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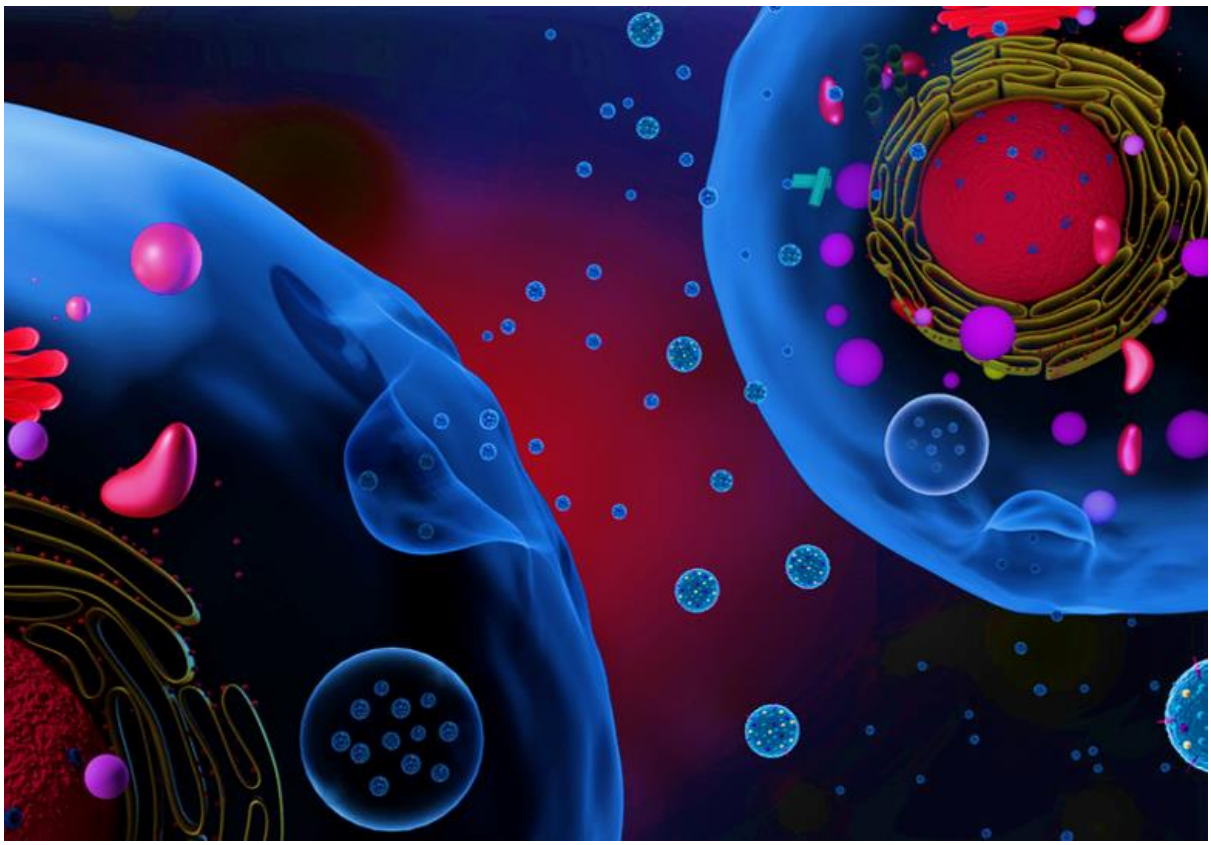
Novel Exosome Technologies Are Going to Transform Healthcare



Neighbouring cells secreting exosomes into the extracellular matrix

A new hope for complex diseases

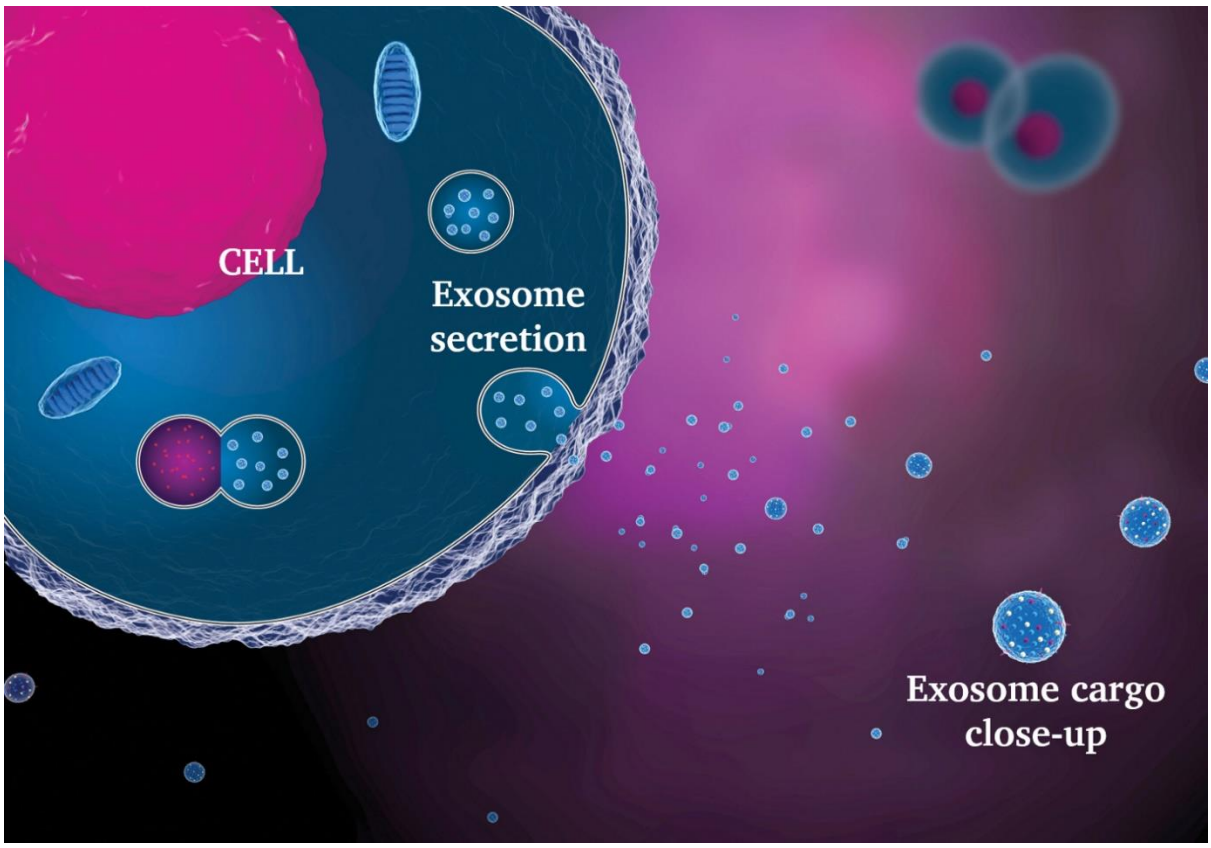
The year is 2029, my mother has just been diagnosed with ovarian cancer after a routine blood test. Some of her blood exosomes were found to carry cancer-specific cargo. Fortunately, her tumour signature is identified quite early and she benefits rapidly from ready-to-use targeted exosome therapy. It inhibits the growth of her tumour, boosts her tumour immune response and resets her health state back to normal. We are more than relieved knowing that she

will be able to continue seeing her grandkids as she used to. In 2021, she would have undergone frequent and painful cancer therapies with uncertain outcome.

Ten years later, she is diagnosed with an early stage of Alzheimer's Disease. Some of her brain-derived blood exosomes indicate an upcoming and progressive memory loss. Off-the-shelf personalized exosome therapy promptly restores her damaged brain cells to maintain her cognitive abilities. I am so happy that she will be able to celebrate (and remember) her granddaughter's 18th birthday in a few years' time.

This is the future I imagine sometimes after long months of demanding work in the lab. These are dreary situations that could be addressed by some of the novel exosome technologies we have been working on. As of today, there are still too many families struck by tragedy due to random biological events that we cannot really control. The good news is that we are now reaching an inflection point. I believe that we can change things for our loved ones and our future selves before the decade is out.

What are exosomes?



Cell secreting exosomes into the extracellular matrix (with legend)

A human is made of 30 trillion cells in average. Think of cells as cities with outer walls. Not only do they interact frequently with neighbouring cities for commerce but also with other distant cities, either in the same country (organ level) or abroad (other body parts). Parts of this large ecosystem influence each other to their own benefit or, sometimes, detriment.

Exosomes are similar to secured shipping containers (thanks to a lipid bilayer envelope which protects inside components from enzymatic destruction) of various sizes (50–150 nm), and loaded with cargo (DNA, RNA, proteins) that are carried between cities by

autonomous vehicles (moving via fluid diffusion). Their features may depend on the terrain, distance and characteristics of the potential receiver(s). Cells constantly send them outside their membranes for various biological purposes. These shipping containers may carry their own passes (specific surface markers) to access certain cities as well as potential identification for random identity checks by national police (immune system). Along the way, some regular travel companions may tag along (protein corona).

As opposed to cellular cities which have enough machinery to be self-sustainable, exosomes cannot live by themselves or replicate, as they are just a collection of materials ready to be used by another city or simply destroyed. Sometimes they may simply carry a message to another city and continue their journey (intercellular signalling). Inversely, emitting cities receive various sorts of material on a regular basis. Targeted cities incorporate cargo and modify their activities to promote or prevent social change (biological activities).

Exosomes are shipping containers for commerce between cells.

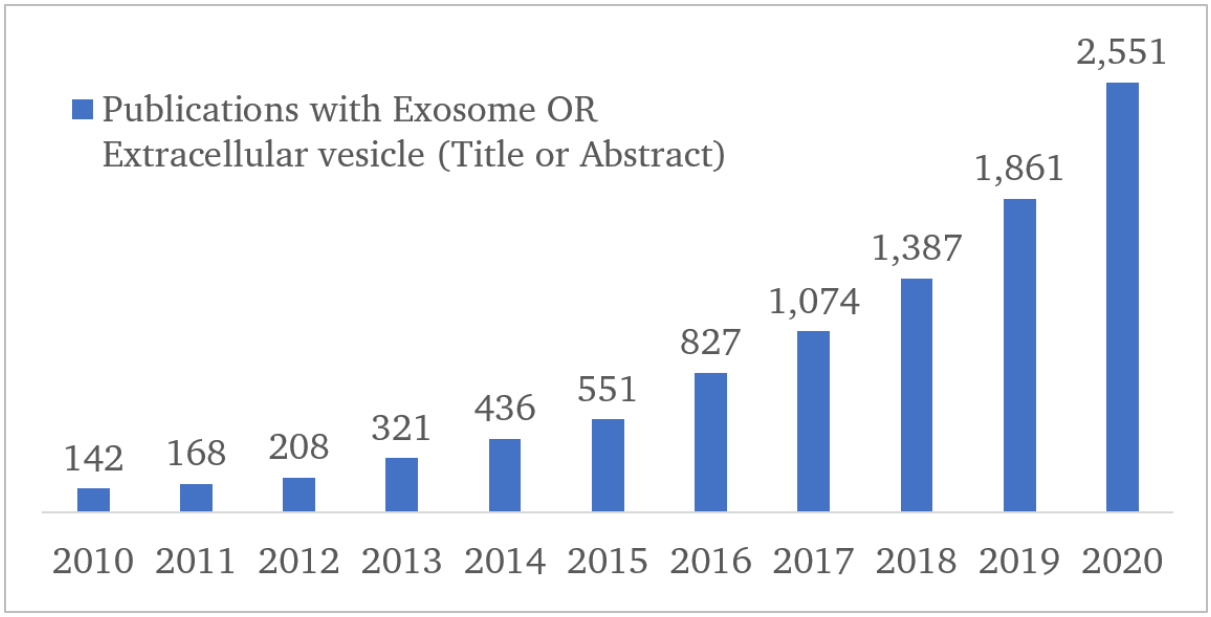
Until recently, researchers believed that exosomes were simply waste bins to be removed in order to maintain the city's balance (homeostasis) but they gradually realized that many of them are in fact important trading systems across the entire globe (body). They can travel across any terrain (such as extracellular matrix, bone, tissue, vessel and even the blood-brain-barrier) and are found in

every biofluid. This fascinating discovery has now been well evidenced by studies over the last few years.

We still don't fully understand why and where some cargos are loaded in the container versus others and precisely how this happens. On the receiving side, we still wonder how this is thoroughly unloaded and used, especially as it may vary depending on the container's sizes, cargo type and 'entry pass' mechanism. There is still much room for learning and great opportunities ahead.

Why now?

First references of exosomes date back to the 1980's and it was only in 1996 that a tiny proportion of the academic community realized that these may be more than just cellular waste. The real breakthrough was in 2006-7 after the dual discovery that exosomes transport and transmit RNA from secreting to receiving cells. In the following decade, the field grew exponentially. Novel technologies were introduced (such as Nanoparticle Tracking Analysis in 2011 or improved Flow Cytometry in 2015) allowing more detailed analyses which, altogether, helped to improve our biological understanding.



Exosome publications per year based on PubMed

Yet, the technological complexity of selecting and analysing exosomes has hampered the field. There are indeed many confounding factors, such as lipoproteins and other circulating particles, which are difficult to distinguish from each other. Exosomes are also very heterogeneous. ISEV (International Society for Extracellular Vesicles) proposed the first experimental guidelines for exosomes in 2014 and updated them in 2018. The latest exponential progress has still managed to outgrow the recently agreed criteria. It follows that some of the past experiments should now be redesigned and many former conclusions would be hard to reconcile. Observers were awaiting more compelling results and remained to be convinced.

Novel exosome technologies can transform healthcare forever.

2020 has however muted many critics. When handled more rigorously, exosomes can become fascinating tools. In a pioneering large scale study, it was demonstrated that exosome protein cargo in blood is specific to the type of cancer a patient has. The same year, the first engineered exosome therapeutic entered human clinical trial for cancer treatment and displayed good tolerability. It was also shown that the therapeutic administration of carefully selected non-engineered exosomes could reproducibly promote the regeneration of damaged tissue *in vivo*. Novel exosome technologies can transform healthcare forever.

Transforming the standard of care

I believe that the current standard of care will be significantly transformed this decade as we are about to change our way of interacting at the cellular level, notably thanks to exosomes: either by ‘reading‘ them to get a snapshot of the current cellular activity (diagnostic applications) or by ‘redirecting/rewriting‘ exosome cargo to modify any specific cell (therapeutic applications).

My next stories will focus on existing and upcoming exosome technologies for both diagnostics and therapeutics: where we are and how we are addressing the remaining technological challenges to control exosomes and build a better future.

About me

I am a biotech entrepreneur, inventor and founder & CEO of Mursla, a Cambridge-based company focused on exosome biomedical

applications. I was trained in biophysics at the University of Cambridge (Cavendish Laboratory) after an international career as a biotech investment banker at J.P. Morgan and a Master of Science in Management at HEC Paris.