

MS ID#: 1452

MS TITLE: Cell-derived Extracellular Vesicles Open New Perspectives for Cancer Research.

### Reviewer 1:

In general, this is a well written review of an expert in the field of micorvesicles with a long experience. Its focus is on extracellular vesicles (EV) for cancer research. However, there are some major and some minor points that need to be addressed to further increase this review.

Major points:

1. The title is Title is a bit misleading, This review's focus is on the clinical impact on EVs. Maybe the title should include that one of the main goals for EVs research is a future impact in therapy.
2. To make the content more understandable, a figure with an overview of the different types of EV would be helpful.
2. As stated in the abstract, a major goal for future usage of EVs both as therapeutic agents and diagnostic markers should be to ensure a standardization of EVs purification and nomenclature. A brief summary of what could be done about that (maybe even a table or figure) would be helpful. A major drawback in the understanding of EVs is the heterogenous nomenclature which makes it difficult for the reader what subkind of EV is talked about (microvesicles, liposomes, EVs, etc)

Minor points:

The readability of the paper is good. It is well written and understandable. However, readability might benefit from a shortening of some sentences.

Abstract:

Page 1; Line 5: This sentence is should be : Moreover, these tumor EVs are conveying specific molecular components, proteins, mRNAs, miRNAs and DNA fragments, some of which actively participate to many cancerization processes in the near or remote tumor environments.

Page 2, Line 22; I do not understand the sentence: The comparison between cancer cells and normal cells should be much easier and worthwhile at the extracellular vesicle level than at the cellular level.

Page 3, Line 13: Should be: State of the art

Page 4; Line 8: Please short the sentence to make it more readable.

Page 4; Emergence of extracellular vesicles in cancer research. This abstract is obsolete. The sentences are too long and need to be revised. Maybe, to express the importance and the growing research in this field, an

overview of papers published on PubMed on this field would be interesting to graphically show to growing impact.

Page 7, Line 16: Please explain PTEN the first time it appears.

Page 9: What are DU 145 prostate cancer cells?

Page 10, Line 2: What is meant by "a higher statistics"?

Page 10, Line 23; "In as much"?, please revise the sentence to make it more understandable.

As a conclusion, this is a good review about an important field in cancer research.

## **Reviewer 2:**

The review Cell-derived Extracellular Vesicles Open New Perspectives for Cancer Research nicely summarizes the recent literature about vesicles, their properties, contents and how vesicles can play a role in cancer progress, as biomarker and as therapeutic tool. The review is well written and all various subjects are well discussed.

Minor remarks:

1 In some sentences the author uses popular language, for instance: first line of the introduction "when I was a young scientist" (pg 2); "in the three kingdoms (pg 3); ""The fight is then beginning" (pg 8). Please remove this popular language because it is distracting.

2 The manuscript is very well written, but two sentences are difficult to read. Please rephrase:

- pg 4. First sentence of Emergence of Extracellular vesicles in Cancer Research: "The increasingly.....oncogenic process"

- pg 5. 2e alinea line7: "Indeed..... body fluids"

3 Extracellular Vesicles is not always shorten to EVs: page 4 line 13, page 9 line 2, page 10 line 29, page 11 line3.

4 On page 4, last sentence, there is written about EVs concentration in plasma, but the levels are given of EV in serum. Is this a mistyping, and do the author means plasma instead of serum in the first sentence of page 5?

5 Page 5 last sentence: microRNA must be miRNA

### Reviewer 3:

The review reads well. Several minor points to be addressed.

1. A few redundancies could be removed when space is a problem. The abstract contains already many details that also appear in the text. It might be shortened and reduced to the main statements.
2. The author did not mention the size, phenotype, concentration and morphology observed by Arraud N in Journal of Thrombosis and Haemostasis in plasma which was more relevant than in serum due to platelet activation.
3. page 6, there are couple of too short paragraphs (only one sentence). Could these be linked together.
4. - Table 1: The "mechanism" is missing in couple of cases. If it is not known, should be written "not known" of "not studied".
5. I suggest to authors to introduce the role of EV in cancer stem cells, a new field of research that growth in importance, as in :

Papi A, De Carolis S, Bertoni S, Storci G, Sceberas V, Santini D, Ceccarelli C, Taffurelli M, Orlandi M, Bonafé M. PPAR $\gamma$  and RXR Ligands Disrupt the Inflammatory Cross-talk in the Hypoxic Breast Cancer Stem Cells Niche, Journal of Cellular Physiology, Vol.229, 11:1595-1606, 2014.

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