

**ID 00504152/Editorial Board Member**

February 23, 2014

Dear Editor,

We would like to thank you for the thorough and instructive review of our manuscript which has further improved it.

Please find enclosed the edited manuscript in Word format (file name: miRNAs and breast cancer\_final - edited8311).



**Title: Micro-RNAs as promising clinical biomarkers and therapeutic targets in breast cancer: quo vadis?**

**Authors: Gerasimos Socrates Christodoulatos, Maria Dalamaga**

**Name of Journal: World Journal of Clinical Oncology**

**ESPS Manuscript NO: 8311, invited mini-review for the Special issue celebrating the 5th anniversary of WCJO (2): Breast Cancer**

The manuscript has been improved according to all Reviewers' suggestions.

- 1) The format has been updated. **REVISED.**
- 2) Revision has been made according to the Reviewers' and Editor's suggestions. **REVISED.**

### **Responses to Reviewer #1**

Review by Gerasimos Socrates Christodoulatos, Maria Dalamaga "Micro-RNAs as promising clinical biomarkers and therapeutic targets in breast cancer: quo vadis?" describes in great details recent achievement in our understanding of relationship between miRNA expression and breast cancer development and progression. Especially they concentrated their attention on differential expression of miRNA during particular steps of development of certain type of Breast Cancer that beginning to be a valid base for building a new diagnostic tools, particularly based on miRNA sending outside of Breast Cancer cells to the blood plasma. Unfortunately missing the full understanding of pluripotential mechanism of action of many miRNA still preventing to be used as a tools for cure of Brest Cancer disease but has quite a promising future as diagnostic tools.

Thank you for finding this manuscript interesting, detailed and promising.

### **Responses to Reviewer #2**

In this review, "Micro-RNAs as promising clinical biomarkers and therapeutic targets in

breast cancer: quo vadis?", Christodoulatos and Dalamaga present a detailed overview of the role of microRNAs in breast cancer etiopathogenesis, providing results from a large series of studies. In addition, they described microRNAs promising role as non-invasive circulating biomarkers with diagnostic and prognostic significance, treatments response predictors and therapeutics targets in breast cancer patients. While this should be undoubtedly a comprehensive work, as a minireview it should be probably shorter giving more relevance to the potential use of miRNAs, as clinical biomarkers and therapeutic targets, rather than listing so many studies.

Thank you for finding our manuscript a detailed overview of the role of microRNAs in breast cancer etiopathogenesis, providing results from a large series of studies. Given that the journal WJCO for this special issue does not have any limits in word count and Tables as seen also in the inviting letter, we have decided to present this manuscript in its present form.

### Major comments

1. The manuscript seems to be too long, especially at the beginning of each paragraph, where several sentences are redundant.

We deleted redundant sentences especially at the beginning of paragraphs. Please note also that the journal WJCO for this special issue does not have any limits in word count and Tables as seen also in the inviting letter. **REVISED.**

2. The paragraph 2.2.1 "Aberrant expression of miRNAs in BC predisposition", is unclear and should be revised as it apparently mix to different concepts that are: a) the fact that many miRNAs are located in "cancer-associated genomic regions" and so they are often disrupted, in somatic cells during tumorigenesis; b) the fact that many SNPs in miRNA genes or in miRNA target genes in germline cells -- and independently from their possible/putative functional effects -- have been analyzed in association (case-control) studies with some resulting associated with increased/decreased breast cancer risk. A separate paragraph exploring "concept b" and possibly titled "SNPs in miRNA genes or miRNA target genes and genetic susceptibility to BC" can be added (see as an example Ryan et al., 2010 Nat Rev).

We thank you for your interesting comment. A separate paragraph exploring "concept b" and titled "SNPs in miRNA genes or miRNA target genes and genetic susceptibility to BC" was added as suggested based on the recommended article by Ryan et al., 2010 in Nat Rev Cancer 10 (6): 389-402. This article was cited in the list of references (#29). **REVISED.**

3. A Table (or more than one, if necessary) including information of the entire Section 2 has to be added. It needs to list all miRNAs that are deregulated in breast cancer, the pathway/s they affect, a description of where/when they affect tumorigenesis (predisposition, initiation, progression or metastasis) and references. This will certainly make easier to the readers obtaining desired information.

4. Similarly, it would be useful to add a Table summarizing information of sections 3 and 4.

Thank you for your suggestions. Since our article is a mini-review and without any

restrictions regarding Tables or Figures, we preferred not to include any Tables but one original figure presenting main mi-RNAs that are deregulated in breast cancer.

### Minor comments

1. The sentence 'MiRNAs are short, non-coding RNAs of approximately 20 to 25 nucleotides in length that are transcribed either from independent genes or from exons or introns of protein-coding genes' (line 15, page 5) should to be moved after the following one, that is 'Since their initial discovery in 1993 during a study of the gene lin-4 in *Caenorhabditis elegans*, more than 2000 molecules have been determined in humans so far, regulating the expression of almost 30% of genes'.

Corrected as suggested by the Reviewer. **REVISED.**

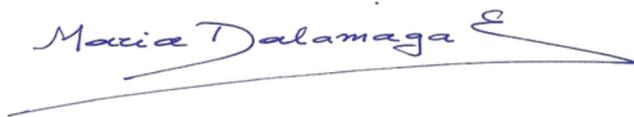
2. The word 'oncogens' is misspelled (page 7, line 9).

Corrected as suggested. **REVISED.**

3. Two consecutive sentences start with 'Finally' (pag 13, line 28 and 31). These need to be revised.

**REVISED** as proposed by the Reviewer.

Sincerely yours,

A handwritten signature in blue ink that reads "Maria Dalamaga" followed by a stylized flourish.

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