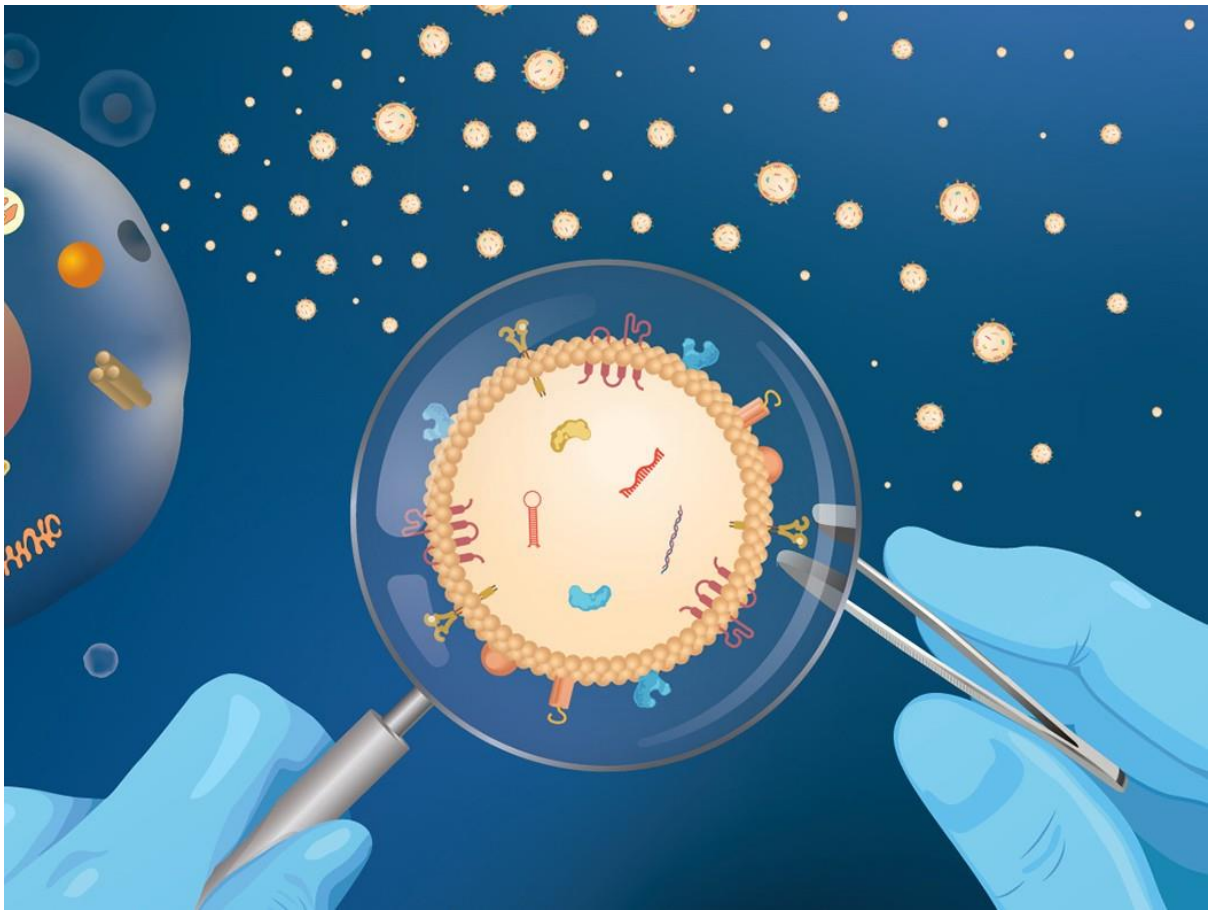
Analysing Exosome Biology Enables Breakthrough Diagnostic Solutions

https://lnkd.in/eR3WASWA



We established previously that ‘reading’ exosome cargo can significantly transform the standard of care for disease management. Today, we are focusing on the diagnostic applications of exosome biology.

We explain how analysing exosome biology leads to new ways of diagnosing disease. We then identify the three engineering challenges associated with this. Finally, we discuss how these

challenges may be overcome by novel technologies such as Mursla's platform.

Analysing exosomes and their biology can transform disease diagnostics

To recap, exosomes are lipid nanovesicles ("bubbles") secreted by our body's cells. They transport biological cargo such as DNA, RNA, and proteins, and can travel over long distances for a diverse range of processes. Exosomes can be found in all biofluids such as blood, urine, sweat, and saliva.

Our cells secrete a multitude of exosome cargo which reflect their biological status: healthy or diseased. Crucially, this information can be accessed via a blood draw for biomedical analysis. This is called a liquid biopsy, a term coined in contrast to the tissue biopsy. Although tissue biopsies are currently the gold standard of disease diagnostics, they are an invasive and impractical means to remove a collection of cells from the body for analysis. By comparison, a liquid biopsy is non-invasive and enables many exciting new applications such as routine cancer screening. As of today, 90% of cancers are still not screened. It is widely accepted that early cancer screening and therefore diagnosis, alone, could save millions of lives per year.

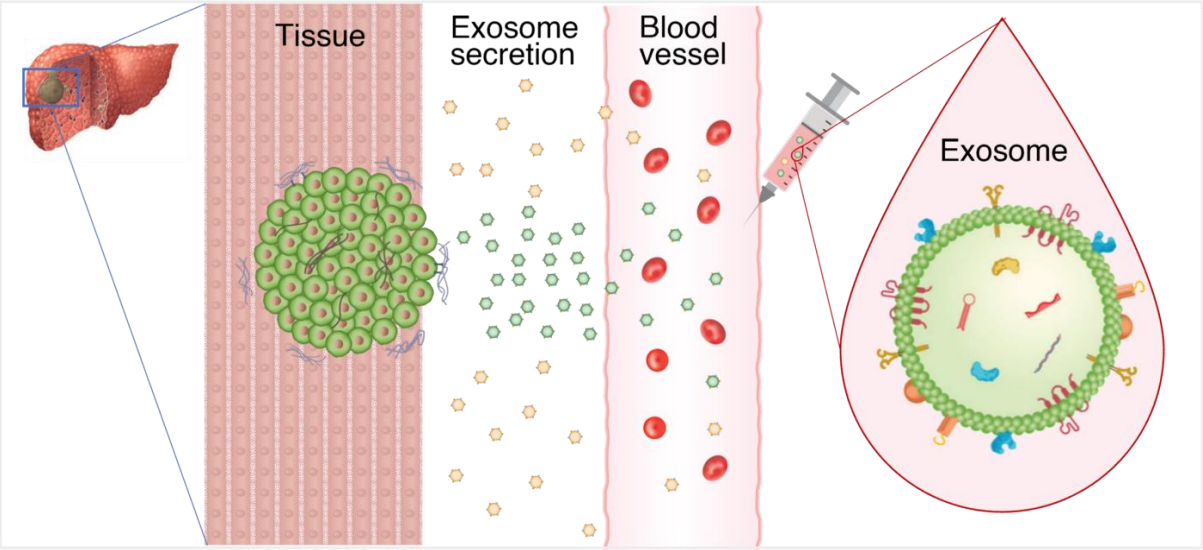


Illustration of an exosome-based liquid biopsy for liver cancer

During the last decade, the first generation of cancer liquid biopsy tests surfaced due to the availability of high throughput DNA sequencing technologies. These tests are based on the analysis of pieces of information from dying cancer cells in the blood called circulating free DNA (cfDNA). A small proportion of cfDNA in the blood may exhibit specific mutations or methylation/fragmentation patterns, enabling the detection of cancer in patients.

Despite these tests showing great potential, they present various limitations which have prevented their widespread adoption in clinics. Notably, there is a low probability that patients with a positive test result actually have the disease. This is called a low positive predictive value (some of you may appreciate how important this metric is following the COVID-19 pandemic). Researchers, clinicians, and patients are now searching for the next generation of tests.

Analysing exosome biology offers many additional advantages, enabling better disease prediction:

(i) Auxiliary to DNA from the cell nucleus, exosomes have other well-preserved biological material from their parental cell such as proteins, RNA, lipids and metabolites;

(ii) Exosomes contain tissue-of-origin markers which indicate to scientists where they came from. For example, specific protein markers show they were ‘made in the liver’;

(iii) Exosomes are continually secreted by living cells, as well as at the early stage of disease, and not only by dying ones.

What are preventing exosome-based tests being implemented in clinicsĭ ?

There are three main engineering challenges associated with the exploitation of exosome biology for liquid biopsy: (1) efficient isolation of disease-related exosomes from blood; (2) the characterisation of exosome cargo with sufficient accuracy and confidence; (3) the ability to scale this process for clinical use.

(1) The efficient isolation of disease-related exosomes from blood

Blood is extremely complex. As such, disease detection techniques cannot be used unless the blood sample is further purified. This ideally involves removing as many particles as possible that are not

disease-related exosomes ('contaminants') whilst preserving the exosomes. Various techniques can be used, either alone or in combination, to isolate material by size, density, antigen type or electrical charge.

However, in practice, the above techniques are not sufficient to isolate the exosomes of interest. This is for a number of reasons: Firstly, the majority of initial exosomes are destroyed or discarded with the contaminants during the process. Furthermore, the purified sample will contain a large number of non-exosomal contaminants, such as lipoproteins, which have a similar size and density but are 1000x more abundant. Finally, the preparation consists of >99% of exosomes originating from healthy tissue and therefore are not indicative of any disease state.

(2) The characterisation of exosome cargo with sufficient accuracy and confidence

Upon purification of the initial blood sample, disease-related exosome cargo can be more easily characterised. Each piece of cargo is a potential biomarker candidate for disease. There are several techniques that can partially analyse nucleic acids (such as DNA and RNA), proteins, lipids or metabolites. This can be done either in a targeted (e.g. PCR, ELISA) or untargeted way (e.g. NGS, Mass Spectrometry).

Unfortunately, none of these methods can guarantee that they are analysing disease-related exosome cargo. This is for the reason that

they may not be sensitive enough, or when they are, they are likely to inadvertently look at the wrong particles.

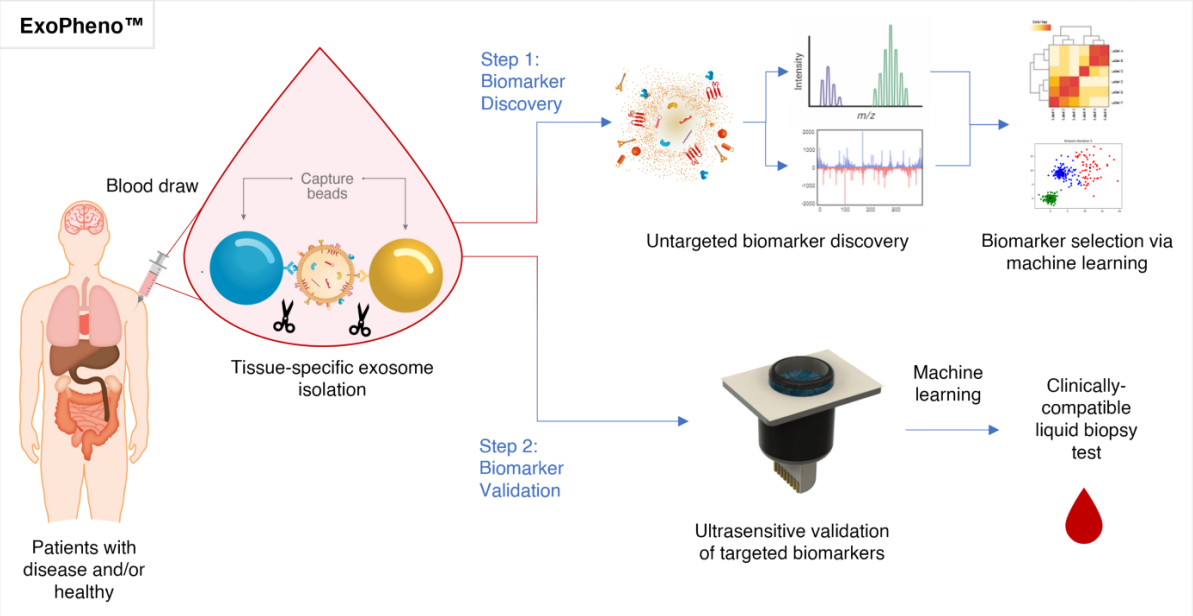
(3) Scaling this process for clinical use

Untargeted characterisation has lots of variability, is very costly and offers low throughput. In contrast, targeted characterisation is more accurate and cost-efficient, but requires the prior knowledge of the biomarker target (which has been poorly explored to date). Additionally, advanced targeting systems nevertheless have a relatively low throughput. Lastly, isolation and characterisation generally require highly technically qualified personnel supported by expensive and specialised R&D equipment.

New exosome technologies are enabling next generation liquid biopsy tests

To address the above challenges, there are ongoing efforts to improve isolation, characterisation and/or scalability in various public and private exosome research groups globally.

For instance, Mursla has been working since 2019 on developing new technologies to address and overcome these engineering challenges. Its novel technology platform called ExoPheno™ offers improved isolation of disease-related exosomes, novel ultrasensitive characterisation systems, and is designed to be compatible with high throughput clinical usage.



ExoPheno™ worfklow: from analysing exosome biology to developing nextgen liquid biopsy test

For the optimisation of disease-related exosome isolation, Mursla validated proprietary tissue-of-origin markers facilitating the removal of most exosomes from healthy organs and other contaminants. In order to achieve ultrasensitive characterisation, it developed two systems: (i) a proprietary multi-omics sequencing workflow for untargeted biomarker discovery and (ii) a novel patented system for the ultrasensitive validation of targeted biomarkers. Lastly, for high throughput clinical use, Mursla developed a workflow that can be used in 96 well plate formats, which are standard in any biolab. These workflows are supported by innovative machine learning methodologies to manipulate large amounts of data and improve its test predictions.

To summarise, we have explored how analysing exosome biology can lead to next generation liquid biopsy solutions. We discussed why existing technologies cannot currently 'read' exosomes at the appropriate efficiency. Finally, we demonstrated how new platforms

such as Mursla technologies can eventually bring exosome-enabled diagnostics to clinics.

In conclusion, I believe that this decade will provide breakthrough diagnostics solutions and transform chronic-disease management such as cancer or neurodegenerative disease. My next blog story will discuss the specific clinical steps to have this available for everyone.

PS: Mursla will publish more details about its patented technology and its upcoming clinical strategy in the coming weeks. Stay tuned!

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.

[1] Despite the technological limitations described above, there is currently one commercialized test which partly relies on the RNA cargo of exosomes from urine. The test is to assess if men with borderline PSA blood levels should consider a prostate biopsy.