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Answering reviewers

Review 1

A clearly written and enjoyable to read expert editorial on CARs. The different issues are appropriately covered and this includes the quality control of the technology. The arguments are well balance. I thought that the work in two other recent June publications could be mentioned. This includes use in T cell malignancies: Mamonkin M et al. A T cell-directed chimeric antigen receptor for the selective treatment of T cell malignancies. Blood. 2015 Jun 8. pii: blood-2015-02-629527. [Epub ahead of print] Also some work on overcoming the cytokine toxicity Song DG et al. A fully human chimeric antigen receptor with potent activity against cancer cells but reduced risk for off-tumor toxicity. Oncotarget. 2015 Jun 19. [Epub ahead of print]

Response: Both of the suggested references have been cited in the revised editorial

Review 2

In this well-written editorial, the authors present a very interesting review on a novel technology for immunotherapy, namely chimeric antigen receptors (CARS). Specific comments: 1) Page 3. Some references would be appropriate for the 2 signal requirement for T-cell activation, e.g. Bretscher & Cohn Science 1970 (PMID:4194660)

Response: This reference has been added.

2) How does CAR technology compare to immunotherapy mediated by monoclonal antibodies against the same target, e.g. anti-CD19 antibodies? A few considerations about this issue would be useful to the critical reader.

Response: The text has been amended to read "It is important to emphasise the unprecedented magnitude of these responses in the context of first in man evaluation in patients with otherwise untreatable malignancy. Furthermore, some of these patients had failed treatment with potent antibody derivatives such as blinatumomab, highlighting the greater potency of the CAR-based approach."

3) Page 7. "Consequently, self-antigens are generally selected for CAR T cell immunotherapy in the hope that on-target toxicity will not emerge upon clinical testing." This sentence is paradoxical and requires further explanations. Targeting self antigens is expected to cause toxicity!

Response: The reviewer is of course correct in making this point. Nonetheless, the lack of truly tumour-specific targets means that most CARs that have been designed to treat solid tumours recognize molecules that are over-expressed on tumour cells, but are found at lower levels in some healthy tissues. To clarify this point, we have re-written this section which now reads: "Consequently, self-antigens that are over-expressed in tumour cells and found at low levels in healthy tissues are generally selected for CAR T-cell immunotherapy. Indeed, targets that are expressed on T-cells, such as CD5, have been successfully targeted in pre-clinical models of T-cell lymphoma[35]. The use of lower affinity targeting moieties may further enhance the safety of this approach, enabling better discrimination by CARs between tumour cells (target high) and healthy tissues (target low)[36]. Nonetheless, previous clinical experience has highlighted the difficulty inherent in negotiating this fine line[37]." In addition, at the suggestion of another reviewer, a Table has been added to provide further information on this and other toxicities associated with CAR T-cell immunotherapy.

Review 3

Chimeric antigen receptors are fusion molecules that may be genetically delivered to T-cells thereby conferring specificity for target antigens on the surface of the tumor. This approach has had some success with elimination of B-cell malignancies. The efficacy of this approach to sold tumors remains poorly defined. Manufacture of the critical molecules and target selection remains a challenge. A nice review of the status of the application of chimeric

antigen receptors to tumor biology is outlined in this manuscript.

Response: no changes required

Review 4

General comments: the authors provide a review related to chimeric antigen receptors (CAR). This excellent and up to date review article will provide much recent knowledge concerning CAR to the readers of this journal. In the manuscript, authors refer to therapeutic trials and adverse events, however, these issues are not sufficiently discussed and a table summarizing these specific points would help the readers.

Response: Two tables have been added that provide a list of clinical trials registered on the clinicaltrials.gov website, together with a table that provides a summary of toxicities that have been linked to this therapeutic approach. Text now reads.. "A summary of clinical trials in haematological malignancy (Table 2) and solid tumours/ other diseases (Table 3) that are currently registered on the clinicaltrials.gov website is provided. Trials were based in USA (65), China (15), UK (5) and 1 each in Japan, Netherlands, Australia, Sweden, Singapore, Switzerland and Israel."

Review 5

General comments: the authors provide a review related to chimeric antigen receptors (CAR). This excellent and up to date review article will provide much recent knowledge concerning CAR to the readers of this journal. In the manuscript, authors refer to therapeutic trials and adverse events, however, these issues are not sufficiently discussed and a table summarizing these specific points would help the readers.

Once again, on behalf of all the authors, I hereby guarantee that neither the submitted paper nor any similar paper, in whole or in part, other than an abstract or preliminary communication, has been or will be submitted to or published in any other scientific journal or on the internet. I can also confirm that all authors have been involved in review of the manuscript. I very much look forward to hearing the outcome of our submission in due course.