

Chaire de recherche de pneumologie expérimentale

Rôle des exosomes dans le transport de récepteurs à tyrosine kinase et l'activation de l'angiogenèse dans le cancer bronchique non à petites cellules

Cornelia M. Wilson



GEIST
Génomique,
Environnement, Immunité,
Santé et Thérapeutiques



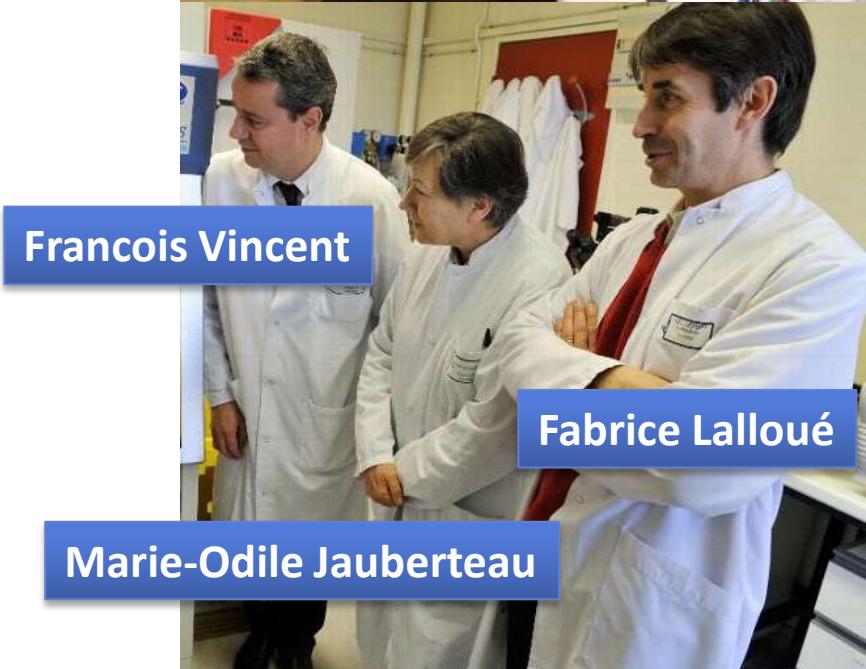
Chaire de recherche de pneumologie expérimentale

- The first chair at the University of Limoges Faculty of Medicine was created in 2006 (5 members)



Cornelia Wilson

Thomas Naves



Francois Vincent

Fabrice Lalloué

Marie-Odile Jauberteau

Lung cancer

LUNG CANCER OUTLOOK

PERSPECTIVE



The screening imperative

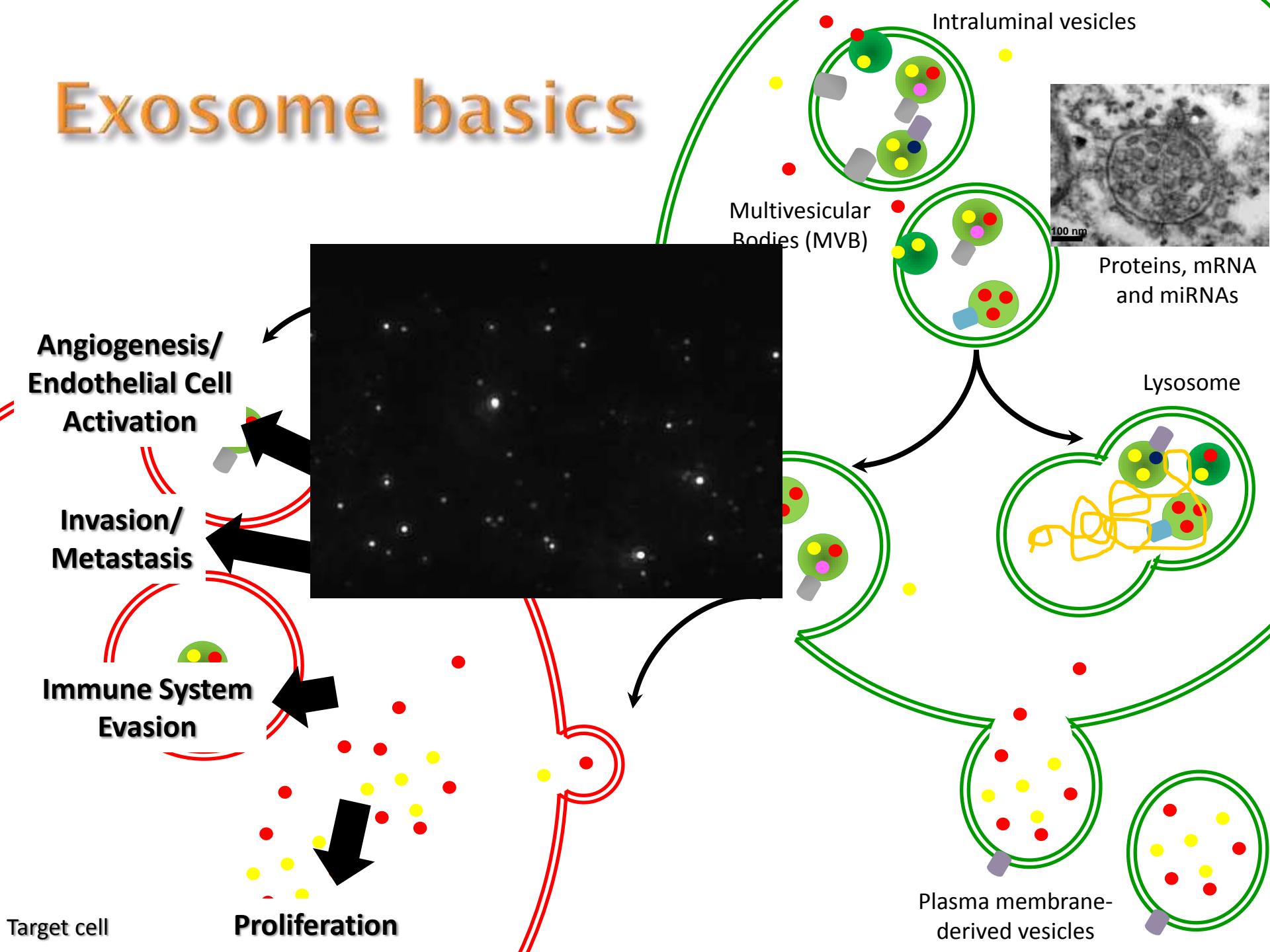
Lung cancer kills more people than any other malignancy. Let's not delay in implementing a screening programme, says **John K. Field**.

Roughly every two minutes during 2012, someone in the European Union (EU) died of lung cancer. Those 268,000 lung-cancer fatalities represented more than one-fifth of all EU cancer deaths. The good news is that screening for lung cancer using low-dose computed tomography (CT) could reduce this enormous burden of mortality through early detection and treatment that improves survival¹. Nearly 75% of lung-cancer patients present with late-stage disease, when effective treatment is unlikely to succeed. However, if the disease is treated at an early stage, more than 70% of patients survive another five years. Lung-cancer CT screening makes

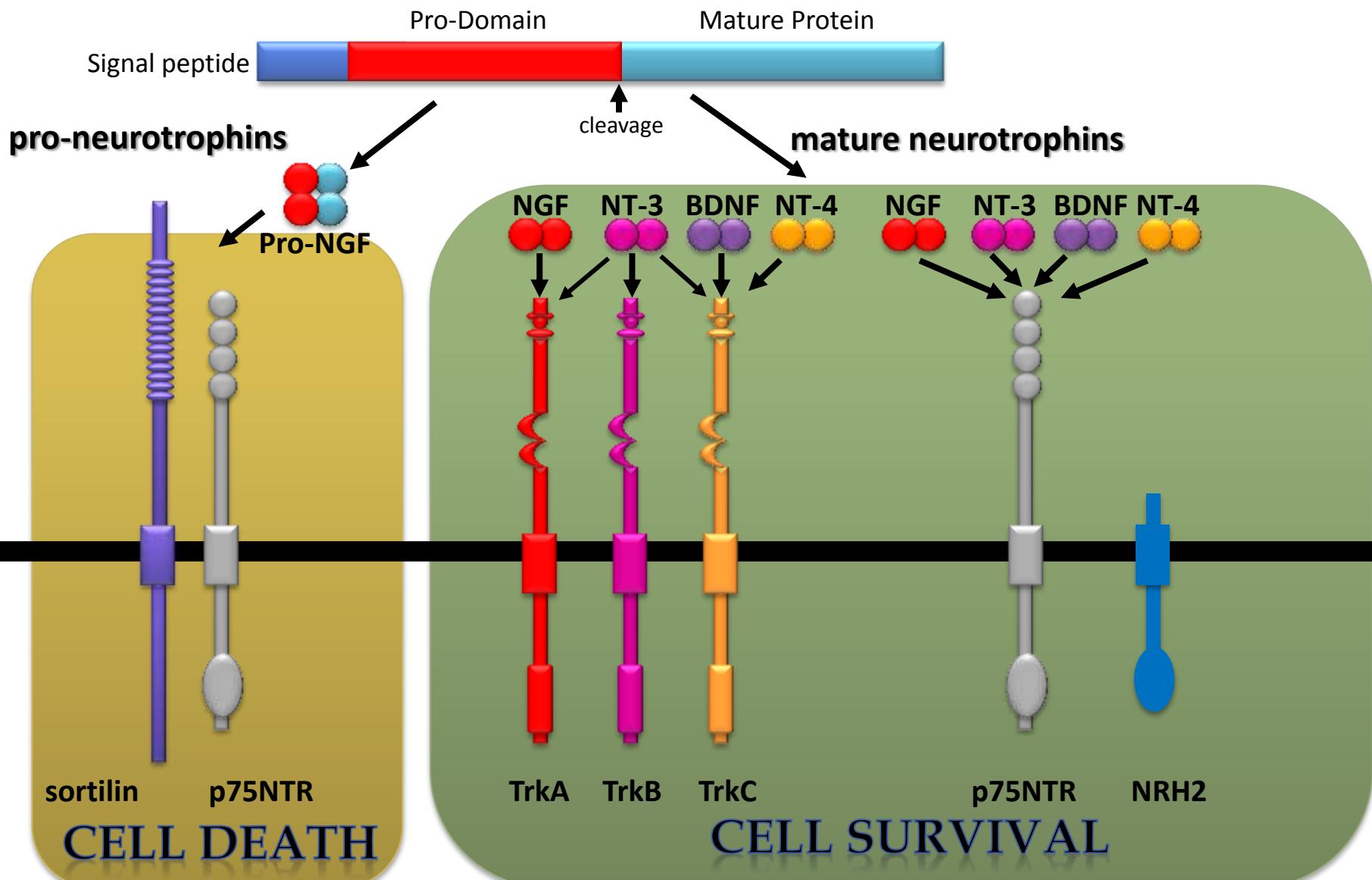
consistent: nodules tend to be highly irregular. Thus a small nodule might show up as large if it is measured along its greatest dimension, creating a false-positive result, and vice versa for a large nodule measured along its shortest axis. That is why it's better to use the volume of a nodule to judge the risk it poses, which was what both the NELSON and UKLS trials did. This radiological approach has gained acceptance in Europe and is highly likely to reduce the number of false positives.

The next question to ask is: 'Who should be screened?' The US Preventive Services Task Force recommends that CT screening should be undertaken in past or present smokers aged 55–80 who meet the

Exosome basics

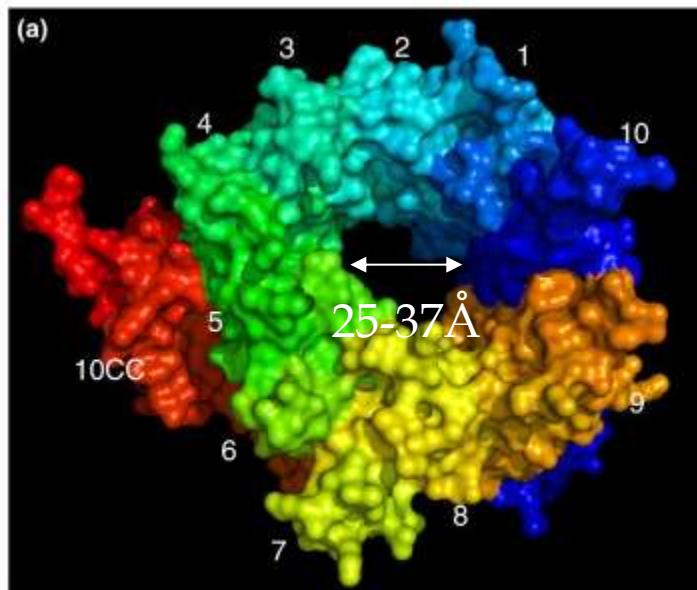


Neurotrophins and their receptors

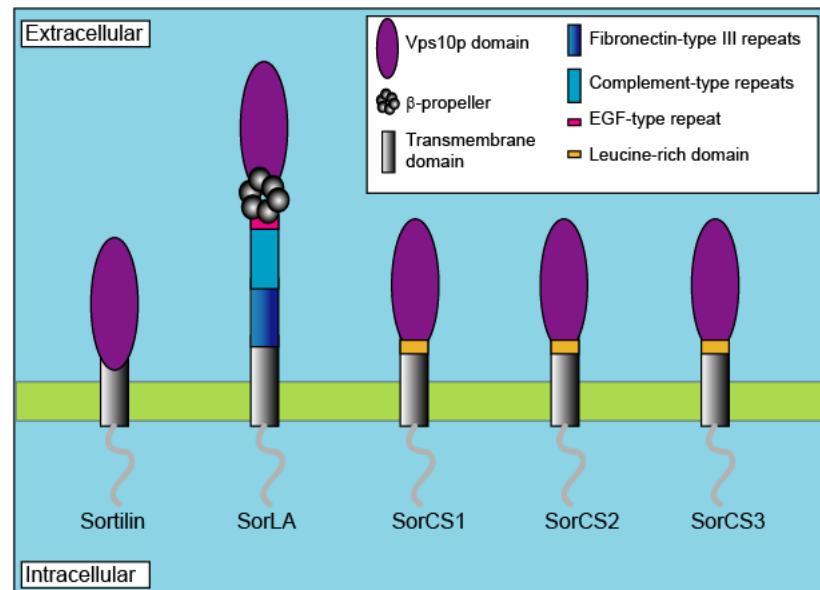


Sortilin

Vps10p domain – beta-propeller with 10 blades forming a tunnel.

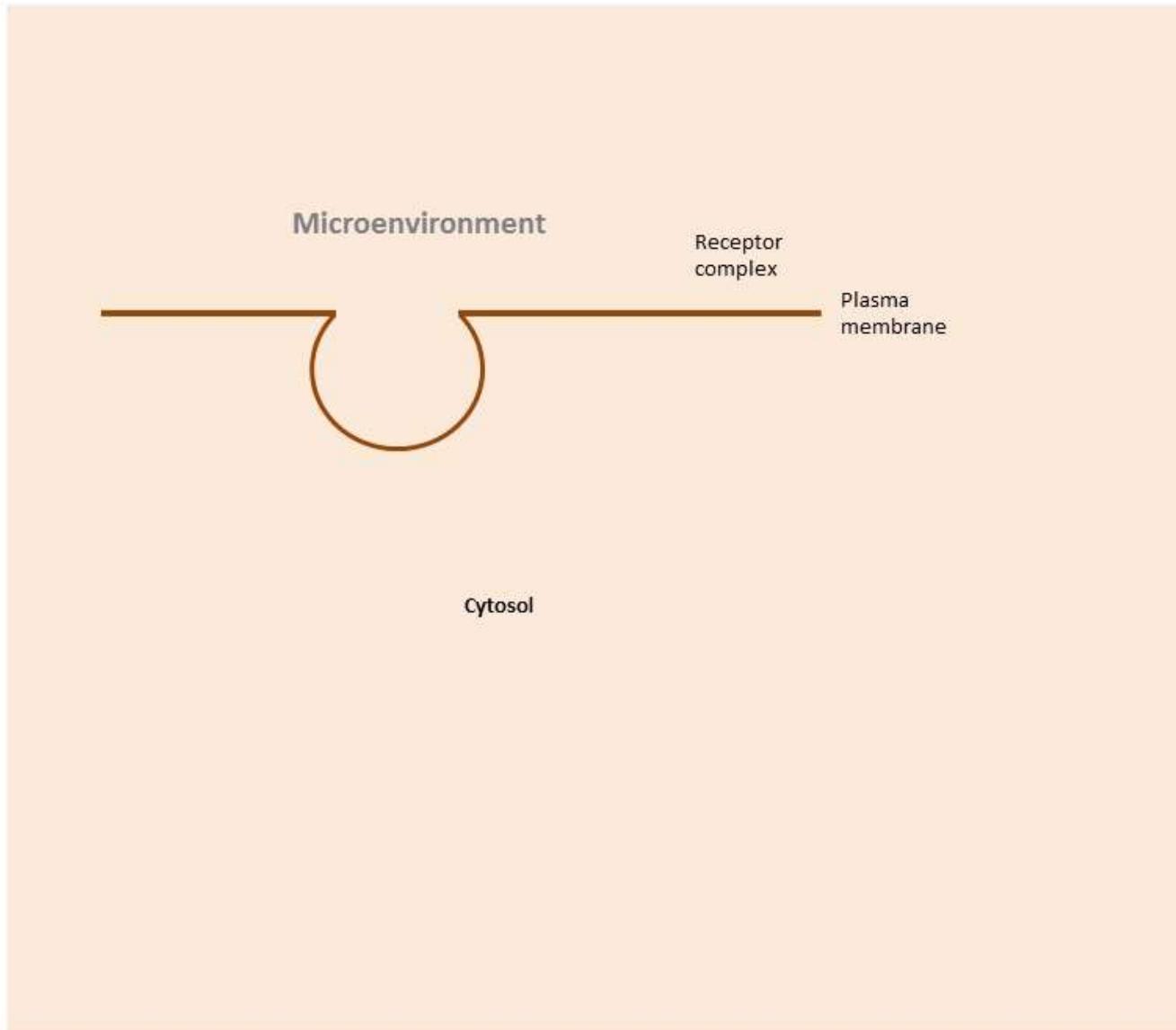


Quistgaard et al., Nat. Struct. Mol. Bio. 2009



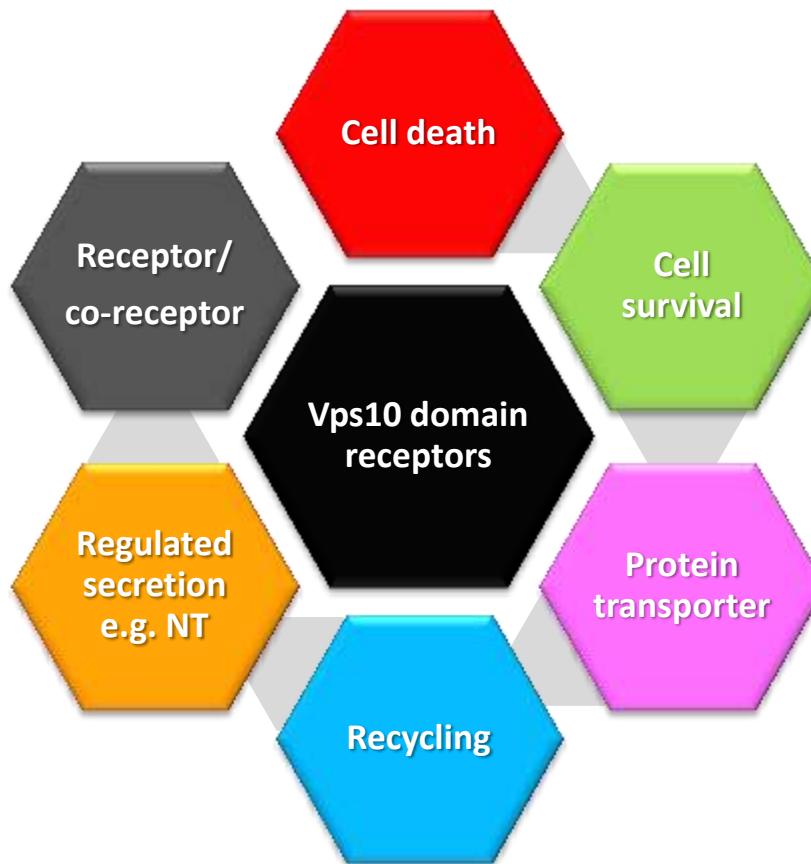
Wilson et al., Drug Metabolism, 2014

Cellular trafficking of Sortilin



Cancer and Neurotrophins

- The multifaceted receptor, sortilin (also called neurotensin (NT) receptor-3) plays a multitude of roles in the cell



ECD

Anti-ECD

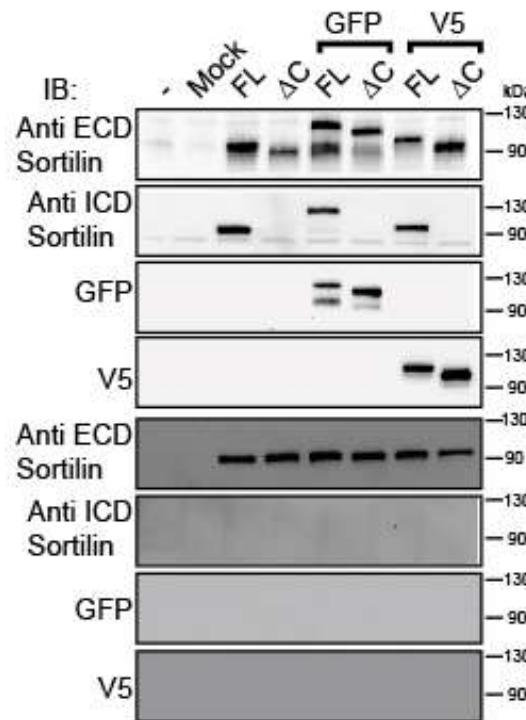
How is sortilin secreted?

TM

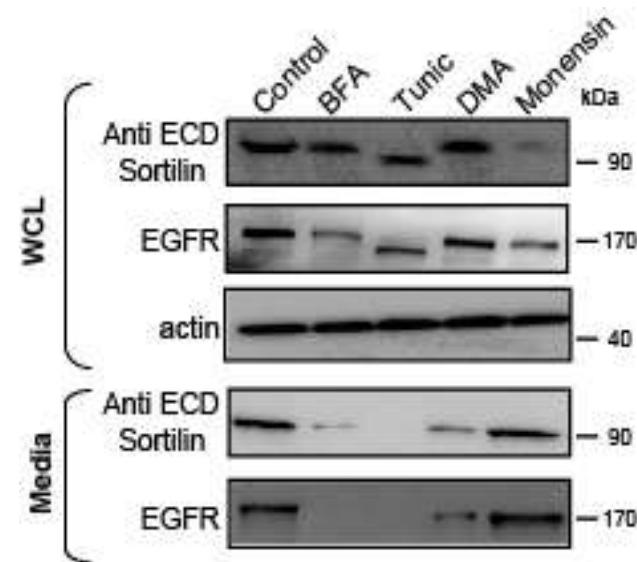
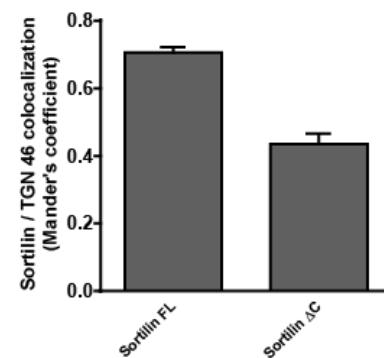
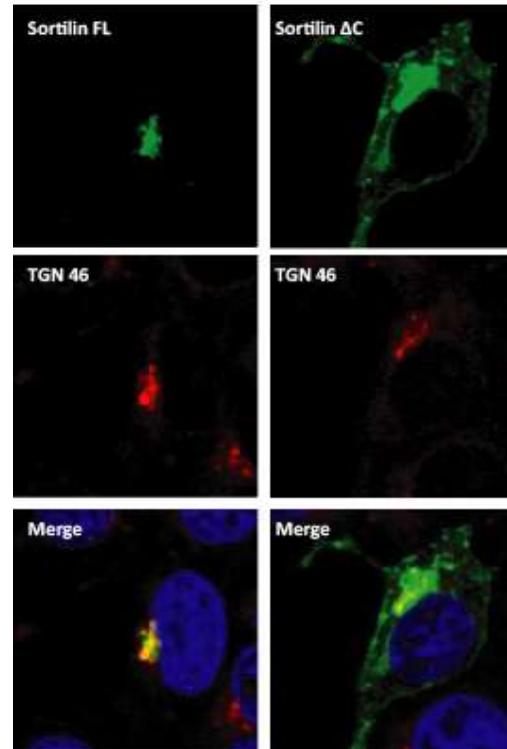
Anti-ICD

V5/GFP

WCL

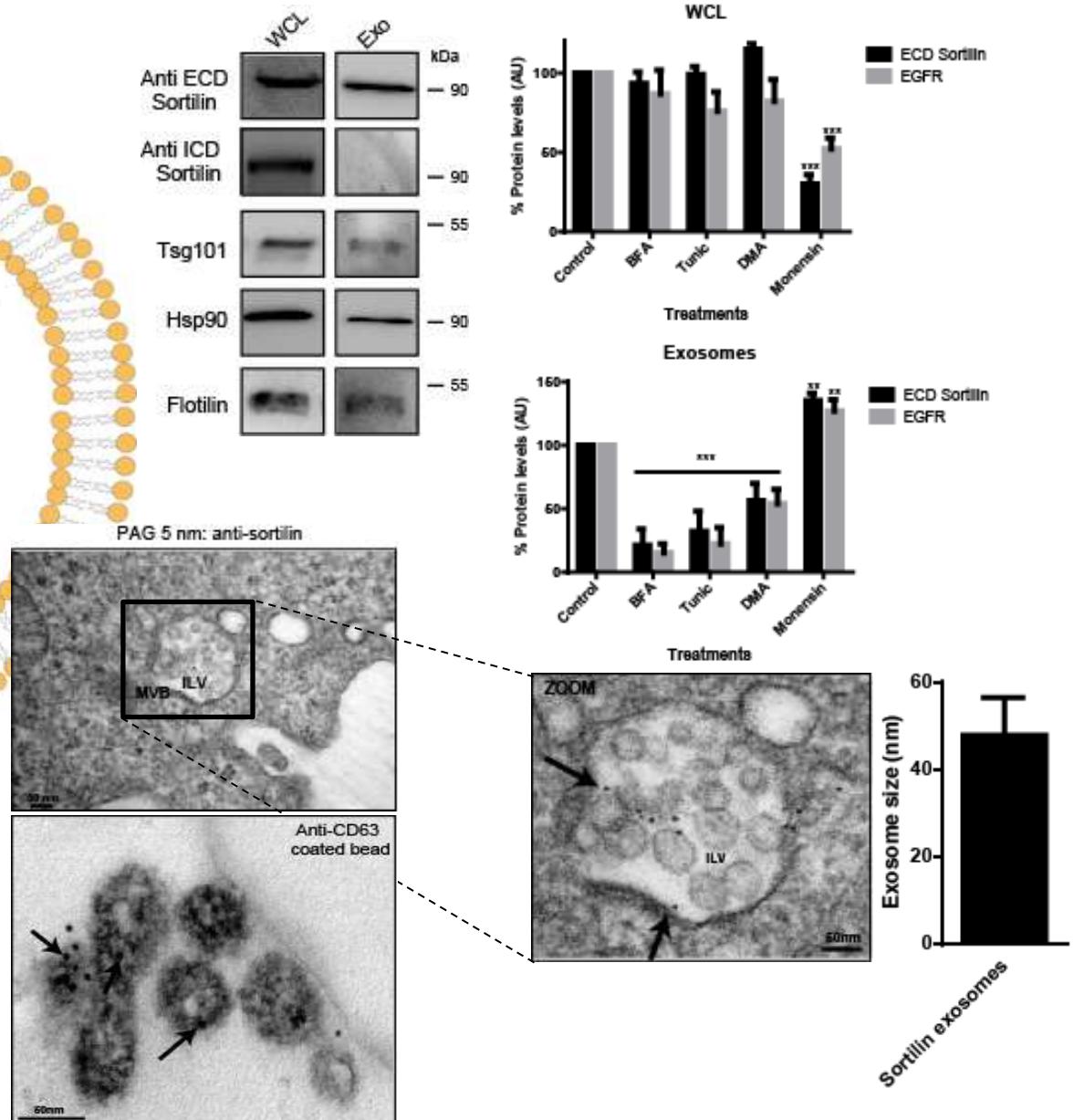
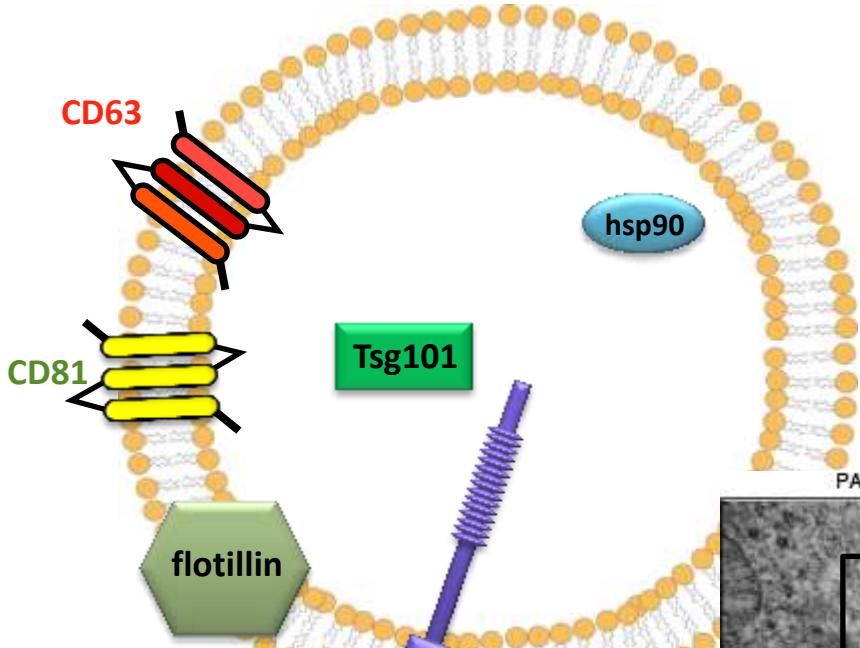


Media



➤ Sortilin uses a canonical pathway

What type of vehicle is used?

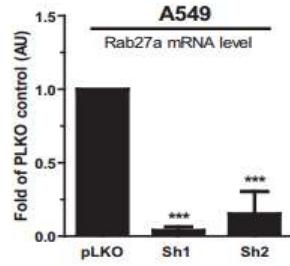
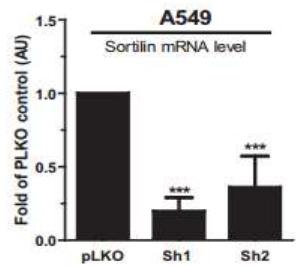


➤ Sortilin can be found in exosomes

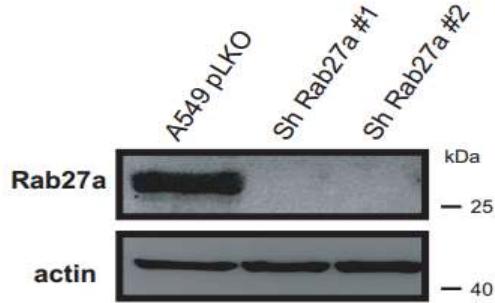
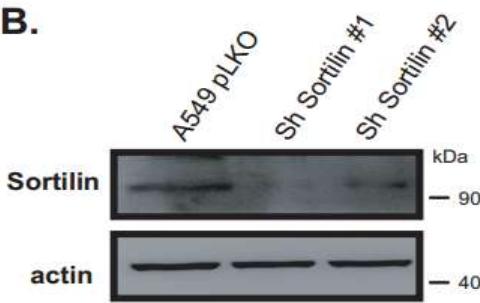
Wilson et al., JCS, 2014

Does sortilin play a key role in exosome release?

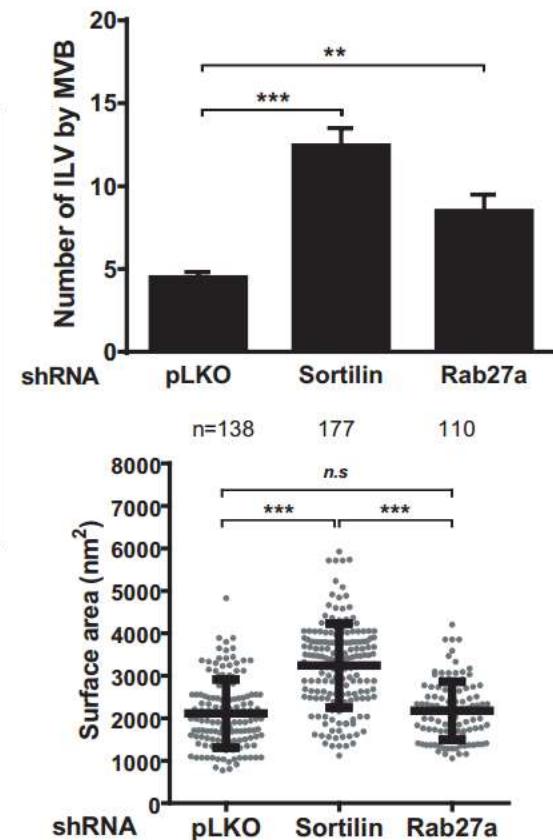
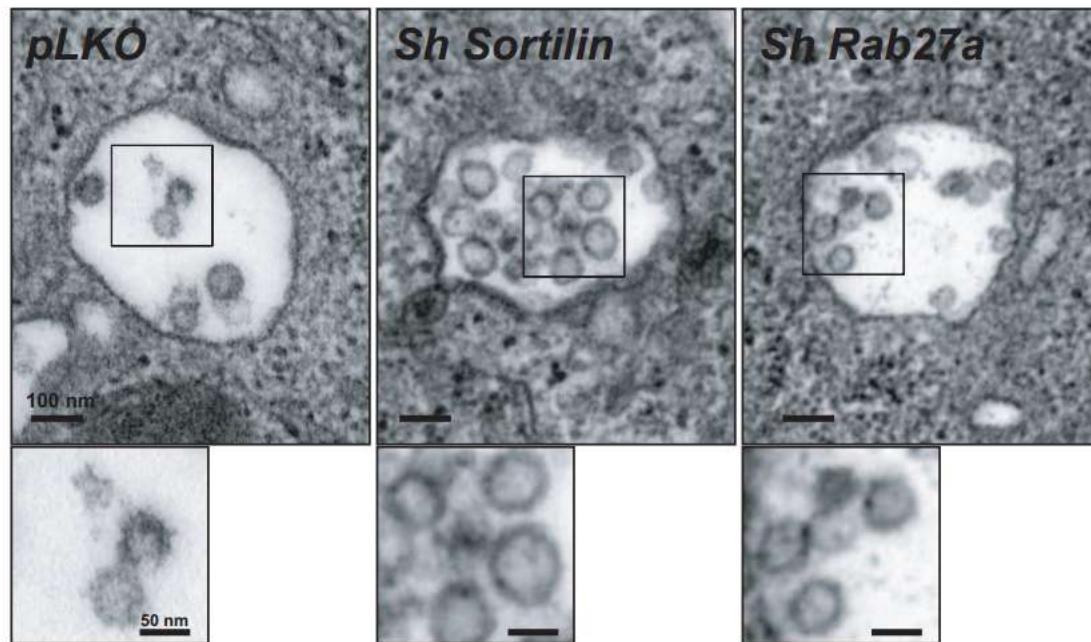
A.



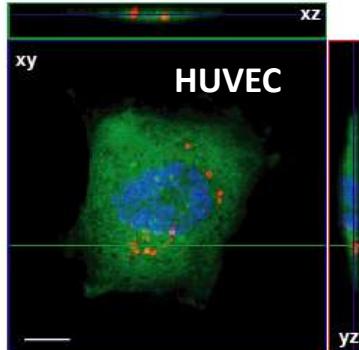
B.



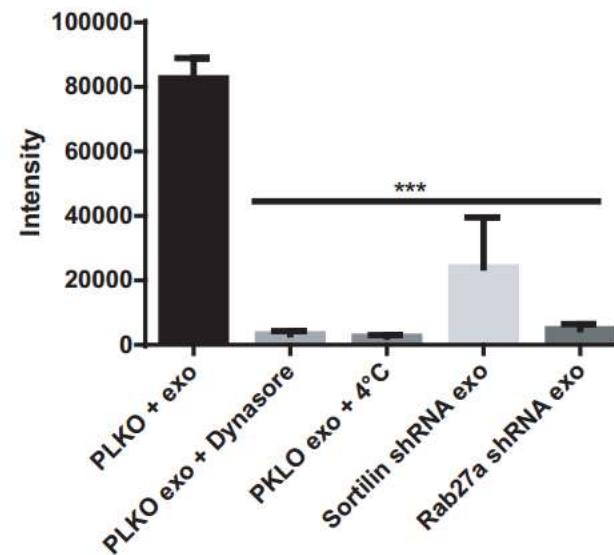
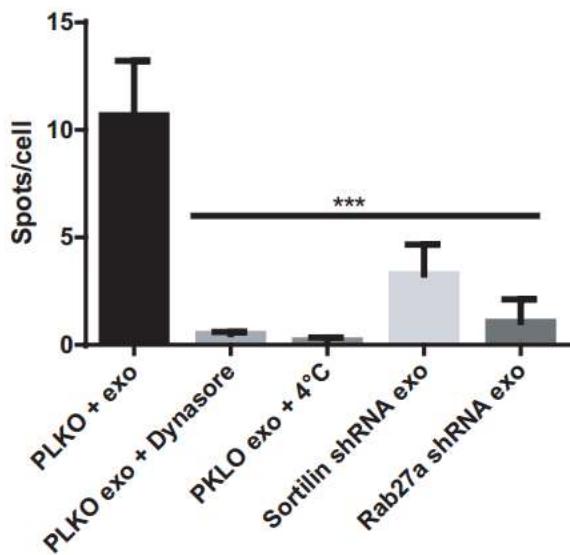
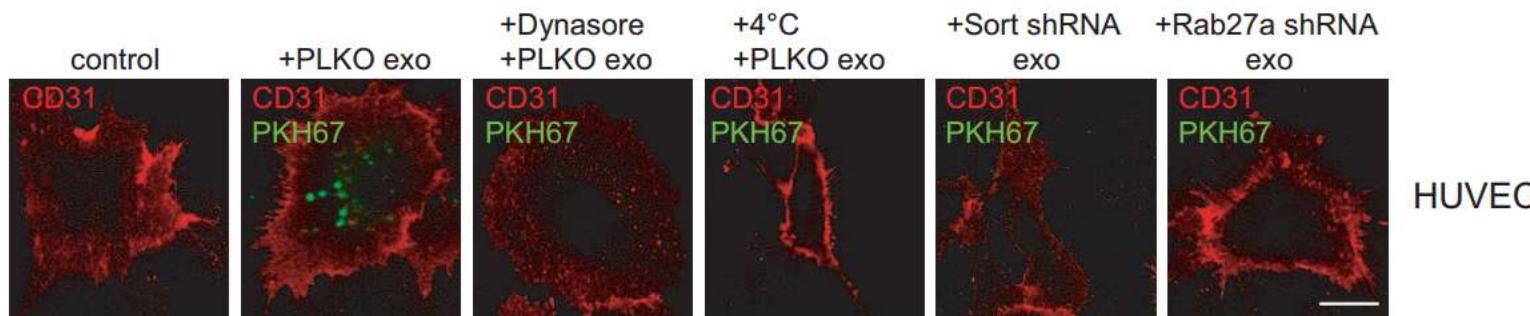
What happens to the MVBs?



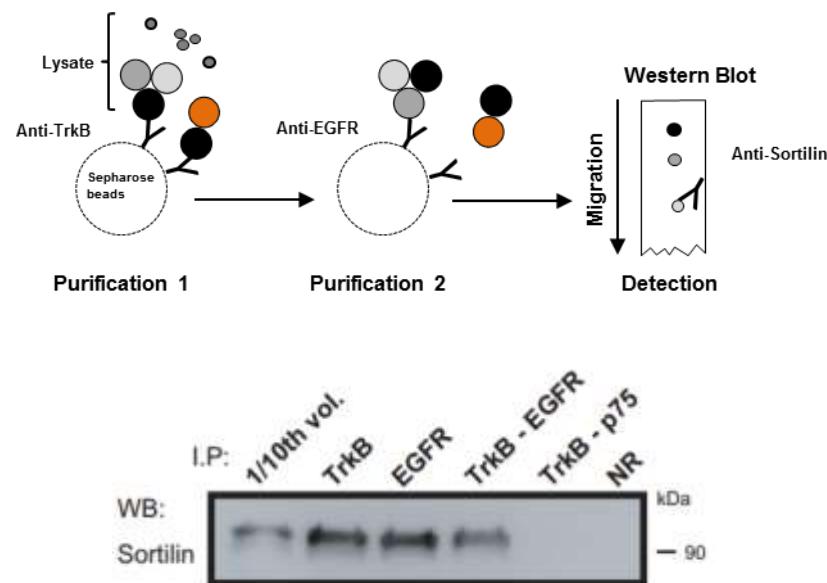
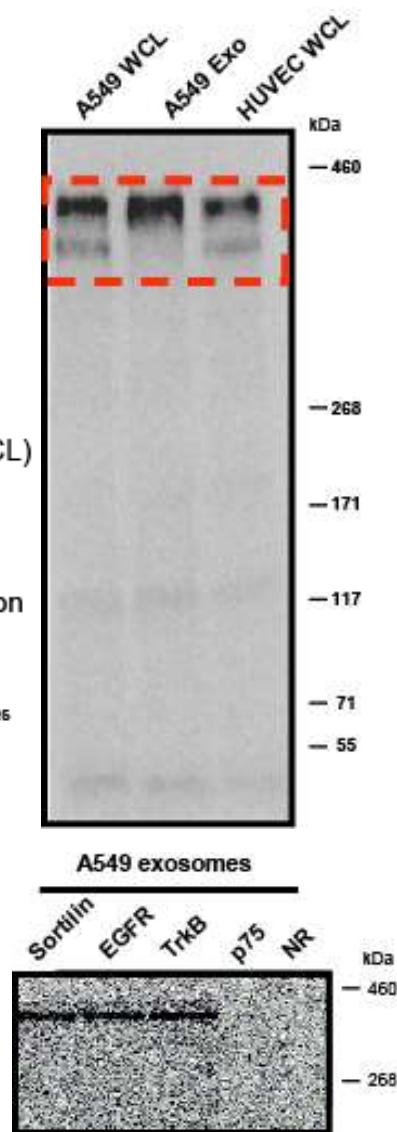
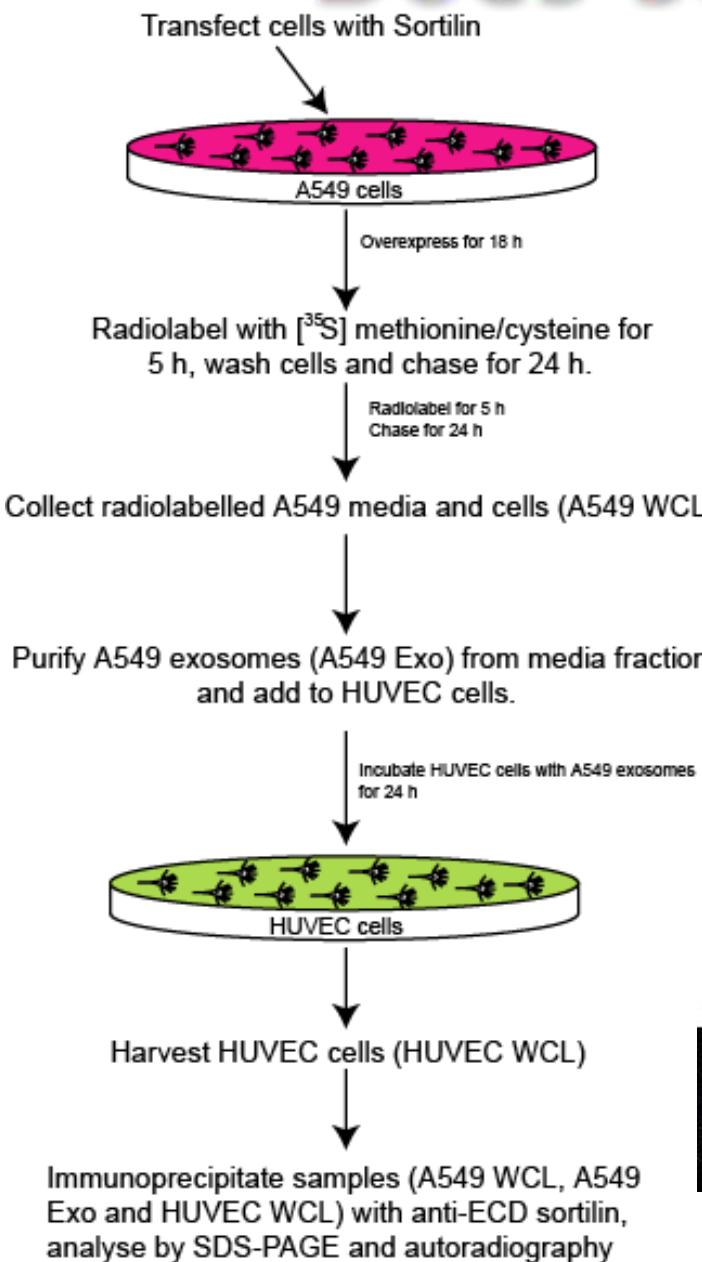
- Size and number of MVB ILVs increase with sh Sortilin



Exosome transfer



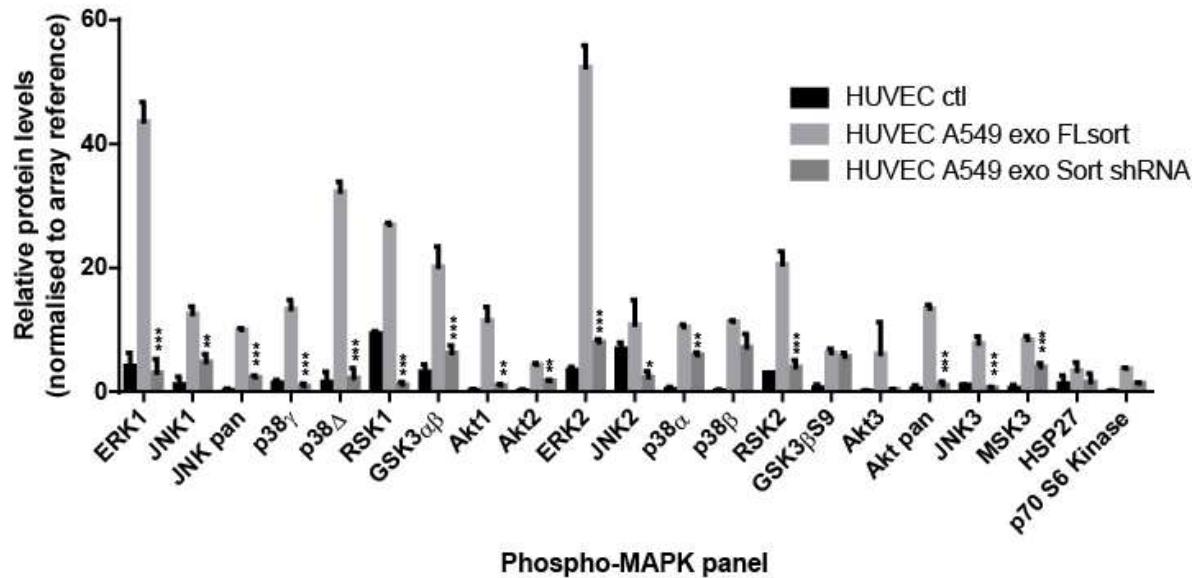
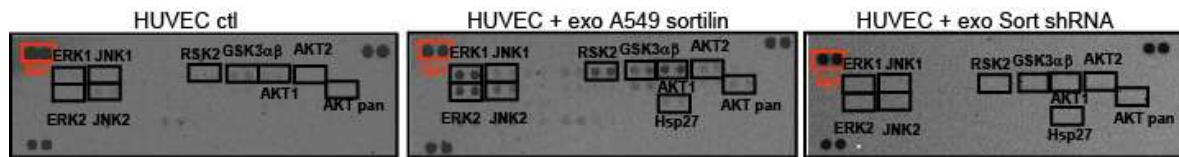
Does sortilin act alone?



➤ HUVEC cells internalise sortilin exosomes

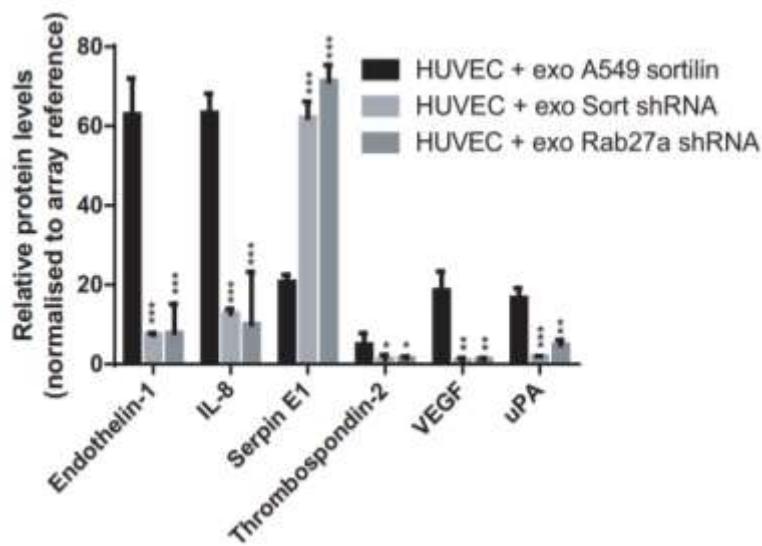
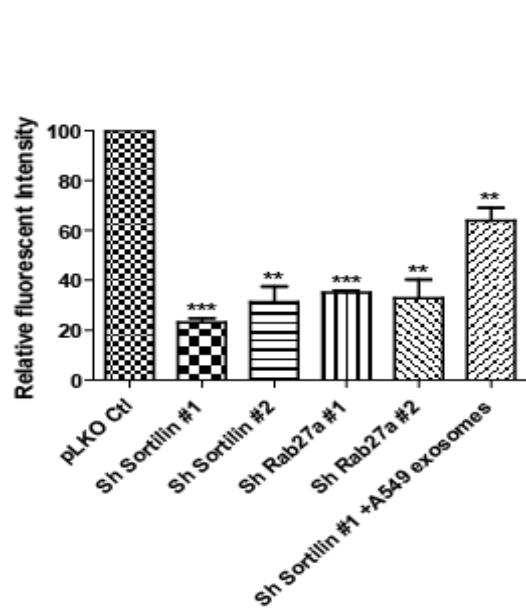
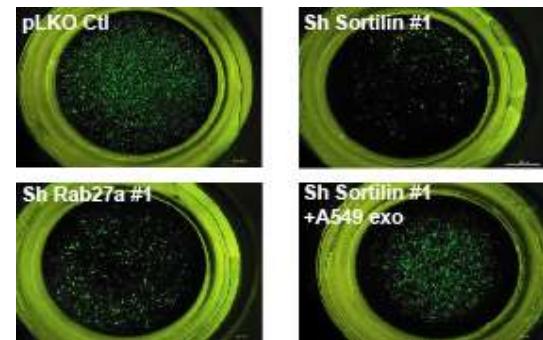
➤ Sortilin forms a novel complex with EGFR and TrkB called 'TES'

What is the consequence of TES exosomes in HUVEC cells?



- TES mediates communication and signaling events between A549 and endothelial cells

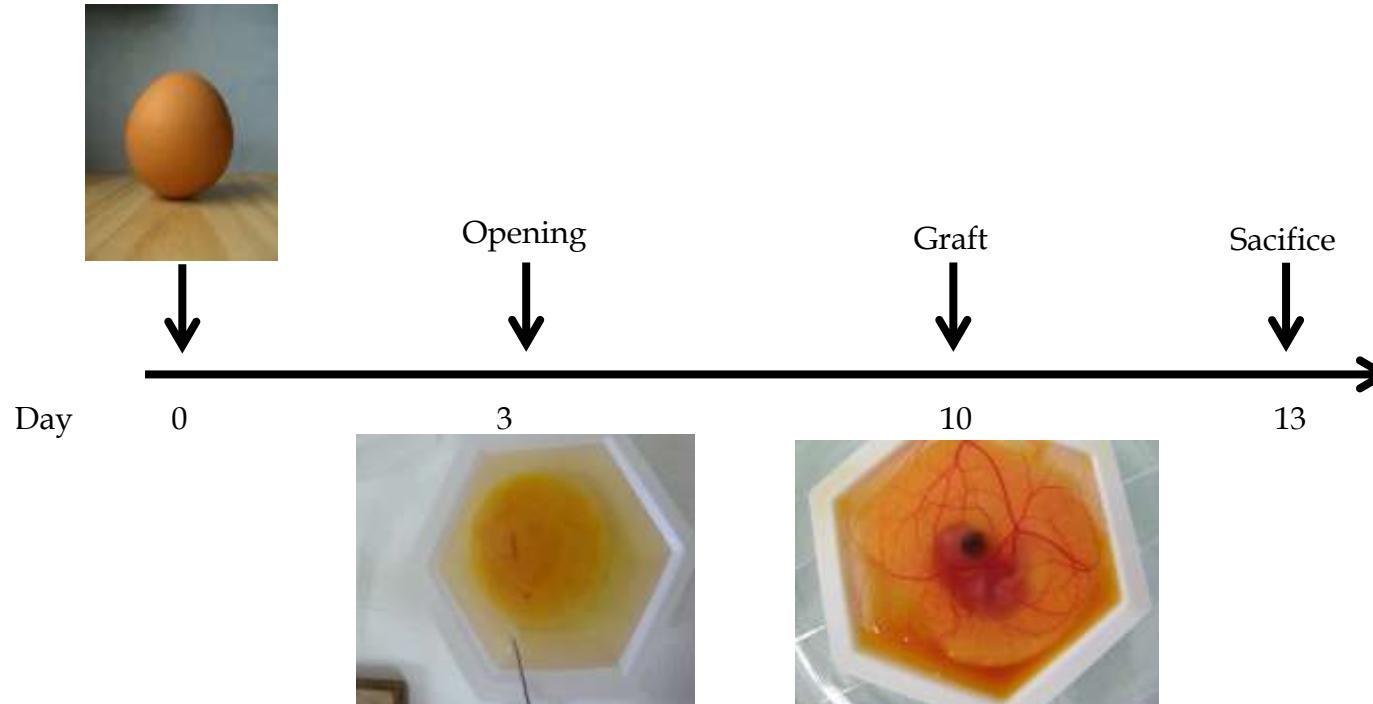
Cell Migration and Angiogenesis



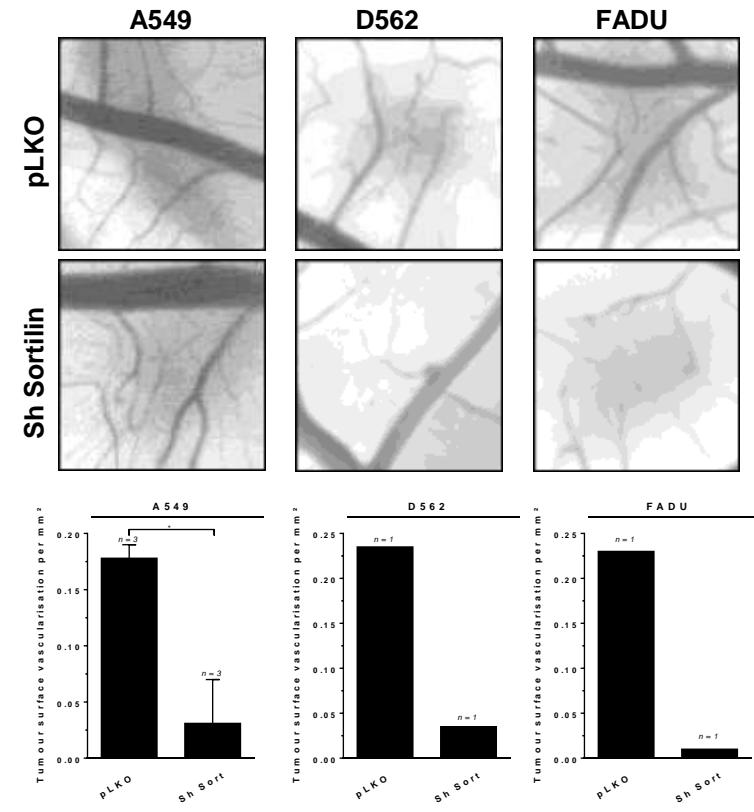
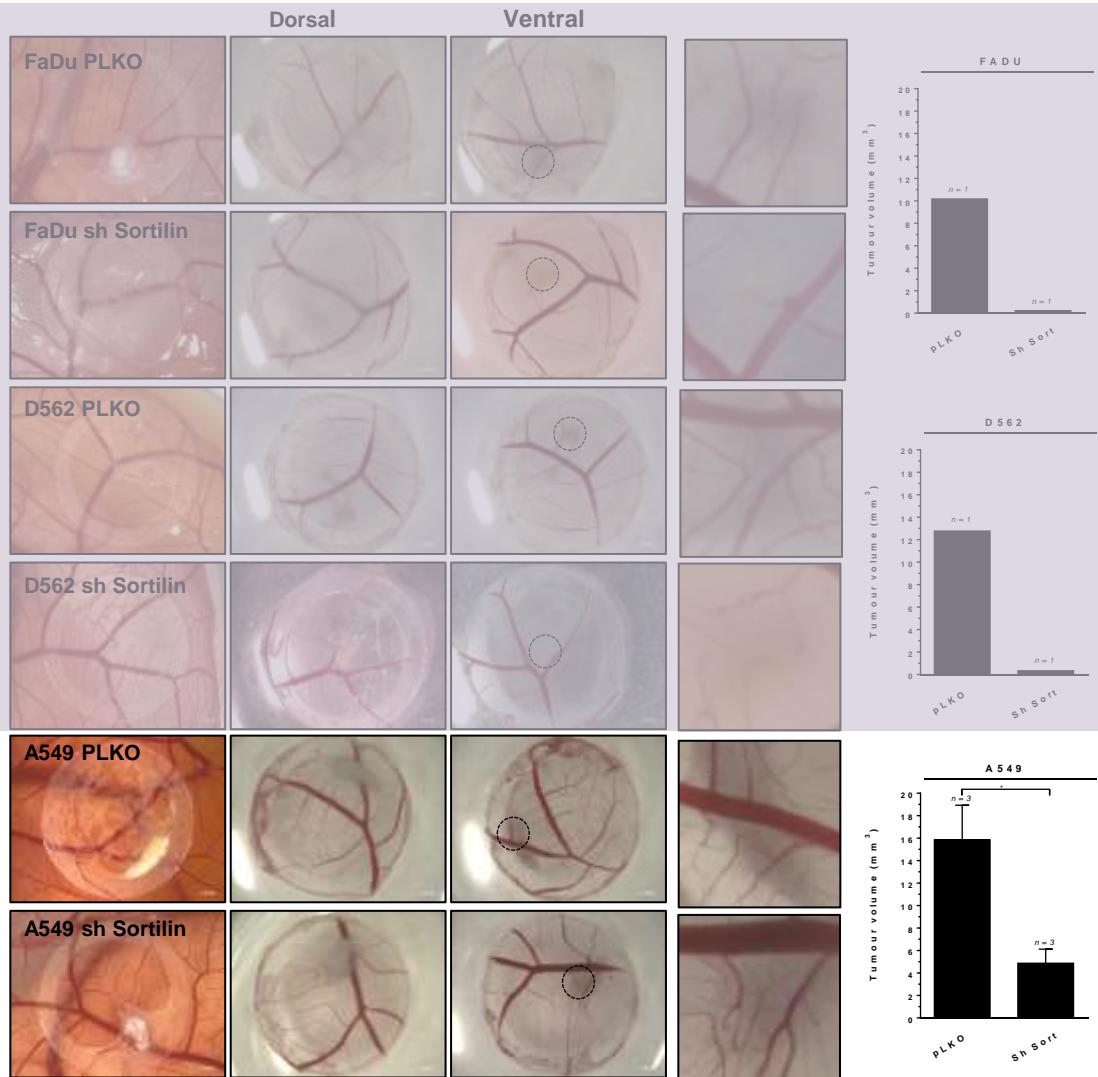
- A switch in the angiogenic factors with a significant elevation of serpin E1 and downregulation of Endothelin-1, IL-8, Tb-2, VEGF and uPA

Do *TES* exosomes play a role in angiogenesis?

Chick Embryo Chorioallantoic Membrane (CAM) Model

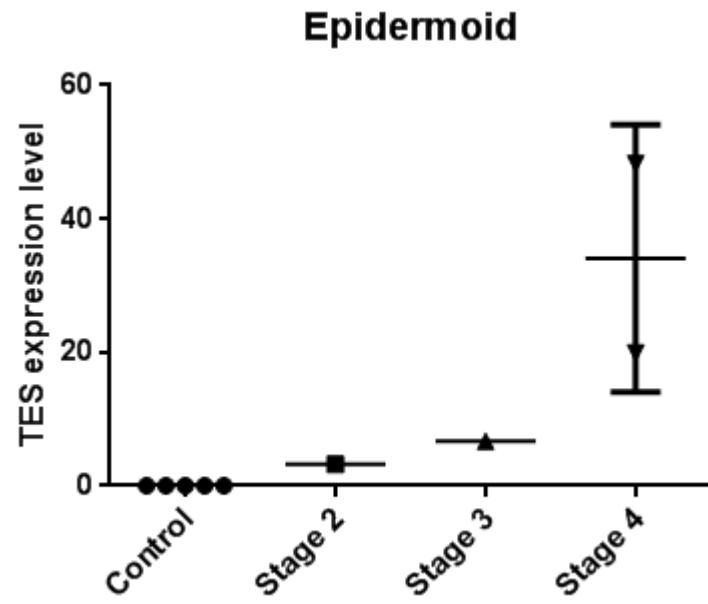
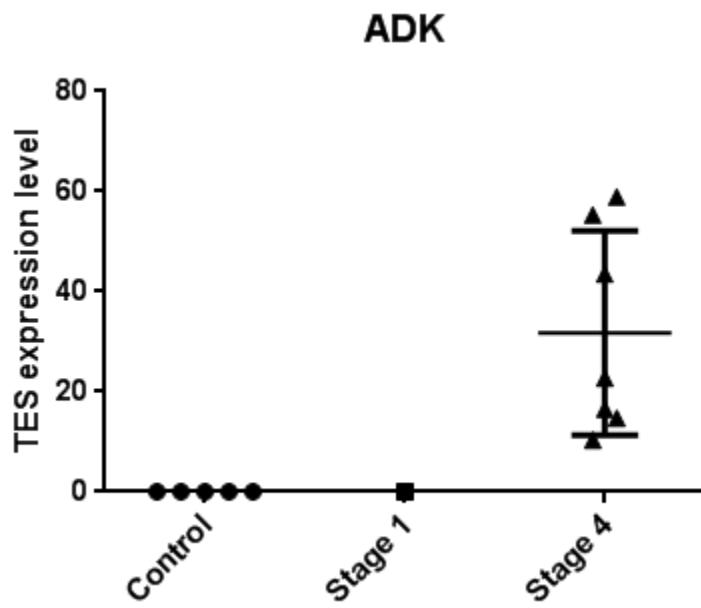


Do *TES* exosomes play a role in angiogenesis?



unpublished data

TES complex in patient exosomes



Conclusions

- Sortilin uses a canonical pathway for secretion and is found in exosomes
- Sortilin is a key component for exosome secretion
- Exosomes contain the novel sortilin complex *TES* linked to two tyrosine kinase receptors, EGFR and TrkB
- The *TES* complex exhibits a control on endothelial cells and angiogenesis activation through exosome transfer
- The *TES* complex exists in the circulating exosomes from lung cancer patients

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The Model

