Reviewer’s report

Title: A novel aspirin prodrug inhibits NFkB activity and breast cancer stem cell properties.

Version: 2 Date: 24 July 2015

Reviewer: Hong Wang

Reviewer’s report:

This manuscript by Frasor and coworkers describes the development of prodrugs derived from Aspirin (ASA) bearing a masked carboxylic acid group through incorporating different ancillary pharmacophores into the ester group of the ASA. This work aims to investigate the possibility to enhance the anti-cancer activities of ASA prodrugs through a new pathway, more specifically through NFkB pathway. In this work several of these ASA prodrugs displayed potent inhibitory activities toward NFkB pathway. Among these inhibitors, GTCpFE, which is a fumarate-based ASA prodrug, was identified as a promising chemopreventive or therapeutic agent in breast cancer. GTCpFE can effectively target breast CSCs through simultaneously inhibiting both COX and NFkB pathways with no cytotoxicity. It is very interesting that the fumarate was found to be essential to elicit inhibitory activity toward the NFkB pathway, but only when it is integrated into the prodrug (GTCpFE) structure.

Overall the work demonstrated in this manuscript is interesting, and should be valuable to the field of drug development. The reviewer thus recommends publication of this manuscript in BioMed Central after minor revisions listed below:

• It stated in the manuscript “While ASA prodrugs have been studied as COX inhibitors, their specific activity on the 101 NFkB pathway remains relatively unexplored”. Please add relevant references if there are any, otherwise, please remove “relatively in the sentence”.
• Add yield to each synthetic step in Figure S1.
• The purity of the ASA prodrugs should be demonstrated either through 1H NMR or HPLC. Please include these data in the revised supporting information.
• The type of the coupling constant should be indicated in the 1HNMR data in the supporting information. For example, report 3J = 6.6, 4J = 1.2 instead of J = 6.6, 1.2, etc.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests