February 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJO.doc)

Title: Protein Kinase Small Molecule Inhibitors for Rheumatoid Arthritis: Medicinal Chemistry/Clinical Perspectives

Authors: Charles J. Malemud, David E. Blumenthal

Name of Journal: *World Journal of Orthopedics*

ESPS Manuscript NO: 8914

The manuscript has been improved according to the suggestions of the reviewers

1) Format has been updated
2) The reviewer's comments have been addressed
3) Changes have been made in the revised manuscript in accordance with the reviewer's suggestions:

Reviewer #1

There were no issues that this reviewer requested we address.

Reviewer #2

1) **Comment**: Which of the amazing quantities of products that have been discovered will have a chance to (become) someday a treatment in RA?
   Response: This is a difficult question to answer prospectively. However, we have already seen that several years worth of pre-clinical development and clinical trials results have led to the FDA approval of tofactinib which is the first small molecule JAK inhibitor that can be used for the clinical therapy of RA. We also pointed out in the paper that several additional small molecule inhibitors for JAK that are being evaluated for the treatment of myeloproliferative disorders (Table 1) may eventually also be employed in the therapy of RA. Finally, we commented that perhaps selective inhibition of JAK3 would be preferable to SMIs targeted to inhibit JAK1/JAK2/TYK2 because JAK3 is not conventionally believed to be involved in hematopoietic cell development.

2) **Comment**: The article deals more with the criteria and composite measures of drug efficacy than with the 'analyse' of possible candidates and why they could be a candidate.
   Response: We believe that in the manuscript we have more than adequately addressed this issue raised by the reviewer. In addition to covering the JAK/STAT pathway, we have discussed in detail why several other signaling pathways involving the MAPK and PI3K/Akt/mTOR pathways are likely to be further

studied for their role in the pathogenesis and progression of RA. We also briefly mentioned that Spleen Tyrosine Kinase (SyK) and protein kinase C-θ (PKC-θ) are being evaluated as well. However, we also clearly pointed out that the Syk SMI, Fostamatinib, has been evaluated in 3 RA clinical trials and although SyK has clearly been shown to be involved in immune-mediated inflammation in RA, the ACR20 criteria response ranged from only 35-38%. This result brings into question the extent to which further development of a SyK SMI will result in a clinically relevant response in patients with moderate-severe RA.

3) **Comment**: Clinicians would like to know the molecules that play a key role in RA physiopathology…
Response: We partially agree with the reviewer and have amended the manuscript by adding the following paragraph to the Conclusions section of the manuscript.

Although SMIs have been primarily targeted to inhibit the activity of JAKs, specific members of the MAPK pathway (e.g. p38-α) and PI3K/Akt/mTOR signaling pathways were also shown to be relevant to the pathogenesis of immune-mediated inflammation associated with RA. Therefore, there are likely to be signaling components of the MAPK pathway, such as the upstream protein kinase, MEK1/2, whose activity is required for phosphorylation of ERK1/2 that may be targeted for further drug development [57] In addition, since one target of STAT activation is it's potential to increase the expression of anti-inflammatory cytokines, such as, IL-4 and IL-10 [37] and the signaling pathways these cytokines activate, it appears justified to consider developing SMIs that inhibit those protein kinases which can suppress the expression of anti-inflammatory cytokine genes.

However, we do take issue with the viewpoint expressed by this reviewer and would in that regard like to respond by the following:

We don't agree with the reviewer that it would be interesting or timely to generate excitement about potential therapeutic targets in the absence of data. The author's have conferred and we agree that we could assemble an impressive list of potential pharmaceuticals that failed in Phase II or Phase III trials, revealing the initial excitement to be premature and ultimately unwarranted. Any author who expressed excitement about any of these pharmaceuticals or molecular targets could be exposed as foolish when speculations are reviewed in the light of the actual data. Thus, we don't intend to express false enthusiasm now and look foolish later just because another party thinks that this is important. Moreover, Dr. Blumenthal as a practicing rheumatologist clearly expresses that he has no insider information on any of the drugs now under development. Dr. Malemud, a basic scientist working in this field probably knows more than Dr. Blumental about potential molecular targets, but Dr. Blumenthal states that he only hears about promising pharmaceuticals when the company has collected positive safety and efficacy data in Phase III trials. Thus, we are not actually in a position to speculate in the way that this reviewer requests. Lastly, it is difficult to obtain any useful predictive information from Clinical Trials.gov, which is our only source about drugs under development that

have not yet generated abstract-worthy data. In that regard, a perusal of the Clinical Trials.gov website lists about 350 phase I trials in RA but the companies are not required to reveal any proprietary information and many of the new molecular entities are described only by letters and numbers, without any information about their structure or their molecular target. Furthermore, we can't blame the companies for revealing little to the public, but it makes it hard for us as manuscript writers without inside information to know what the company considers to be promising. Since the reviewer who suggested that we perhaps "gin up" excitement prematurely did actually recommend that the article be published, we think that our intended addenda to the Conclusions section of the paper (see above) should be considered an honest attempt to address the reviewer's request and good enough.

4) **Comment:** Reducing the length of some of the sentences in the Introduction on page 7.
Response: We agree and have attended to this comment.

5) References and typesetting were corrected. DOI identifiers have been added.

Thank you again for publishing our manuscript in *the World Journal of Orthopedics*.

Sincerely,

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