Reviewer's report

Title: Sirolimus inhibits key events of restenosis in vitro/ex vivo: Evaluation of the clinical relevance of the data by SI/MPL- and SI/DES-ratio's

Version: 1 Date: 18 August 2006

Reviewer: Robert L Wilensky

Reviewer's report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Major comments:
1. This is a confusing manuscript to read and suffers from the lack of clear hypothesis or aim. Indeed, the authors have already demonstrated the effects of sirolimus on the SI/MPL ratio (Int J Cardiol) as well as the effects of sirolimus on gene expression (FASEB J). Therefore, it is difficult to understand the aims of the current studies; as a result the flow of the manuscript is difficult to follow as well.
2. Figure 1 is difficult to understand. The legend is not very illustrative and the conclusions reached by the authors are not clear. For example, it is stated that SRL decreased expression of ICAM-1 in HCAEC with a p<0.05, however, in looking at the figure there is little difference between control and the 0.01, 0.1 and 1 ng/ml SRL doses. For HUVEC the effect of 1 ng/ml SRL appears minimal. Furthermore, the authors do not comment on the apparent increase in the number of HUVEC expressing ICAM-1 but at decreased intensity in the 10,100,1000 ng/ml doses. For HMSMC I detect no differences at any SRL level. The authors should attempt to describe the findings in more detail.
3. Why was ICAM-1 chosen as a marker of inflammation rather than NF-kB, NADP(H), VCAM, etc.
4. To truly evaluate the theoretical relevance of SI/MPL and SI/DES ratios the authors need to perform an in-vivo study.
5. The Abstract and Discussion should be rewritten as they are difficult to follow.
6. How did the authors determine the presence of true post-PTCA neointima and differentiate it from “plaque-intima.” (Page 7, 3rd paragraph).
7. There does not appear to be a dose-dependent effect of SRL on migration (Page 10, 3rd paragraph, Figure 2). This lack of dose-dependency should be discussed in greater detail. The term “dose-dependent” should be stricken.
8. Figure 5: Neointima was decreased in the balloon treated group compared to the control group at 56 days. What is the explanation of this finding.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

Minor comments:
1. Abbreviations should be better defined.
2. Page 15, 3rd paragraph, last sentence. How does the presence of atherosclerosis result in senescent macrophages?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I have equity interest in Johnson & Johnson and am a member of a Scientific Steering Committee for Johnson & Johnson. I do not believe that this represents a competing interest.