Reviewer's report

Title: Discovery of potential anti-infectives against Staphylococcus aureus using a Caenorhabditis elegans infection model

Version: 1 Date: 10 September 2013

Reviewer: Frederick Ausubel

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MAJOR COMPULSORY REVISIONS:
This is a relatively straightforward and informative manuscript. My major concerns are that it is difficult to conclude very much from the screening of the extracts since the active compounds in the extracts are not identified. For this reason, I think that it makes more sense to focus the paper on the synthetic compounds. The authors have essentially performed an SAR analysis since all the synthetic compounds tested are related to the compound shown in Figure 1. The structures of the other compounds tested should be shown in a supplementary Figure. Moreover, what can be learned from this SAR analysis should be discussed.

MINOR ESSENTIAL REVISIONS:
1. Page 3 lines 12 and 13: Delete last two sentences in Methods section
2. Page 4 lines 1 and 2: I think this is an over interpretation. The compounds could target something in the bacteria that prevents them from accumulating in the intestine.
5. Page 7 line 8: Name of the company?
7. Page 13 line 4: Define how it was determined whether a hit was positive.
8. Page 15 line 9: “cloudy” is not very quantitative. Why wasn’t the OD600 measured?
9. Page 21 lines 5-14 and Supplemental Figure 2: These should probably be modified in light of the following reference that describes a liquid killing assay in which the worms are not preinfected: Kirienko, N.V., D.R. Kirienko, J. Larkins-Ford, C. Wählby, G. Ruvkun, and F.M. Ausubel (2013) Pseudomonas

10. Figure 1: This shows the backbone of the synthetic compounds. Since all the compounds tested are related to this structure, it is not necessarily surprising that the hit rate among the synthetic compounds was so high. This point should be discussed.

11. Figure 3: What is the rationale for showing selective data in Figure 3 rather than all the data?

12. Figure 4: Some of the extracts are in different solvents. The solvents by themselves would be the appropriate controls for these extracts. Why is there 0% survival in many samples but 20% in the controls?

13. Figure 5: The text states that treatment with hit compounds restores wild-type behavior, but the worms treated with compounds are smaller than the control worms feeding on E. coli. The text should be reworded accordingly and some explanation offered for the observation.

14. Table 3: The MICs for many of the compounds are very high (2000 µg/ml). Although potentially interesting as “probe” molecules, compounds with such high MICs are not suitable for drug development. This should be discussed.

**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