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Continued use of MDA-MB-435, a melanoma cell line, as a model for human breast cancer, even in year, 2014

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It is a matter of significant concern, that the articles which refer MDA-MB-435 cell line as a breast cancer cell line are still being published in peer reviewed journals of international repute, even in 2014. Questions have been raised, for the last 14 years or so, about its origin and caution has been advised against using the cell line as a model for breast cancer.^{1–5} The origin of the cell line, notwithstanding few contradictory reports,^{6–8} has been established to be of melanoma.

The MDA-MB-435 cell line was originally derived from pleural effusion of a female breast cancer patient in 1976 at MD-Anderson, Houston, TX, USA. Ever since the 'MDA-MB-435' cell line has been in use in established laboratories as a model for human breast cancer, worldwide. However, gene expression studies of melanoma and breast cancer,^{1,2} CpG island promoter hypermethylation,³ SNP array investigation,⁹ and miRNA expression,¹⁰ have determined that the available MDA-MB-435 cells are of melanoma origin and not that of breast cancer. Further, Rae *et al.*,⁴ in a more exhaustive study, employing whole battery of molecular techniques (karyotyping, comparative genomic hybridization, microsatellite polymorphic markers, bioinformatics analysis of SNP, and gene expression data) on the MDA-MB-435 cells obtained from repositories and various research laboratories, concluded that 'All currently available stocks of MDA-MB-435 cells are derived from M14 melanoma cell line', implying the usage of the cell line as a model for breast cancer as erroneous. These studies, unquestionably determined that the currently available MDA-MB-435 cells are not the original MDA-MB-435 cells obtained from the breast cancer patient but are misidentified M14 melanoma cells, and the original stock of MDA-MB-435 breast cancer cells were lost.^{4,5,11} Consequently, The American Type Culture Collection (ATCC, <http://www.atcc.org>) and The German Collection of Microorganisms and Cell Cultures (DSMZ, <http://www.dsmz.de>) characterized the cells and reclassified them as melanoma cells, sometime in 2012. Corrections were also made on the websites of other cell repositories (European Collection of Cell Cultures (ECACC, <http://www.hpacultures.org.uk/collections/ecacc.jsp>), The Japanese Collection of Research Bioresources (JCRB, <http://cellbank.nibio.go.jp>), and RIKEN Bioresource Center Cell Bank (RIKEN, <http://www.brc.riken.go.jp/lab/cell/english/guide.shtml>)).

However, a quick Pubmed search revealed that 36 research studies that mistakenly used the MDA-MB-435 cell line as a model for breast cancer are published in international peer reviewed journals, such as: *Nature Cell Biology*,¹² *Nature Communications*,¹³ *Journal of Experimental and Clinical Cancer Research*,¹⁴ *Cell Death and Disease*,¹⁵ *PLoS One*,¹⁶ *Molecular Oncology*,¹⁷ *Archives of Pharmacol Research*,¹⁸ *Acta Pharmaceutica*,¹⁹ *Tumor Biology*,²⁰ *Journal of Molecular Medicine (Berl)*²¹ etc., even in 2014. The search also revealed publication of 247 such articles between 1 January 2008 and 12 December 2014, even after the MDA-MB-435 cell line was declared to be a melanoma cell line, in 2007. A total of 890 published studies have used the cell line as a model for human breast cancer till date (Pubmed, 12 December 2014). Some of the notable studies of recent past have used the MDA-MB-435

cells for investigating: (i) anti-proliferative effect of 2-methoxyestradiol which is in phase I/II clinical trials for treating breast cancer,²² (ii) effect of herceptin on the breast cancer cells, using MDA-MB-435,²³ (iii) EphB6 receptor effect on invasiveness of human breast carcinoma cells,²⁴ (iv) a protein target for immunotherapy of triple-negative breast cancer,²⁵ and (v) anti-PTHrP antibody mediated enhancement of anti-proliferation ability of cancer drugs,²⁶ which is now established to be a melanoma cell line. Such a continued mistaken use and acceptance of such articles for publication in scientific journals adds to the confusion and the questionable data generated using inappropriate models continue to populate cancer research data bases, used by academicians, researchers and pharmacologists.

In addition to the MDA-MB-435 cell line, various other non-breast cancer cell lines are also being used to study breast cancer.²⁷ By year 1999 itself, 45 cell lines were reported to be cross contaminated by the originators.²⁸ Since then, the list of the cross-contaminated/misidentified cell lines has grown substantially, as indicated by the list on the Database of Cross Contaminated or Misidentified Cell lines.²⁹ Nevertheless, employing mischaracterized/misidentified cell lines to study human diseases, particularly cancer, cannot be sporadic and publishing such misleading data should and must be contained. Continued dissemination of faulty data through publications, inspite of few initiatives taken up by certain journals (*Breast Cancer Research*, *Cancer Research*, *PNAS* etc.) to discontinue the usage of unauthentic/misidentified cell lines indicates a lack of concerted effort and underscores the need for a cohesive, coordinated and comprehensive approach as opposed to isolated steps by few journals.

In view of the widespread use of cell lines in understanding physiological pathways and pathophysiology of human diseases, we call upon the editors of the concerned journals to form a consortium along with the major cell depositories, funding agencies, and cancer researchers across the globe. The consortium can undertake the task of re-characterizing/re-classifying and establishing the true origin of the cells, once for all, taking advantage of the latest molecular biology, proteomics and metabolomics techniques and bioinformatics tools. Once the identity of the cell lines is determined conclusively and the cell lines are re-classified, appropriate guidelines may be framed and publicized. Although, such task is onerous, bringing such awareness about the validity of the cell lines will be of importance and make a significant contribution to cancer research. In the meanwhile, it may be incumbent on the Journals, to stop accepting studies that have used incorrect cell line model to investigate a disease and to compile a list of published studies that have used wrong cell lines to study disease, and circulate and publicize the list widely.

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