**Reviewer's report**

**Title:** Elevated 14,15-EET by Upregulated Cytochrome P450 2C8, 2C9 and 2J2 and Downregulated Soluble Epoxide Hydrolase Associated With Aggressive Human Breast Cancer

**Version:** 3  
**Date:** 29 July 2014

**Reviewer:** BRuce Hammock

**Reviewer's report:**

**Summary:**
This is a nice paper showing that an increase epoxides of ARA and a decrease in diols is associated with breast cancer in tissues obtained from 40 human cancer patients. A series of assays show in mRNA and protein of CYP2C8, C9, and 2J2 as well as epoxide hydrolase an increase in enzymes that increase EETs is associated with breast cancer and an increase in sEH is protective. So this is an associative study but a strong one. The paper is made stronger by an experimental study in MDA cells si RNA knockdown of P450s reduced cell migration while sEH over expression increased it. The publication is beautifully written in perfect English. The data support the conclusions and the authors are appropriately cautious about their conclusions. I suggest acceptance with minor changes.

**Minor Essential Revisions:**
Title, change ‘by’ to ‘associated with’. By implies cause which is not shown.
Eliminate use of ‘epoxygenases’, this is commonly used and miss used in the field. There are some bacterial P450s that make fatty acid epoxides exclusively. They can be called epoxygenases. Miss using the term in this context implied the P450 listed specifically make epoxides is wrong. They do omega and omega-1 OH, allylic hydroxylation and many others. It also implies other P450s do not make epoxides of fatty acids (1A1, 2D6, etc) this also is wrong.
Page 3 the statement “EETs have been linked with cardiovascular disease, diabetes and several cancer diseases.” Can be interpreted that the like is not favorable. Actually EETs reduce CV and diabetes, pain and inflammation. On cancer the EETs and sEH can be pro angiogenic or strongly anti angiogenic. See two recent papers by G. Zhang. The wording should reflect biological reality.
Page number 5, line 78 and 79: Mentioned EETs as inflammatory whereas they are anti-inflammatory.
Page number 6, line 96: "...CYP2J2 expression, and the molecule.." should be written as "CYP2J2 expression, and the enzyme..."
Immuoassay of molecules that are lipophilic with high degrees of freedom are well known to be non selective particularly in a complex matrix. The Detroit R and D antibody is no exception. I cannot say to not use these data, but the authors
should caution that the immunoreactivity they detect has not been rigorously associated with EETs or DHETs.

Be consistent in how references are referred to consumption[12]. A word [12]. And A word [12] are all used.

Do not say ‘five folds’ rather five fold. This is nutty English convention.

Page 8 ask if selectivity of antibodies was evaluated at least on SDS page. Santa Cruz Biotechnology is known for antibodies that detect multiple proteins.

Page 12. Limit to 3 significant figures.

Page number 14, line 274: reference number 10 and 3 should be placed/written in a common bracket.

Page 15. Be careful using the term ‘specific’ there is no such thing as receptor specific or specific EET receptors. One could say EET receptor or selective EET receptor. Specific is a good term to avoid.

Statistics are fine at this level. Page number 21, line 451: "P value calculated by..." should be written as "P value is/was calculated by .."

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests