

Extracellular Vesicles in Metastasis, and their Evolutionary Aspects

Scott Bonner

DPhil Student, Prof M Wood Lab

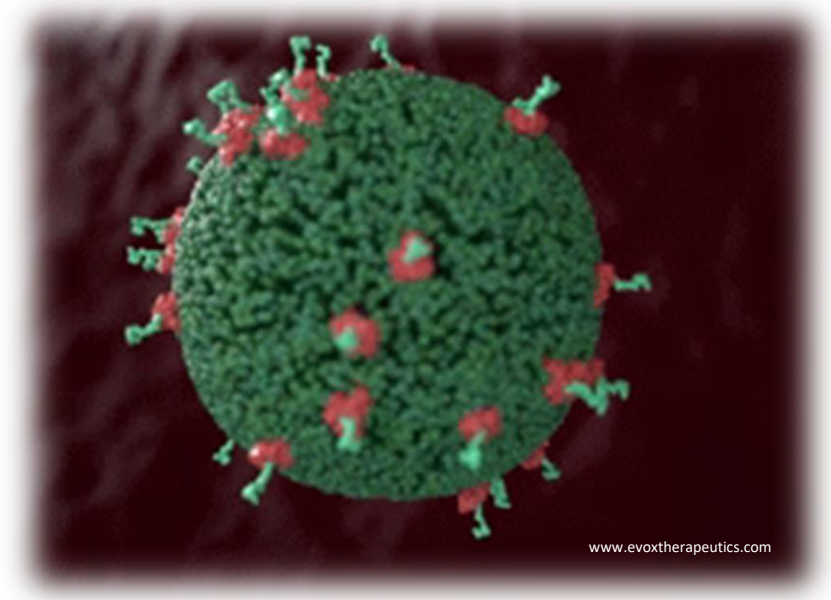
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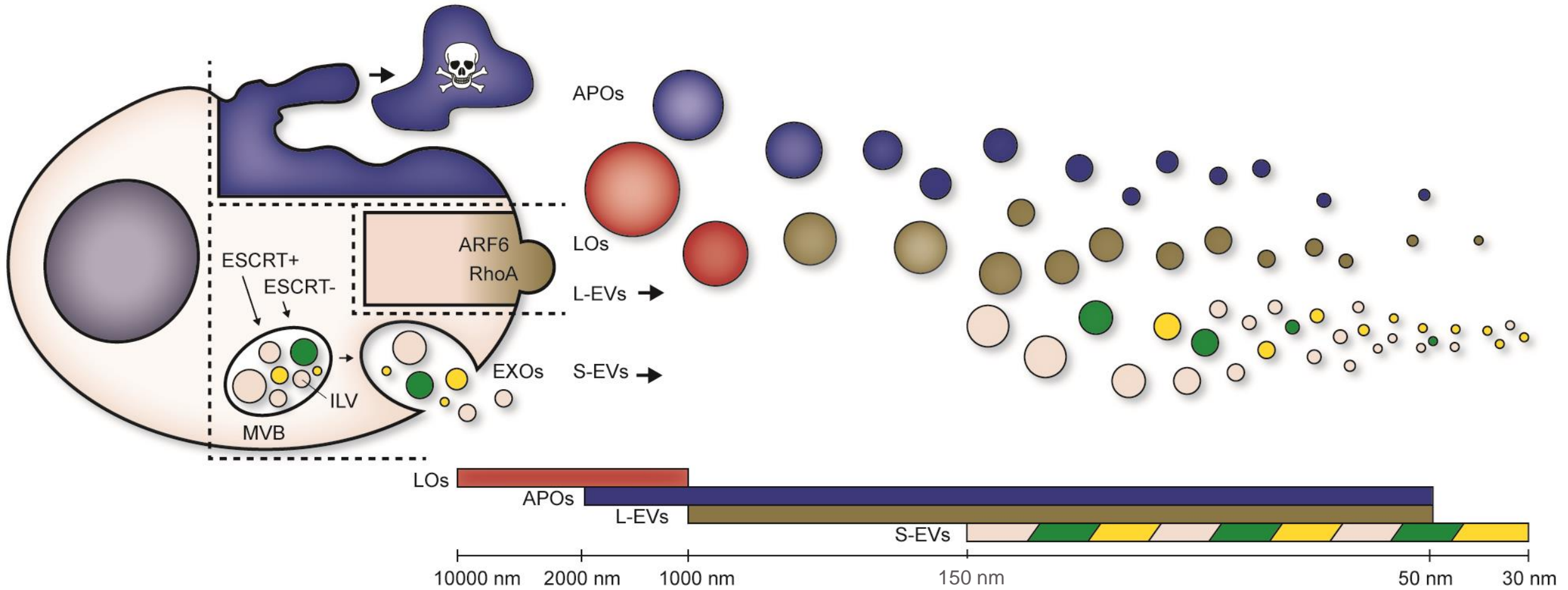
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Extracellular vesicles

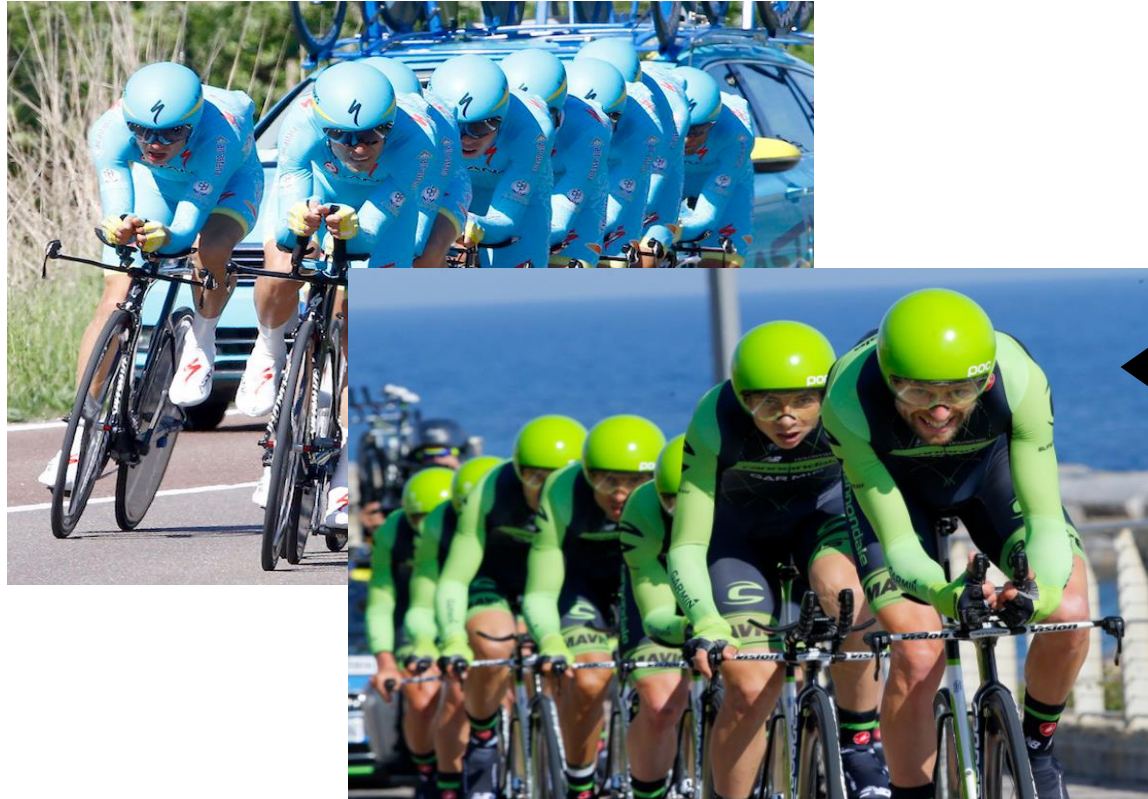
- Extracellular vesicles (EVs) – Nanoscopic, lipid bilayer enclosed membrane vesicles.
- Released by cells.
- Originally thought to be a mechanism of eliminating waste from cells
- Important mediators of intercellular communication.
- Attractive biomarkers and targeted biotherapeutic platform.





Willms et al., 2018; doi.org/10.1038/srep22519

EV heterogeneity



EVs according to us



EVs according to nature

EV heterogeneity

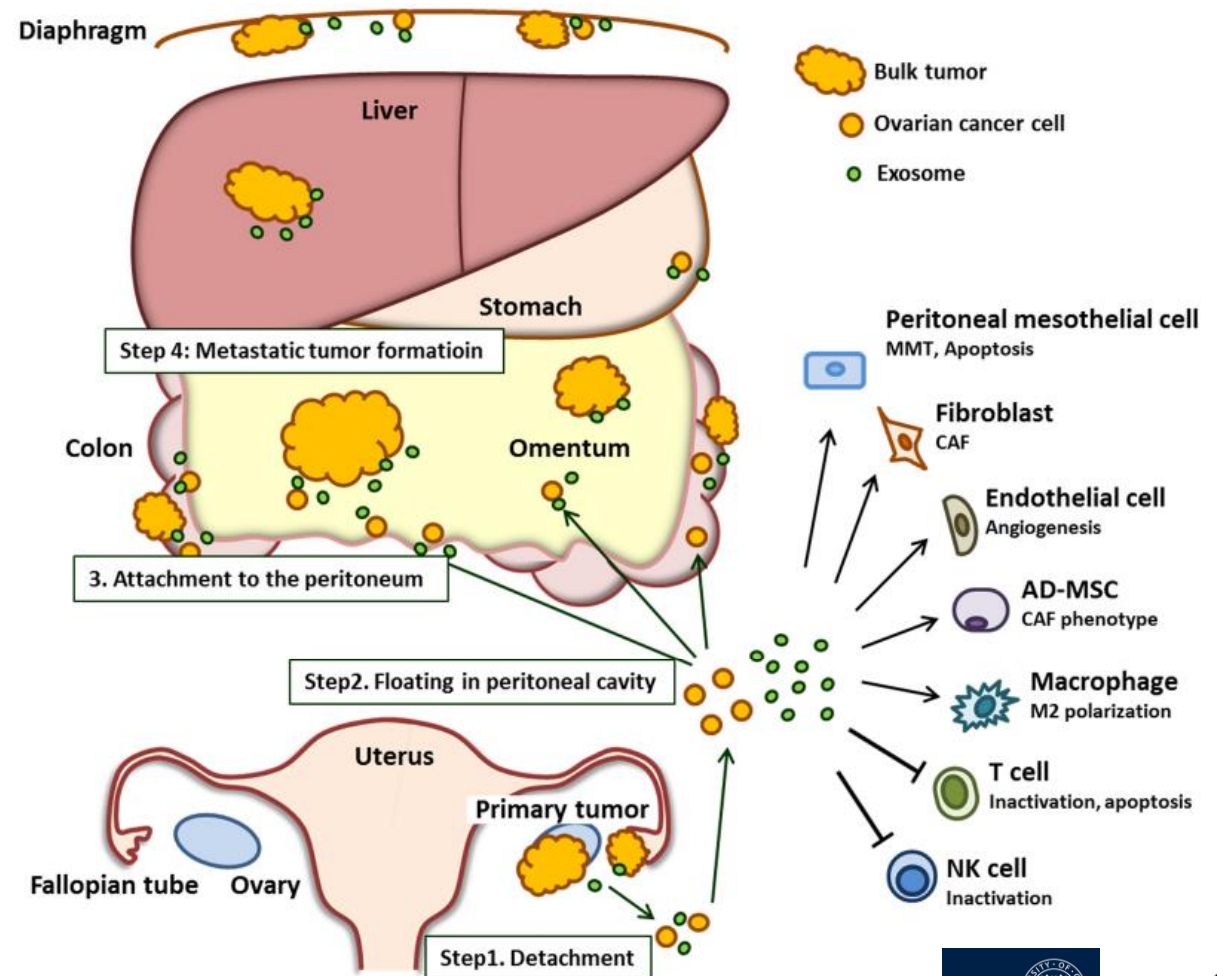
- Secreted EV populations are vastly heterogeneous
- EVs exert diverse biological effects on recipient cells.
- Sources of EV heterogeneity:
 - Cell type
 - Cell state
 - Biological processes
 - Different biogenesis routes
 - Stochastic effects
- Heterogeneity could impact the intricate biological processes underlying cancer biology.



Role of EVs in cancer

- EVs involved with influencing primary tumour microenvironment and at distant sites to facilitate metastasis.
- In ovarian cancer (OC) direct dissemination of tumour cells into the abdominal cavity through peritoneal fluid.
- Adhesion / tumour cell attachment of exfoliated OC-cells to mesothelial cells, followed by establishment of metastatic growths.

Nakamura *et al.*, (2019). *Cancers*, 11(8), 1147.



Putting the EV into EVolution

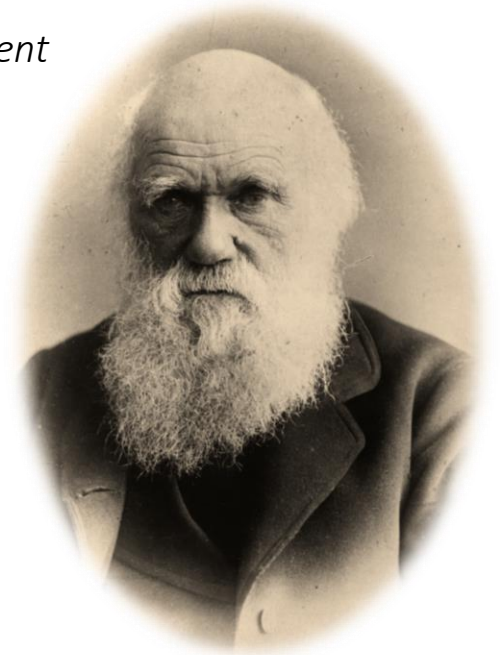
- What do extracellular vesicles have to do with evolutionary biology?
- The story of EVs predates the 20th century.
- Charles Darwin predicted the existence of cell derived particles in his rejected theory of “pangenesis” though with a different context...

*“Physiologists maintain, as we have seen, that each unit of the body, though to a large extent dependent on others, is likewise to a certain extent independent or autonomous, and has the power of increasing by self-division. I go one step further, and assume that each unit casts off free **gemmules** which are dispersed throughout the system...”*

“...when supplied with proper nutriment, multiply by self-division, and are ultimately developed into units like those from which they were originally derived.”

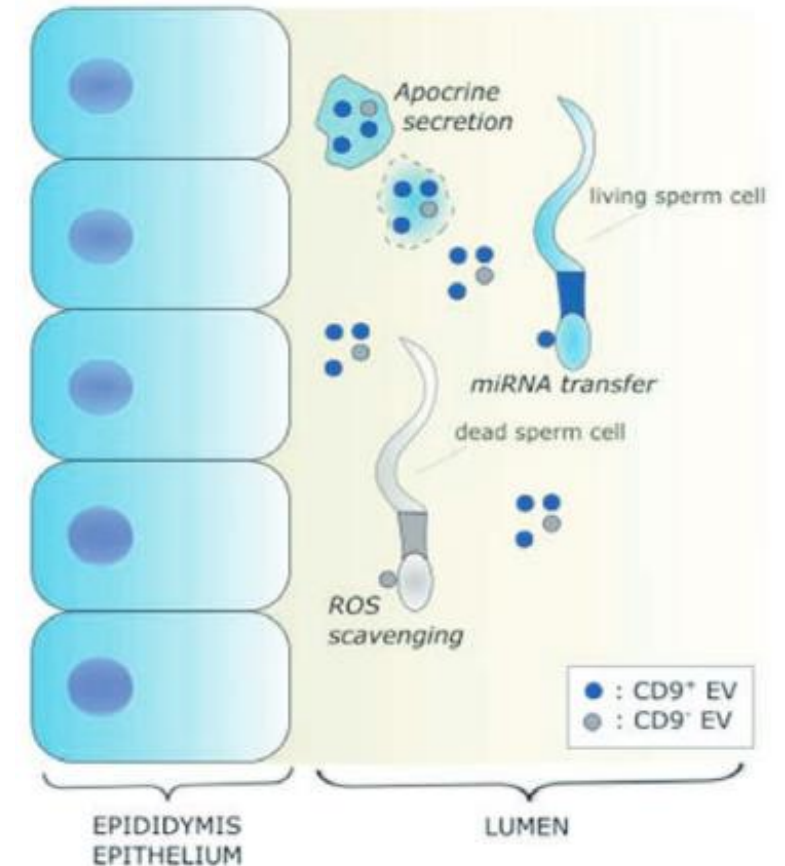
“They are collected from all parts of the system to constitute the sexual elements, and their development in the next generation forms a new being.”

Darwin, C. R. 1875. *The variation of animals and plants under domestication*. London: John Murray. 2d edition. Volume 2.



Putting the EV into EVolution

- Darwin's Pangenesis theory of inheritance was wrong.
- However, Darwin's theory should be credited for the concept of cell-cell communication through extracellular molecular carriers.
- EVs have also been suggested to deliver their cargoes between somatic cells and germs cells...

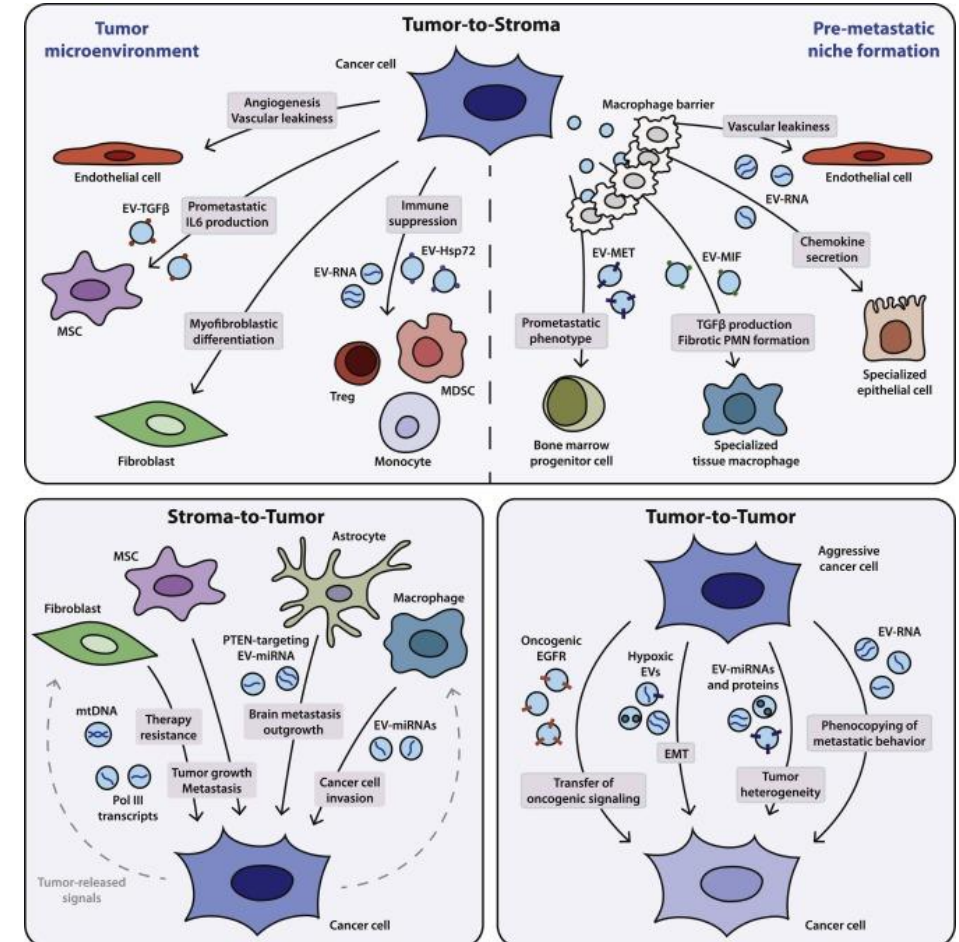


Maciel and Mansuy, 2019; <https://doi.org/10.2533/chimia.2019.356>

Putting the EV into EVolution

- The role of EVs in cancer demonstrates some of Darwin's ideas on a somatic level.
- While the potential effects of EVs on the germ line, and thereby evolution, are being investigated, EVs exhibit quasi-evolutionary processes in cancer growth and development.
- Heterogeneous EV populations will have differing effects on these processes

Bebelman et al., 2018; <https://doi.org/10.1016/j.pharmthera.2018.02.013>



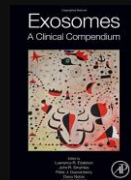
Conclusion

- Extracellular vesicles (EVs) are heterogenous, cell derived nanoparticles that are important mediators in physiology and pathophysiology.
- Subpopulations of EVs exist that are phenotypically and functionally distinct from one another.
- In ovarian cancer EV subpopulations seem to play distinct roles in the establishment of pre-metastatic niches and subsequent metastatic growths.
- EVs can be observed to have quasi-evolutionary effects in a cancer model and may yet prove to influence the germ line and inheritance.

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Scott Bonner MBio, DPhil Student
Prof. Matthew Wood's Lab,
University of Oxford, Department of Paediatrics,
Email: scott.bonner@wolfson.ox.ac.uk
Linkedin: [linkedin.com/in/scott-bonner-38a881106](https://www.linkedin.com/in/scott-bonner-38a881106)



Edelstein, L.R., Smythies, J.R., Quesenberry, P.J. and Noble, D. eds., 2019. *Exosomes: A Clinical Compendium*. Academic Press.



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