December 14, 2012

From: Zhijian Lu

RE: revision of manuscript 993

Dear Reviewer and Editor,

Thank you very much for your kind consideration of our manuscript. We wanted to use this opportunity to discuss the current status of therapeutic antibody discovery. We find that there are two levels of challenges. One is the lack of proven targets, and the other the un-conventional nature of potential new targets. We dedicated the section “Target Space” to address the first level of challenge, which we consider as the overriding issue for therapeutic antibody discovery today. We then spread out the technical challenges into subsequent sections, which reflect the characteristics of the new target classes currently being worked on by the pharmaceutical industry. To follow the reviewer’s advice, we explicitly added the biochemistry challenge to the antigen preparation for these new targets and mentioned several solutions being applied.

We have also addressed the format issues per Editor’s instruction. Please find the responses below in underlined bold text.

Warm regards,

Zhijian,

In this paper, Dr. Lu Z et al., have described and summarized a number of methodologies developed for creating therapeutic monoclonal antibodies in biotech and pharmaceutical companies, which includes hybridoma, humanization, phage display, yeast display, and transgenic rodents. This review may be interested by readers from industry and some of academic labs that focus on drug development based on these mentioned different approaches. Several points listed below should be addressed for improvement of this manuscript prior to consideration of acceptance.

1. The major focus of this paper is to describe the five individual technologies used in antibody-based drug pipeline. It should be summarized in a clear and understandable format comparing these approaches such as a table containing their advantages, disadvantages, available drug samples, action or targeting mechanisms, and clinical disease treatment or trials, etc.

**A. We added a table to highlight the several antibody discovery approaches and listed a few key comprehensive references. We assume that readers interested in this topic are fairly familiar with the accomplishment of the field, and would like to stimulate the readers by presenting our views on the current status.**

2) The article does not include a section to discuss on future challenges, which is important for the authors to stimulate themselves and readers to potentially circumvent current problems as well as lead to future development of novel technologies. In fact, the title involves “the challenges and how to face them”. Therefore, this section is essential.

**A.** **We completely agree with the reviewer on this point. We think there are two levels of challenges facing therapeutic antibody discovery, one is on strategic and the other tactical. We articulated the strategic challenge in the “Target Space” section, with the main point being that available target for therapeutic antibody discovery is the bottleneck, and we summarized two broad industry efforts for target discovery where antibody approach may help. We now also added tactical challenge in the revision which relates to the potential new targets being multispanning membrane proteins and the difficulties in preparing antigen for them. We then described potential ways to overcome this challenge (at the end of “Hybridoma” section).**

3) The paper primarily updates the technologies involved in antibody-based drug development and does not discuss on other drug methodologies such as small molecules. Thereof, the title of this paper should add an “antibody” word to avoid a broader scope of this review that does not mention or explain other types of drug development.

**A. We followed the advice and changed the title to “Frontier of Therapeutic Antibody Discovery: the Challenges and How to Face Them”.**

4) There is little description of yeast display. As for the new field, it should be technically described more.

**A. We added a brief description of a common form of yeast display. The references in that section contain more comprehensive technology review for interested readers.**

5) Many abbreviations should be provided with full names, particularly at first time. What are CDR, SDR, sdAb, scFv and NGO? There are two times of listing full name and abbreviation of NGS on p7 & 9; please delete the second full name on p9. Likewise, a full name and its abbreviation must be shown in the first time rather than the second time; please correct “FACS” on p9 & p10.

**A. We have completely addressed the issues.**