Reviewer's report

Title: ARG098, a novel anti-human Fas antibody, shows strong cytotoxic effects, suppresses synovial hyperplasia, and prevents cartilage destruction in rheumatoid arthritis.

Version: 1 Date: 20 April 2010

Reviewer: Paul-Peter Tak

Reviewer's report:

Major Compulsory Revisions:

1) The major novel findings reported in this manuscript are the efficacies of the ARG098 antibody in inducing apoptosis in RA FLS in vitro and in the SCID-HuRAg model, as RA FLS, in vitro or in vivo, have been reported to be resistant to Fas-dependent apoptosis in these settings. The authors report the superior effect of of ARG098 in inducing apoptosis in Jurkat cells and RA FLS compared to historical attempts. To make this claim, the authors need to show ARG098 side by side with another anti-Fas antibody such as CH-11. In particular, they should examine dose responses of another Fas antibody in Jurkat cells, and find concentrations of this antibody and ARG098 which induce comparable levels of apoptosis in Jurkat. Then, the two antibodies should be compared at these concentrations in RA FLS. Only then can the authors claim any superiority of the ARG098 compound.

2) While the authors attribute the historical lack of efficacy of anti-Fas antibodies on RA FLS to, among other things, their need for multimerization, a very good recent study by Pundt and colleagues (Arthritis Res Ther, 2009, 11/1/R16) demonstrated that RA FLS susceptibility to FasL-induced death was exquisitely dependent upon the proliferation rate of cells in vitro, as well as cell cycling status and culture confluency. The authors need to take into consideration that their positive results with ARG098 are secondary to tissue culture conditions –eg., there is no evidence in the methods section that they serum-starve their FLS or achieve cell cycle arrest.

3) The authors ignore a number of important manuscripts published on this topic such as effects of PI3 kinase signaling in RA FLS resistance to Fas-dependent apoptosis from the group of Pope, and others. Additionally, they fail to examine the effect of their antibody on synovial macrophages, an important synovial population reported to be resistant.

4) Both introduction and discussion sections are unnecessarily long, a result of inadequate organization and internal redundancies – both sections could be shortened by 33-50%.

5) Extreme care should be given to grammatical errors appearing throughout the
manuscript.

Minor Essential Revisions:

1) Type fonts and sizes for labelling of figures and figure axes should be standardized throughout manuscript.

2) Figures 1, 2 and 4-6 are very similar in format of data presentation – giving some textual explanation within the figure as to the cell type studied (beyond doing this in the figure legend) would be helpful for readers in quickly interpreting data.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**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