-MSCs proliferation rate constantly and decreases the time required to reach confluence compared to FBS culture condition." Incorrect grammar.

INTRODUCTION
Line 3, Page 1: "Mesenchymal stem cells (MSCs) has been a popular tool…" Subject-verb disagreement.

Line 21, Page 1: "hypoimmunogenicity… anticancer…"

Line 39, Page 1: "Furthermore, different batches of FBS also give …"

Lines 52-59, Page 1: Confusing statements.

Line 7, Page 2: "…culture remains a challenging task."

MATERIALS AND METHODS
Line 16, Page 1: Define RRP.

Lines 16-20, Page 1: "PRP were activated through repeated freeze-thaw cycles, and platelet lysates produced by these methods were centrifuged to separate the platelet lysate from other debris."

Line 45, Page 1: "small pieces"

Line 49, Page 1: "or 0.031"

Line 5, Page 2: Define hWJMSCs-CM.

Line 7, Page 2: "Growth factors assays including IGF-1…" An incorrect and incomplete sentence.

Line 9, Page 2: "The growth factors concentration were…" Subject-verb disagreement.

Line 22, Page 2: "R&D System"

Lines 24-29, Page 2: An incomplete sentence.

Line 58, Page 2: "where t is the time of the culture"

Line 38, Page 3: "six-well plates"

Lines 11-14, Page 4: "P values <0.05 were considered as statistically significant."

RESULTS
Lines 31-34, Page 1: "For proliferation assay, WJ-MSCs were isolated and cultured in supplementation of huPLABO and FBS." This sentence does not seem to relate to the rest of the paragraph.

Lines 38-40, Page 1: "At passage 4, WJ-MSCs cultured in all culture conditions also displayed a fibroblast-like morphology (Fig. 1)." What is "cultured in all culture conditions" referring to?

Lines 56-59, Page 1 - Lines 1-3, Page 2: "The optimum concentration of huPL-ABO in culture medium was 0.250 mg/ml and 0.125 mg/ml (Fig. 2). Due to insignificant difference between the concentrations in terms of WJ-MSCs population doubling time (PDT), the concentration of 0.125 mg/ml was used for huPL-ABO concentration in all comparison between FBS and huPL-ABO." It is not clear how the optimal concentration of huPL-ABO was determined. In addition, there was statistically significant difference among the groups.

Lines 11-20, 47-57, Page 2: Repetitive statements.

Line 9, Page 3: "…morphology of chondrocyte, osteocyte, and adipocyte were observed from the culture." Subject-verb disagreement.

DISCUSSION
Lines 2-5, Page 1: Confusing statements.

Line 7, Page 1: "short time periods"

Line 18, Page 1: "This study showed that huPL-ABO is rich in PDGF-AB and TGF-<beta>1…" What to compare with?

Lines 20-29, Page 2: "Therefore, freeze-thaw method in preparing huPL-ABO is preferable due to its high efficiency and safety in releasing growth factors from PRP for clinical application, because the method does not require any additional substances that have possibility to stimulate immunologic reaction in-patient when the WJMSCs grown in huPL-ABO is administered into the patient." A lengthy and confusing statement.

Lines 42-44, Page 2: "Both cell populations…"

Line 47, Page 2: "The presence of this population was extremely…" What is "this population" referring to?

Line 51, Page 2: "…eliminate these contaminating cells…" What are "these contaminating cells" referring to?

Line 4, Page 3: "…since they can still fully differentiated further toward chondrogenic." Incorrect grammar.

Lines 4-12, Page 3: "The inhibitory effect only caused the MSCs to preserve their stemness and minimizing the risk of entering senescence and transformation, thus lead to shorten MSCs culture that can be of particular interest in clinical application." An awkward statement.

Lines 33-38, Page 3: "MSCs are expanded using autologous platelet lysate technique show no evidence of malignant transformation in vivo, following implantation of MSCs." An awkward statement.

Tables
Tables 1, 2: How about these growth factors in FBS?

Table 1: Some numbers are incorrectly presented.

Figures
Figure 2: Which passage of WJ-MSCs? How was this passage determined?

Figure 5: Figure legend is different from the relevant description in Materials and Methods.

References

References 1 and 17 are incorrect citations.

Reviewer #2:
The authors tried to develop a culture system for the isolated mesenchymal stem cells from Wharton's jelly with the lysates from human platelets (huPL). They demonstrated that the proliferation, gene expression, and differentiation potential of MSC cultured with the lysates were similar or better than those cultured with fetal bovine serum. The further defined the potential cytokines/growth factors in the huPL to show the potential active constituent in mediating MSC growth/survival in their culture system. Overall, their work is important in paving a way for a totally defined system of culturing MSC and, thus, is recommended for publication in Biomarkers and Genomic Medicine.
1. If possible, show the figures of flow cytometry rather than just percentages.
2. Replace the pictures of the P4-FBS and P8-huPL in figure 1. The black patches in the background make it difficult to visualize the cell morphology.
3. Add scale bars to the figures 1 and 5
4. Clarify the statistical analyses for each p-value in the comparisons. For example, student's t-test, one-way ANOVA, or two-way ANOVA shall be stated, instead of "parametric statistics".

Dear Editor,

I am pleased to resubmit for publication the revised version of "Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJ-MSCs)proliferation"; Ms.Ref.No.: BGM-D-15-00002. I appreciated the constructive critcisms of the Editor and the Reviewers. I have addressed each of their consern as outlined below.

Reviewer comments

Reviewer I

The manuscript, BGM-D-15-00002, entitled "Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJMSCs) proliferation" reports a protocol for propagation of human WJ-MSCs as an alternative to xeno-free medium. This finding is important in identifying a potential translational application for stem cell research. However, multiple grammatical errors and ambiguous statements are throughout the manuscript, and some methods and experimental results require further clarification. The comments are listed below.

Thank you for the revision comment, we already checked it all and make a revision according to your comment. For some comments we give the further explanation as listed below.

1. ***ABSTRACT. Lines 7-8: "…under two different conditions: 10% FBS (as the standard control medium), 20% FBS, 0.250; 0.125; 0.063 and 0.031 mg/ml huPL." 10% FBS is not mentioned in the paper; there are more than two conditions.***
2. ***ABSTRACT. Line 10: No data about "stemness genes expression."***
3. ***ABSTRACT. Lines 16-17: "The optimum concentration of huPLABO in culture medium was 0.250 mg/ml…" This concentration is different from what is mentioned in Discussion.***
4. ***RESULTS. Lines 56-59, Page 1 - Lines 1-3, Page 2: "The optimum concentration of huPL-ABO in culture medium was 0.250 mg/ml and 0.125 mg/ml (Fig. 2). Due to insignificant difference between the concentrations in terms of WJ-MSCs population doubling time (PDT), the concentration of 0.125 mg/ml was used for huPL-ABO concentration in all comparison between FBS and huPL-ABO." It is not clear how the optimal concentration of huPL-ABO was determined. In addition, there was statistically significant difference among the groups.***
5. ***TABLES. Tables 1, 2: How about these growth factors in FBS?***
   Growth factors in FBS was not measured in this study.In this research we want to know the concentration of that growth factor. The supplementation of basal culture media with FBS is common practice in cell culture and the concentration of FBS's growth factors was already known.
6. ***FIGURES. Figure 2: Which passage of WJ-MSCs? How was this passage determined?***
7. ***FIGURES.Figure 5: Figure legend is different from the relevant description in Materials and Methods.***

Reviewer II

The authors tried to develop a culture system for the isolated mesenchymal stem cells from Wharton's jelly with the lysates from human platelets (huPL). They demonstrated that the proliferation, gene expression, and differentiation potential of MSC cultured with the lysates were similar or better than those cultured with fetal bovine serum. The further defined the potential cytokines/growth factors in the huPL to show the potential active constituent in mediating MSC growth/survival in their culture system. Overall, their work is important in paving a way for a totally defined system of culturing MSC and, thus, is recommended for publication in Biomarkers and Genomic Medicine.

1. **If possible, show the figures of flow cytometry rather than just percentages.**
2. **Replace the pictures of the P4-FBS and P8-huPL in figure 1. The black patches in the background make it difficult to visualize the cell morphology**
3. **Add scale bars to the figures 1 and 5**
4. **Clarify the statistical analyses for each p-value in the comparisons. For example, student's t-test, one-way ANOVA, or two-way ANOVA shall be stated, instead of "parametric statistics".**

   We already mention the statistical method used. We used one-way ANOVA to analyse the data.

Ms. Ref. No.: BGM-D-15-00002R1
Title: Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJ-MSCs)proliferation
Biomarkers and Genomic Medicine

Dear Dr. Wahyu Widowati,

I am pleased to inform you that your paper "Human Platelet Lysate (huPL) enhance the Wharton's Jelly-derived Mesenchymal Stem Cells (WJ-MSCs)proliferation" has been accepted for publication in Biomarkers and Genomic Medicine.

For publishing need, please provide the signed copyright transfer agreement (http://www.j-bgm.com/webfiles/images/journals/BGM/BGM_CTA.pdf).

Please note that you will receive the electronic page proof via e-mail by the publisher approximately 3-4 weeks. It is imperative that you return your corrected proofs as quickly as possible then.

Thank you for submitting your work to Biomarkers and Genomic Medicine.

Yours sincerely,

Li-Chen Yen, Ph.D.
Managing Editor
Biomarkers and Genomic Medicine

Dear Prof. Widowati,

I am sorry that your article is still under editing process. As the figure editing in the first proof is not good enough for publication, we request the production team to modify it and it takes some time. You article could be online accessed within 2 weeks.

I apologize for any inconvenience this caused. If you have any question, pleas feel free to contact me. Thank you.

Kind regards,
LiChen Yen

Dr. Wahyu Widowati,

Thank you for your kind notification.

Your article will be published in the coming issue BGM Vol.7 No.3, so we will proceed with this version.

If you have any question, please feel free to contact me. Thank you.

Best regards,

LiChen Yen
Managing Editor
Biomarkers and Genomic Medicine

Dear
Li-Chen Yen, Ph.D.
Managing Editor
Biomarkers and Genomic Medicine

Thank you very much for your trust, so our article can be published at Biomarkers and Genomic Medicine Journal as reputable International Journal. I will send copy right agreement as soon as possible.
Thank you

Regards

Dr. Wahyu Widowati., M.Si
Medical Research Center
Faculty of Medicine
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Jl. Prof drg. Suria Sumantri No.65

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