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ROR1 Can Play a Role in Breast Cancer Cell Growth Datoya Brown Tissue Culture & Hybridoma Technology BTCH 440-01 Dr. Lawrence Flowers 27 November 2012 Introduction Receptor tyrosine kinases (RTKs) are known to be key regulators of normal cellular processes such as differentiation, migration, proliferation and survival, but they also have a critical role in the development and progression of many types of human cancers. Before the published work concerning ROR1 was available it was unknown whether other cancers besides leukemia expressed ROR1 or whether its expression had functional and clinical significance. This paper investigated whether ROR1 had any consequence to breast cancer. Using a high-affinity mAb specific for ROR1 (4A5) to examine human breast cancers, this study demonstrated that ROR1 is expressed in human breast cancers and is indicative of potential targets for breast cancer therapies. Building on prior research the authors affirmed that the ROR1 associations with human breast cancer contributed to tumor-cell growth and survival via the activation of PI3K, AKT, and cAMP-response-element-binding protein (CREB). In lieu of reading this article for review, it is apparent that certain deficiencies are observed in context composition. In the initial remarks authors do not define any relevant terms that are used throughout the paper. There is essentially not enough background information given to orient the research. Referencing prior research did however, serve as slight insight. The references given are noted in the references section of paper to guide further reading into the subject matter. To dually note, the majority of the references are recent, being published from a year range of 1992 to 2011. This information is important because the most recent data also employs

established precedents. These references are used mainly in support of the research, and not necessarily any information that could be used for negation. Authors did not clearly state a specific hypothesis to be tested for the study. Although not directly mentioned the expected outcomes/results could be derived from the prior research cited using ROR2 knockout mice and ROR1-deficient mice. Yet, human disease for the ROR protein mutation was nonexistent. Elaboration of the aforementioned could have illuminated the appropriate known information regarding human disease. Materials & Methods Research conducted was reviewed and approved by an appropriate Institutional Review Board (IRB) for the use of human subjects and also experiments using mice were also approved of following relevant guidelines. The experimental design employed the use of various methods fully described in the context of the article. Cancer cell lines were cultured with appropriate methods, the control used was not fully described in this section however was listed in results as normal breast tissues. Immunochemistry did not note whether fresh frozen tissues were used. Using immunochemistry, the authors did not note how the level of ROR1 binding was calculated, only how it was scored. The blinded studied in regards to animal genotype would have been more sufficient if genetics could have been integrated. With methods described the only other methods that stated the use of a control is flow cytometry and expression microarray analysis. Authors did not list completely full wording of the many abbreviations listed in this section. A valued recommendation would be to use all abbreviations in full the first time they are used in the manuscript. All references were given for methods and procedures not described in detail for prior studies. Experiments listed in

this section could be repeated with the information given. Results The results are presented appropriately given the limitations inherent in the observational nature of the study. However, the limitations, specifically unanswered questions regarding why there are differences between patient ROR1 levels need to be discussed in more detail. In Figure 1, authors make note of ductal breast adenocarcinoma staining from patients, but neglect to mention other breast regions that are predisposed as cancerous regions. When examining expression of ROR1 association with adverse disease characteristics authors note they promptly let the reader know that the breast cancer cell lines that they were studying were found to lack a certain hormone receptor essential for women, which was an estrogen-receptor. This is indicative because it could lead to better prognosis for patients who are suspects or susceptible to the disease Currently, this section of the paper is not poorly written, but the editing skills are poorly presented in the material. In the third sentence of the results section, there is a complete separation between what is presumably supposed to be “…ROR1 comparable to that of…" Advice for the authors of this article would be to send it back to the editors and tell them it is not " finished" enough to be considered for full publishing. Even if they had a competent editor make corrections, I find it difficult to believe that many readers would take the time to read through the paper with inadequate background to understand the results. The description of the findings from the luciferase assay was incomplete and shortened only form conservation of text. Overall figures are accurately displayed and labeled, Figure 2C could however be enlarged for better viewing of significant points. The data presented in this section was

appropriately analyzed statistically via the use of standard Ï‡2 test, two-tailed Students t-test using log ratios, ANOVA using a designated software program for provided accuracy. The significant value used was a standard scientific p-value of 0. 05. When examining the role of Wnt5a in ROR1-dependnet activation of PI3K/AKT/CREB signaling and enhanced tumor growth authors listed no information on dosage or duration of use. The summation of the results support the original purpose of the research, which was to determine if in fact ROR1 would be a factor in human disease as it was found associated in mice. This article proves to be at the forefront of recent studies validating curative measures for a disease that has stricken numerous populations. Discussion Overall this manuscript is a comprehensive and well-written paper concerning protein insufficiency in developing breast cancer. One could argue that the initial sections dealing with the pathophysiology through the clinical manifestations of ROR1 levels (as well as most of the tables and figures) could be deleted in the interest of journal space considerations since most of this is numerical data that could be listed instead of illustrated.. On the other hand, it makes the paper comprehensive and more useful to the relatively inexperienced journal article reader. The remainder of the paper hits the key literature review with respect to the potential treatment aspects for studying ROR1 and provides reasonable recommendations for practice based on this literature. The study addresses a novel question of significant importance, is well written, and uses largely appropriate methodology. Authors utilized different clinical manifestations for patient sampling of cancerous breast tissues. Differentiation of tumors substantiated and made distinction between facts

and speculation of whether the ROR1 was localized due to unknown sources. General conclusions drawn from the authors were supported and the aforementioned results section is categorically interpreted. With findings that silenced ROR1 expression in breast cancer cell lines could be used to evaluate its function on tumor, cancer cells were more sensitive to spontaneous apoptosis and had an impaired cell growth. Based upon these collective results presented in the context of the manuscript indicate that a substantial subset of human breast cancers expresses ROR1 and such expression may be associated with aggressive disease. Due to selective expression of ROR1 by neoplastic cells and its apparent role in promoting tumor-cell growth, ROR1 may serve as a potential target for development of anti-cancer therapies. This ultimately has significant impact on the scientific community warranted publication References Zhang S., Chen L., Cui B., Chuang H-Y., Yu J., et al. (2012) ROR1 Is Expressed in Human Breast Cancer and Associated with Enhanced Tumor-Cell Growth. PLoS ONE 7(3): e31127. doi: 10. 1371/journal. pone. 0031127