Reviewer’s report

Title: Cross-species comparison of aCGH data from mouse and human BRCA1- and BRCA2-mutated breast cancers

Version: 2 Date: 29 March 2010

Reviewer: Alexander Borowsky

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Major Compulsory Revisions: None.

Minor Essential Revision: Figures are labeled incorrectly. It appears that the text figure references and the figure legends match, but the letters for the subpanels in several figures are not correct. EG fig 1 the first 3 panels across the top are collectively labeled "A" but should be A, B, and C. Figures 3 and 4 have a similar problem.

Supplementary Figure 1 is very helpful. Could it be added as an included (rather than supplementary figure) and could the same type of figure be provided for the human tumors? Lastly, is there additional phenotype data available on each of the tumors? The tumor type breakdown in SupFig 1 in the top part with p53 alone is a sort of teaser that makes me wonder about the rest of the tumors (including the ones with "unknown" histology.)

Discretionary Revisions:

I am left with some general questions that might be addressed by the substantial data in this paper. Although the data is complex, and the authors have done an admiral job of presenting it, there seems to be some underlying questions that could be answered or addressed. I will try to keep this simple also.

If: 1. p53-/- leads to increased rates of oncogenic driver mutations/CNAs, and 2. adding either Brca1 -/- or Brca2 -/- increases this rate and 3. mutations and CNAs are the primary drivers of breast cancer of all types.

Then: All breast cancer sub-types should be represented, and the sub-type distributions percentages should be the same as "spontaneous".

Alternatively: Some breast cancer sub-types may be driven by p53 and or Brca1 and or Brca 2 specific types of CNAs, while some may not. (This paper shows that WC gains and losses are more common with p53 alone, and smaller amplifications and deletions are more common with Brca1 or 2 in combination, for example).

This concept is alluded to in the introductory comments, but might be brought back in the discussion.

Some have suggested that the tumor suppressor knockout mice (esp p53-/-) are a specific class of GEM with tumor types mimicking the most common spontaneous tumors in mice, and that these are Wnt "pathway" tumors with phenotypes uncommon in human breast. Would it important to address/cite this
concept?

Myc has emerged as the major driver in common between all groups of mice and human cancers in this study. Can the mice and or humans be divided into myc amplified v. myc non-amplified groups, and does this distinction carry any phenotype or other prognostic associations? Similarly, RB loss?

A major question in this type of analysis remains. What is the rate of "driver" CNAs as compared to "passenger" CNAs?

With respect to the Aurka in Brca2, this is consistent, but does not yield a consistent phenotype. Instead, the authors point out that Brca2 carriers have tumor type distributions parallel to spontaneous. Do these finding suggest that Aurka acts in concert with Brca2 loss to hasten genomic alteration rather than being an independent driver?

I don't understand the statement that "...engineered with telomere dysfunction.... represent BETTER models for comparative oncogenomics." alternative or different perhaps, but why "better"?

Ultimately, I agree with the conclusion that differences should be taken into account, but I would be specific about tumor suppressor KO mice, the tumor types in these mice, and draw the distinction from oncogene KI mice which do (may?) have more specific phenotypes (and may also require critical driver "hits" to complement the oncogene).

Additional Discretionary Revision Ideas:
It would be helpful to label the locations of the myc, rb, aurka (and maybe some pertinent negative like erb2) on the cgh plots. This info is in the tables, I guess, and the tables are interesting to scan through, but they make me cross-eyed.

Level of interest: An exceptional article

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

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