

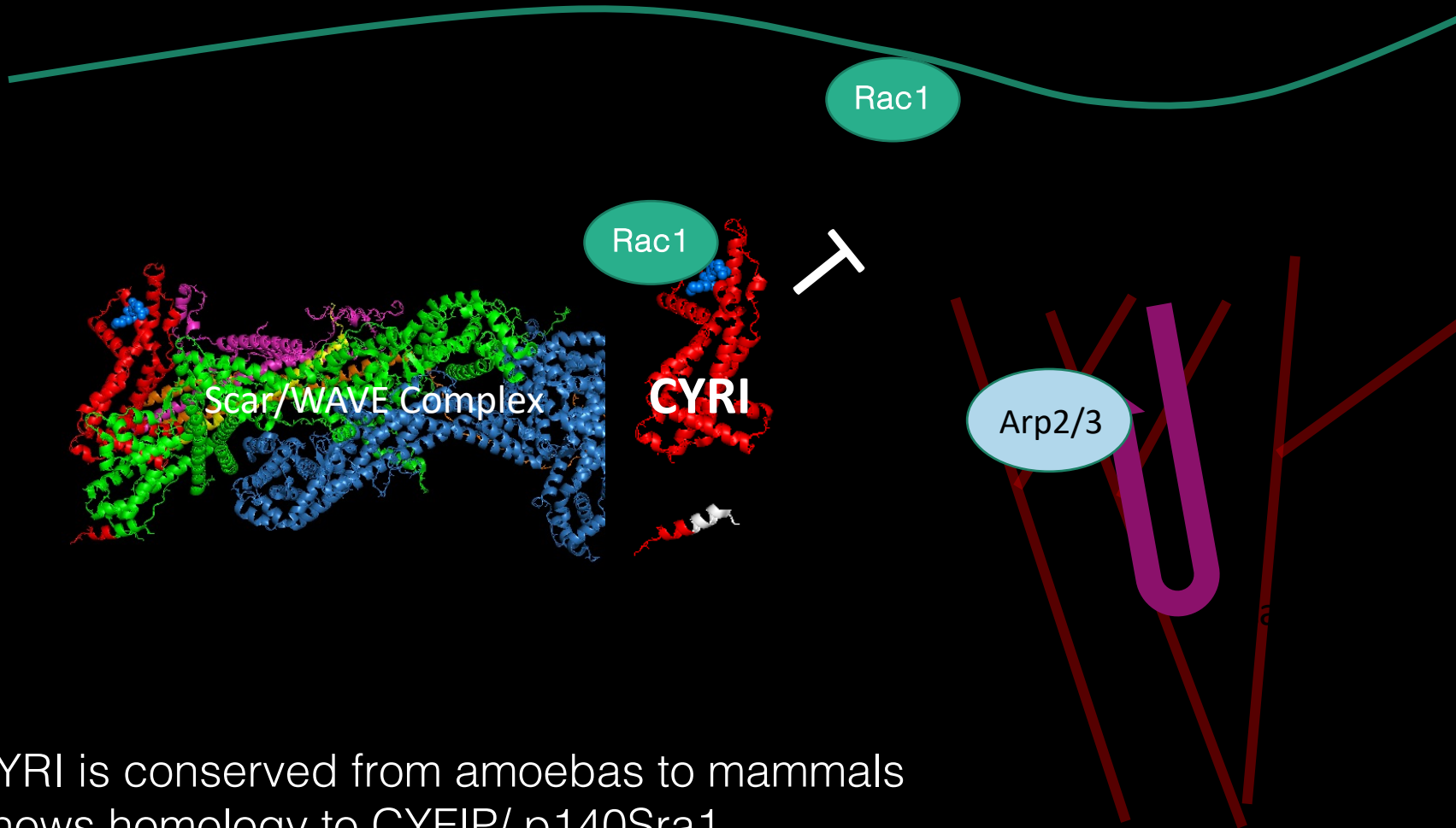


**METABO 2023 NICE**

**Control of nutrient uptake in pancreatic cancer**

Laura Machesky, Department of Biochemistry  
University of Cambridge

# CYRI promotes lamellipodia dynamics with Scar/WAVE



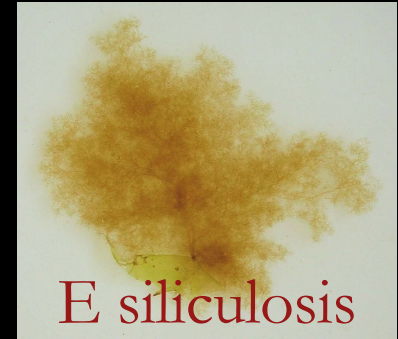
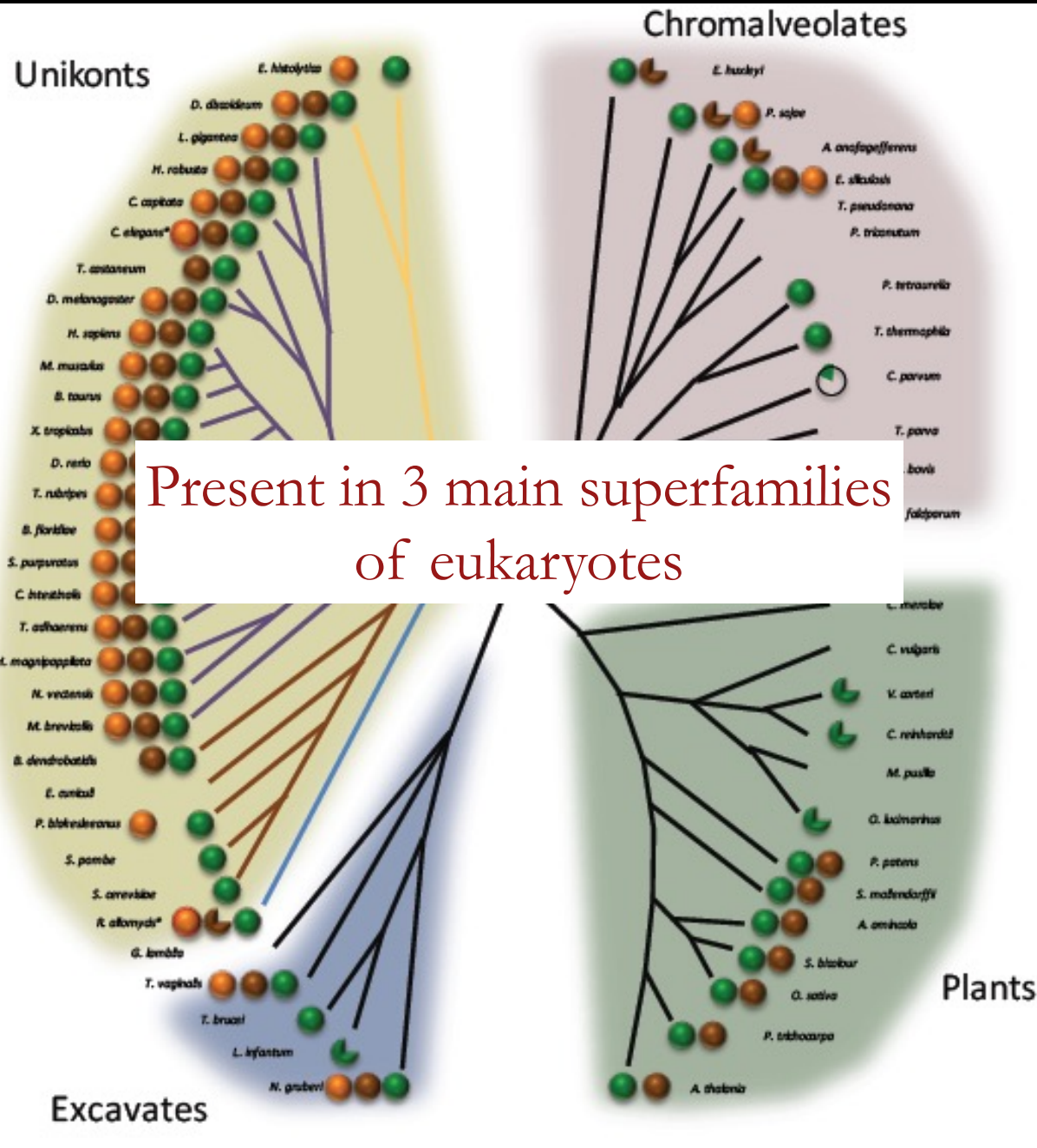
CYRI is conserved from amoebas to mammals  
Shows homology to CYFIP/ p140Sra1  
Mammals have CYRI-A and CYRI-B  
Conserved NT-myristoylation and RAC1 binding

Fort, Batista et al., Nature Cell Biol. 2018  
With Robert Insall lab



*H. sapiens*  
*D. melanogaster*  
*D. discoideum*  
*D. rerio*

Not in yeast



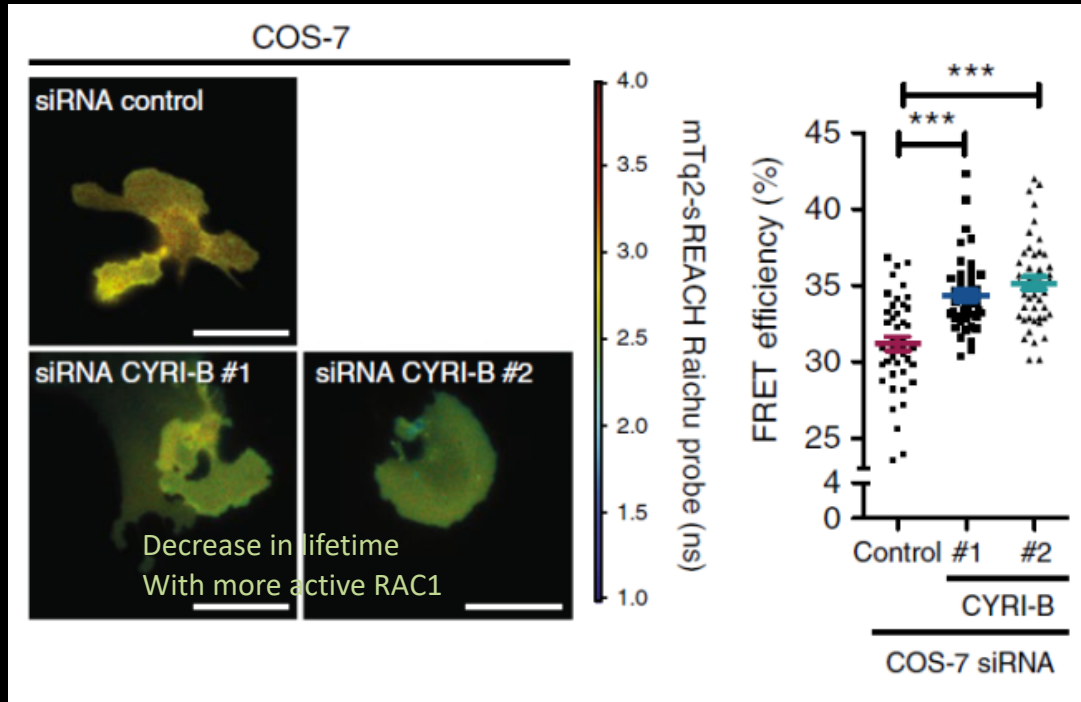
*E. siliculosus*



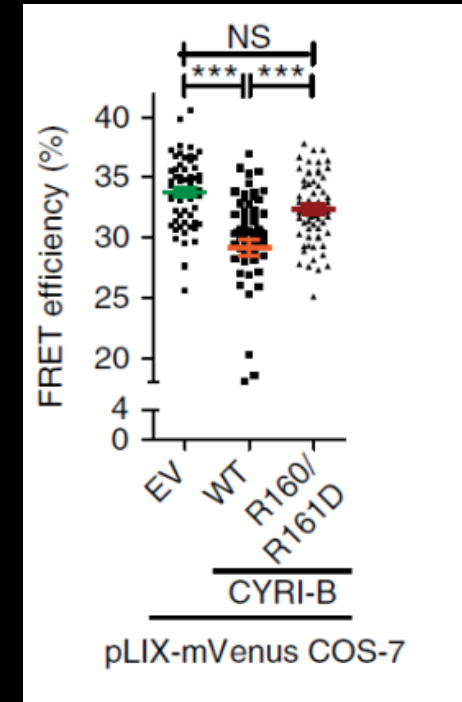
*T. vaginalis*

# CYRI-B opposes RAC1 basal activation

Depleting CYRI-B enhances RAC1 activity

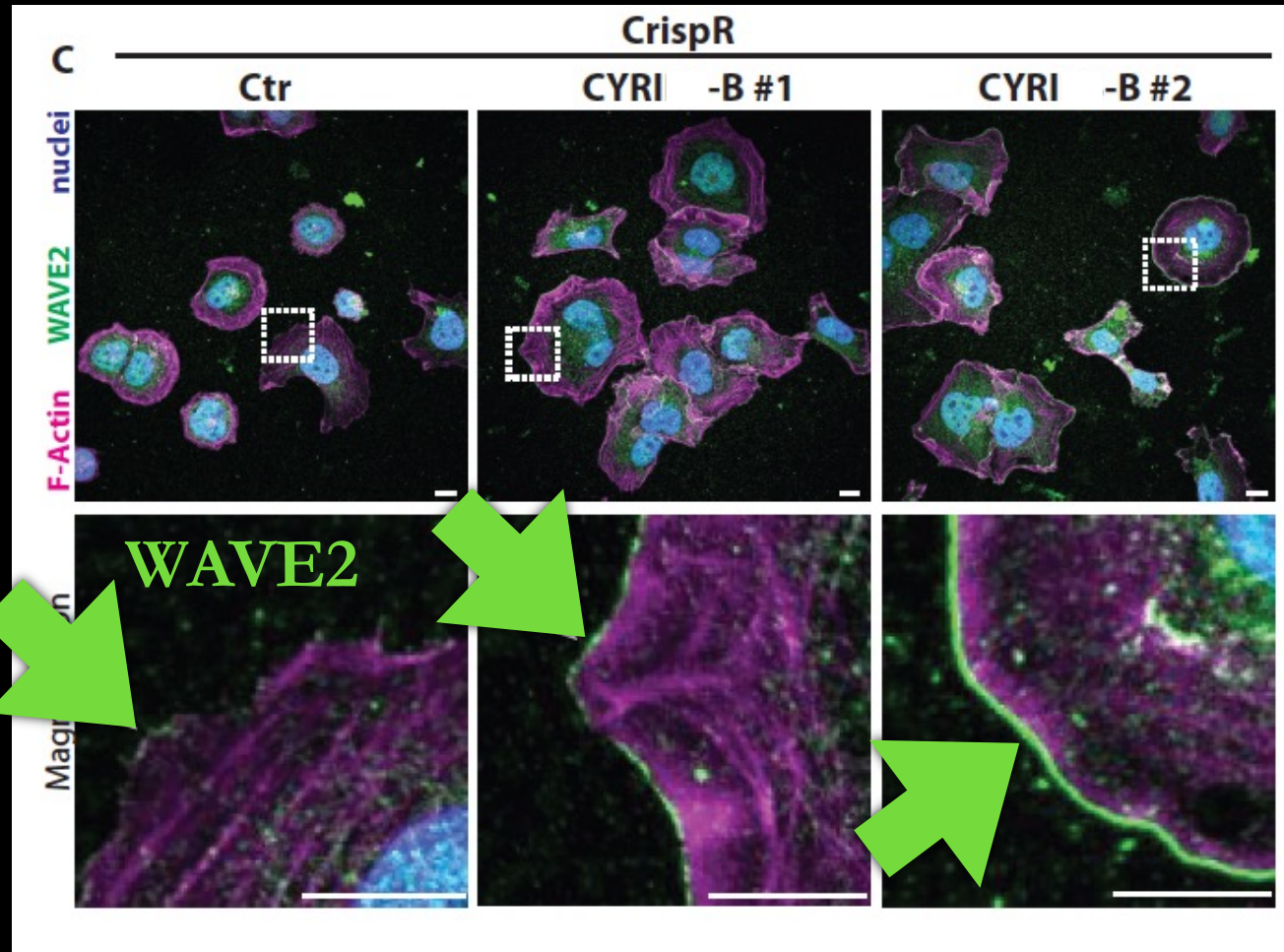


Overexpressing CYRI-B dampens RAC1 activity



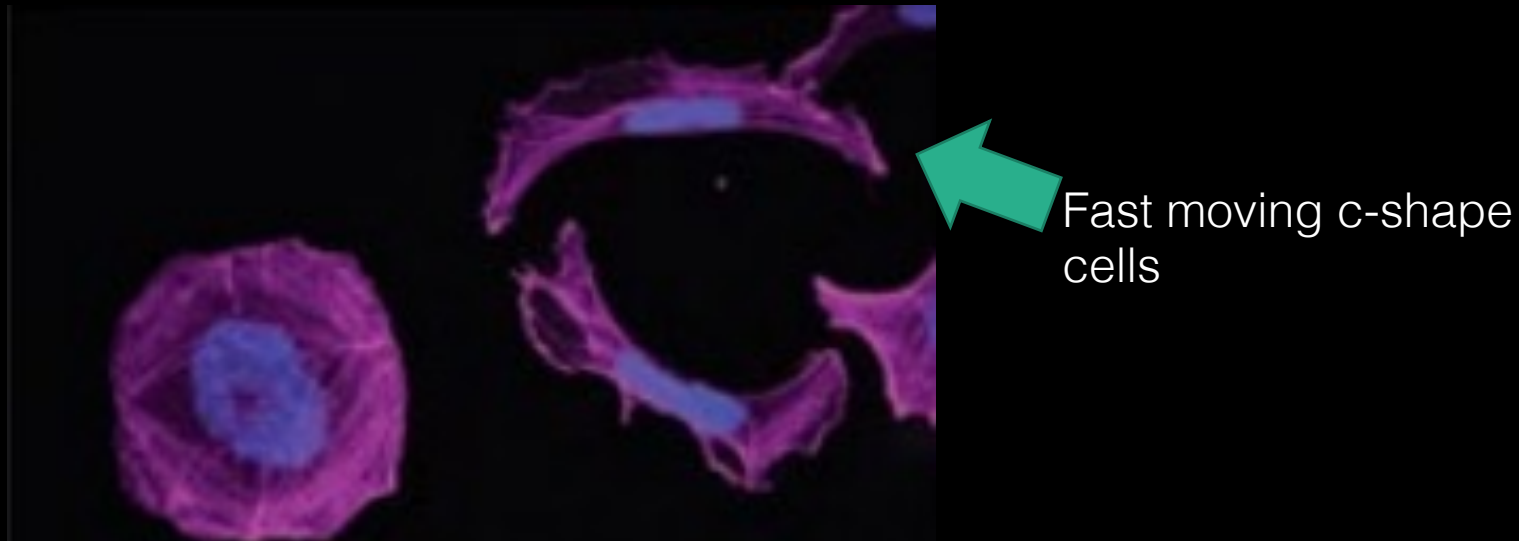
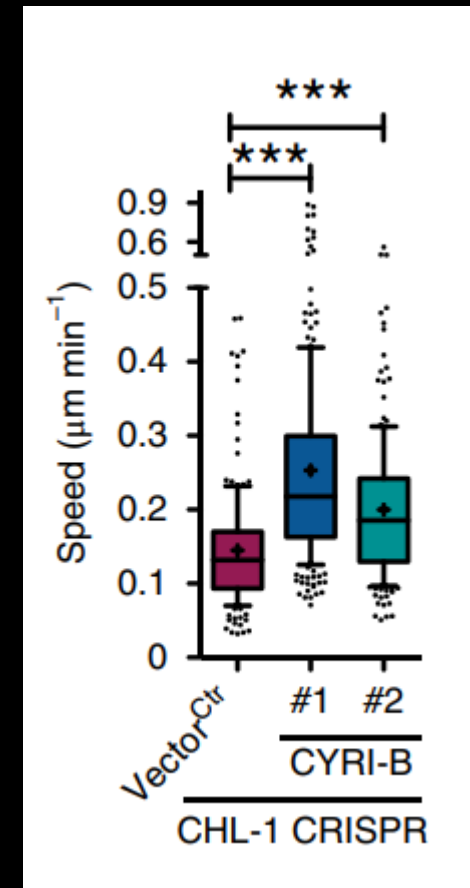
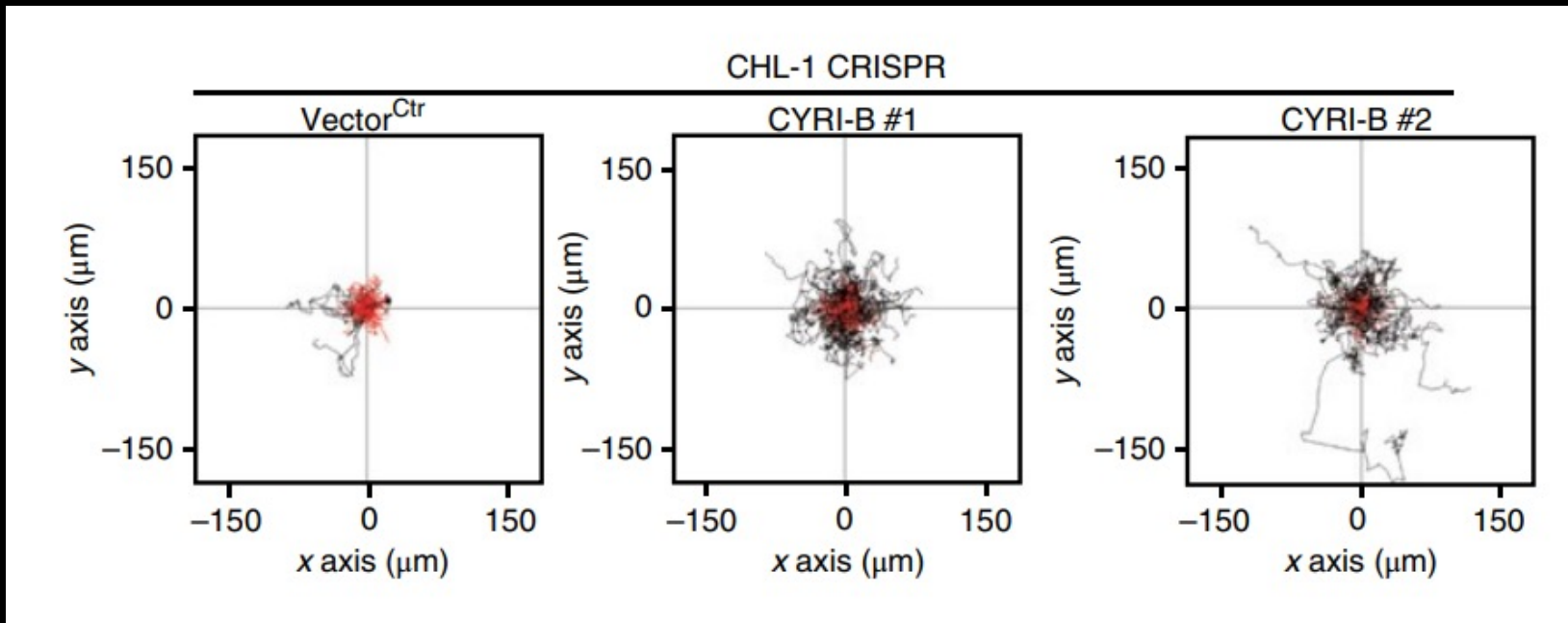
CYRI-B may act as a buffer of RAC1 – but the mechanism is unknown

# CYRI Restricts Lamellipodia



Recruitment of CYRI makes lamellipodia more dynamic

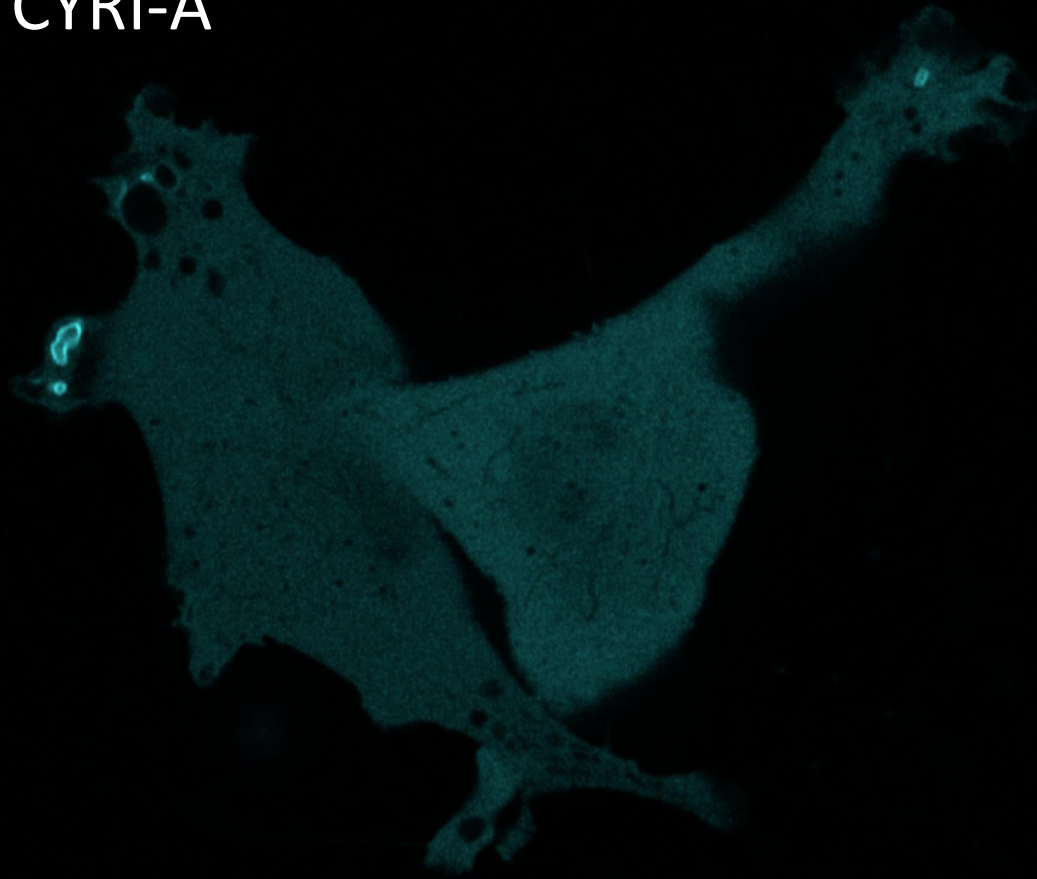
# Loss of CYRI-B can increase migration speed





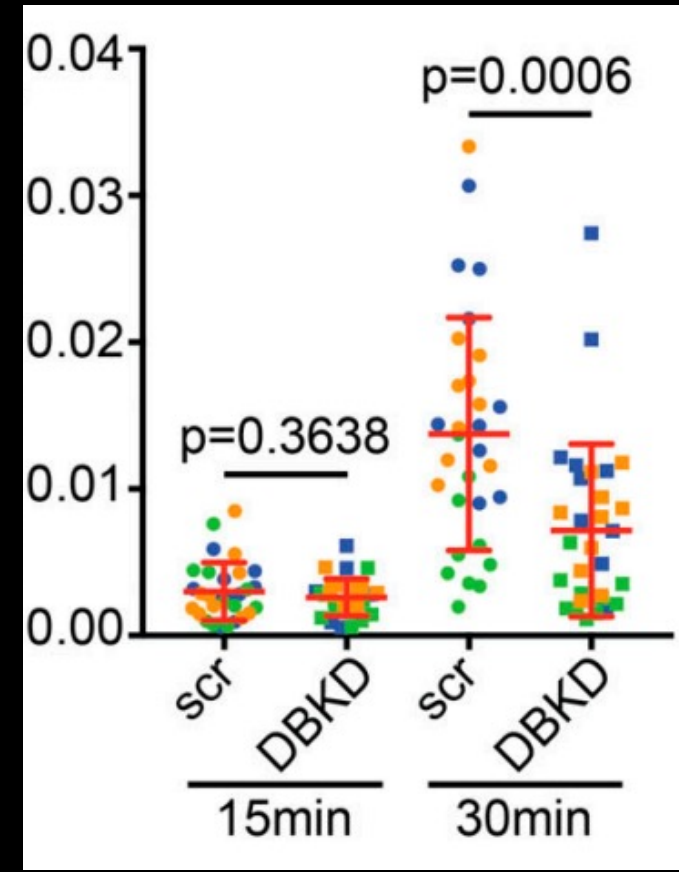
# CYRI Proteins Regulate Macropinocytosis

CYRI-A



10  $\mu$ m

CYRI-A/B double KO shows severe Impairment of macropinocytosis



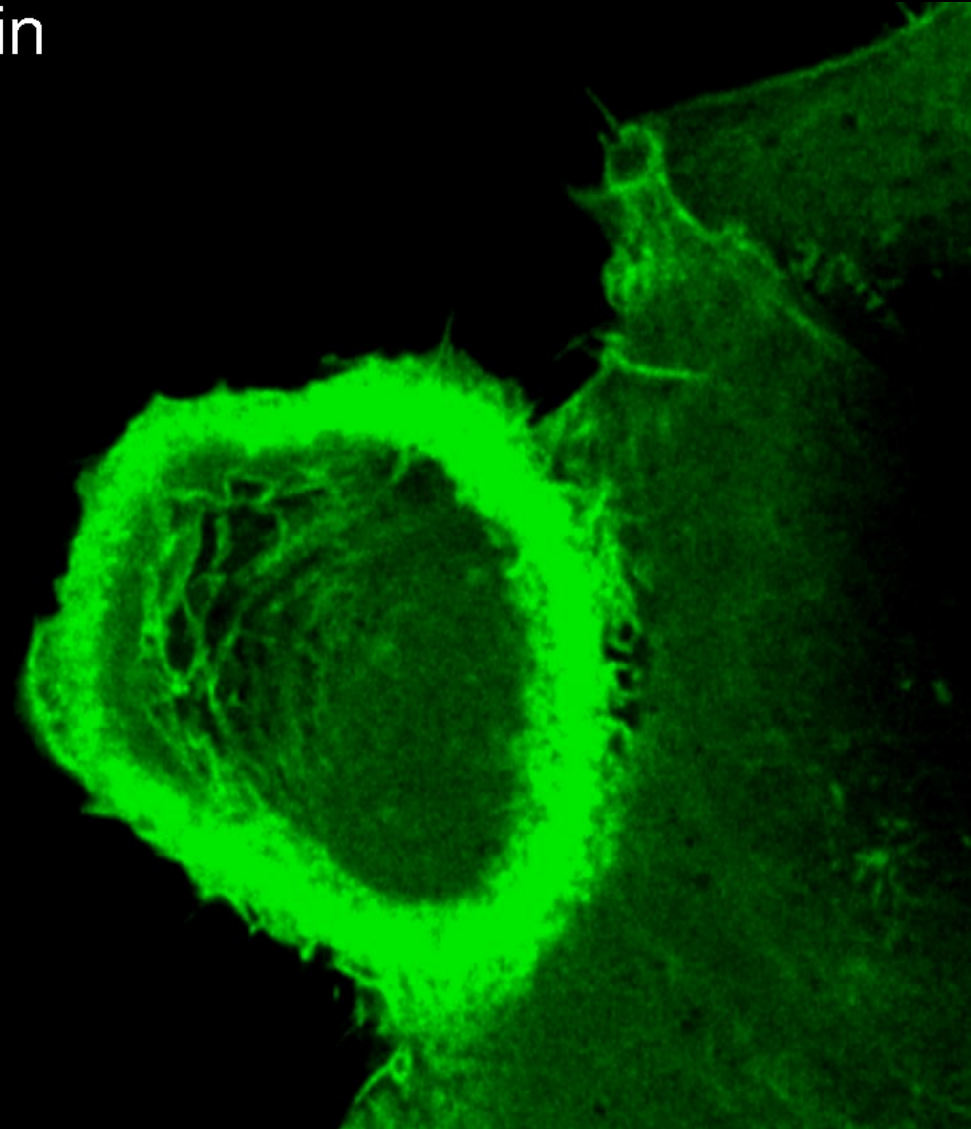
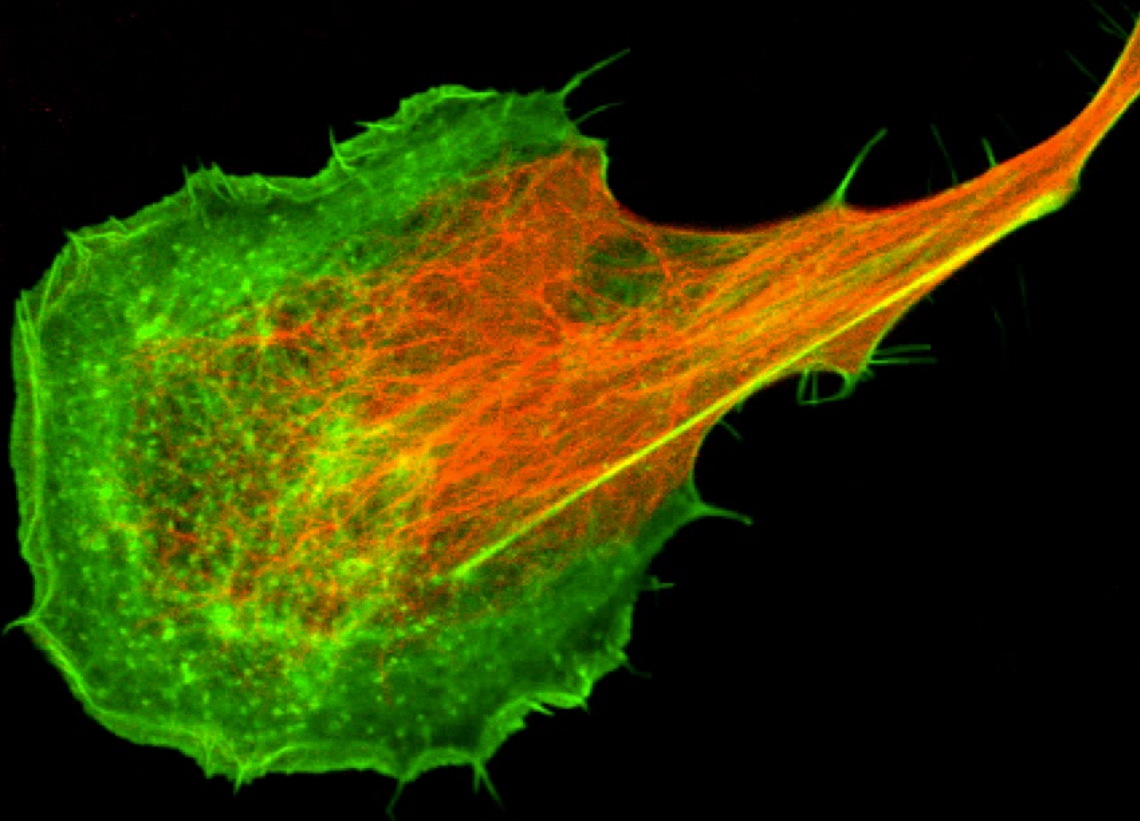
# To eat or to walk? Macropinocytosis vs Migration

00:00

Macropinocytosis fuels tumour growth

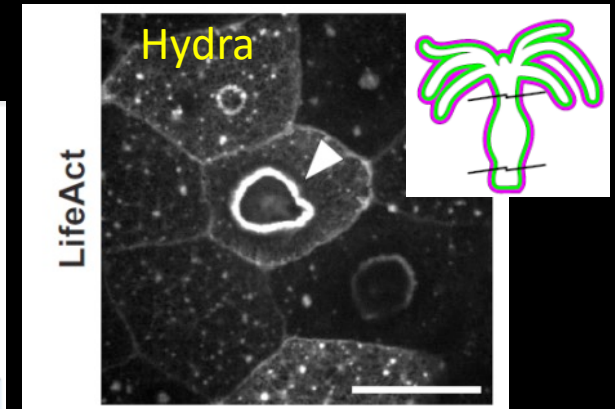
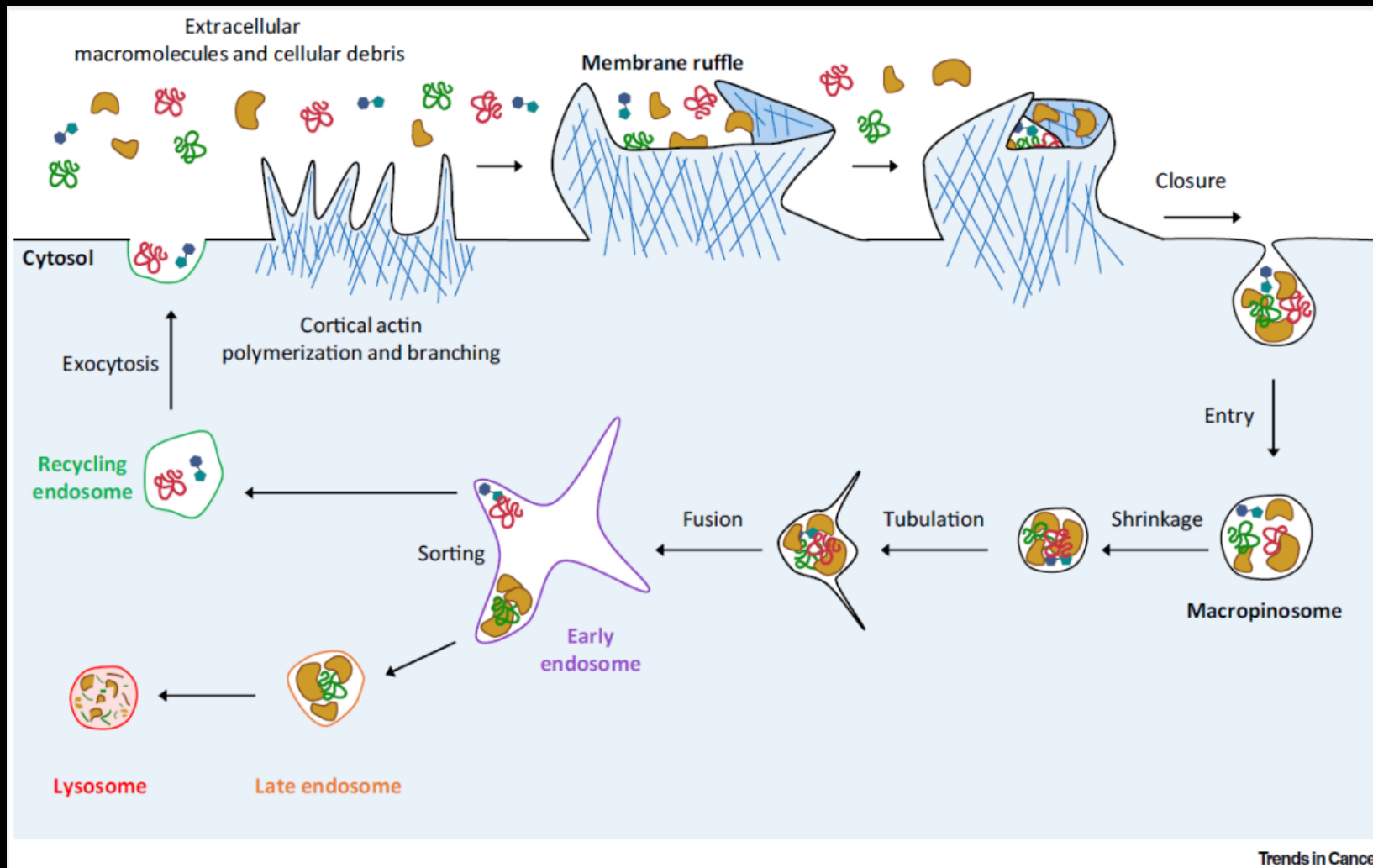
Cell crawling leads to invasion and metastasis

0 min





# Macropinocytosis is a fundamental process



bioRxiv preprint doi: <https://doi.org/10.1101/2021.12.03.471193>;



Veltman et al. eLife 2016;5:e20085. DOI: 10.7554/eLife.20085



# Why do we care about macropinocytosis?

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Uptake of nutrients- Proteins, lipids, cell debris, fuels tumour growth during starvation

Uptake of chemotherapy- Nab-paclitaxel, nanoparticles

Antigen presentation- dendritic cells

Control of adhesion and signaling- chemotaxis, anchorage-dependent proliferation

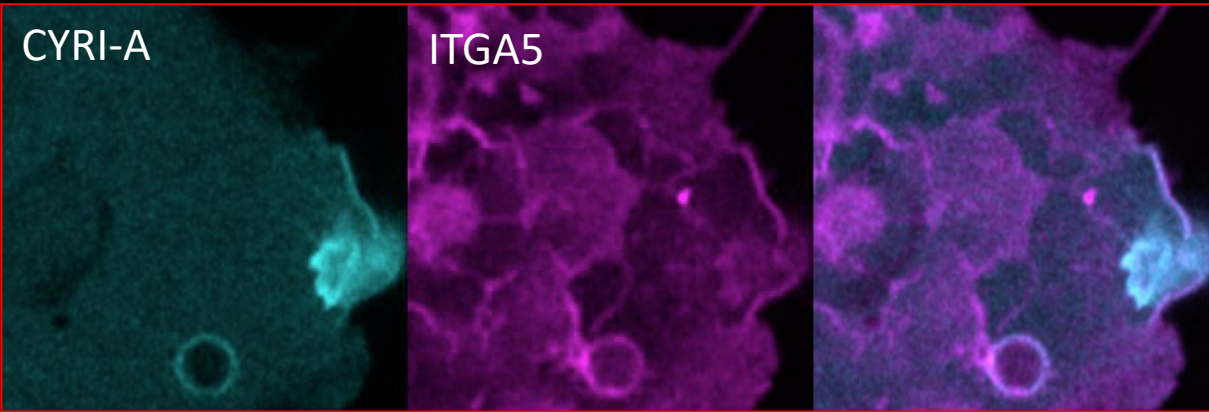
## LETTER

doi:10.1038/nature12138

### Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells

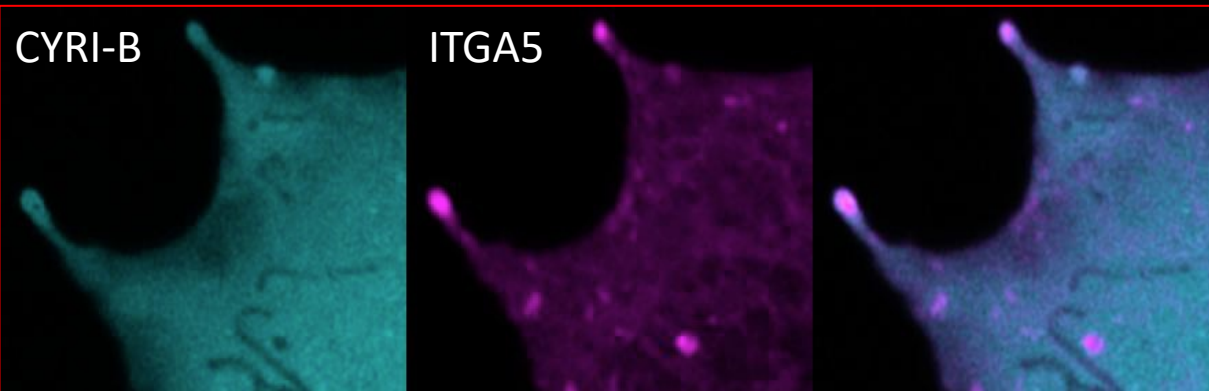
Cosimo Comisso<sup>1</sup>, Shawn M. Davidson<sup>2\*</sup>, Rengin G. Soydaner-Azeloglu<sup>1\*</sup>, Seth J. Parker<sup>3\*</sup>, Jurre J. Kamphorst<sup>4</sup>, Sean Hackett<sup>4</sup>, Elda Grabocka<sup>1</sup>, Michel Nofal<sup>1</sup>, Jeffrey A. Drebin<sup>5</sup>, Craig B. Thompson<sup>6</sup>, Joshua D. Rabinowitz<sup>4</sup>, Christian M. Metallo<sup>3</sup>, Matthew G. Vander Heiden<sup>2,7</sup> & Dafna Bar-Sagi<sup>1</sup>

# CYRI-mediated macropinocytosis recycles integrins



CYRI-A/B depletion results in excess ITG $\alpha$ 5 $\beta$ 1 on the cell surface

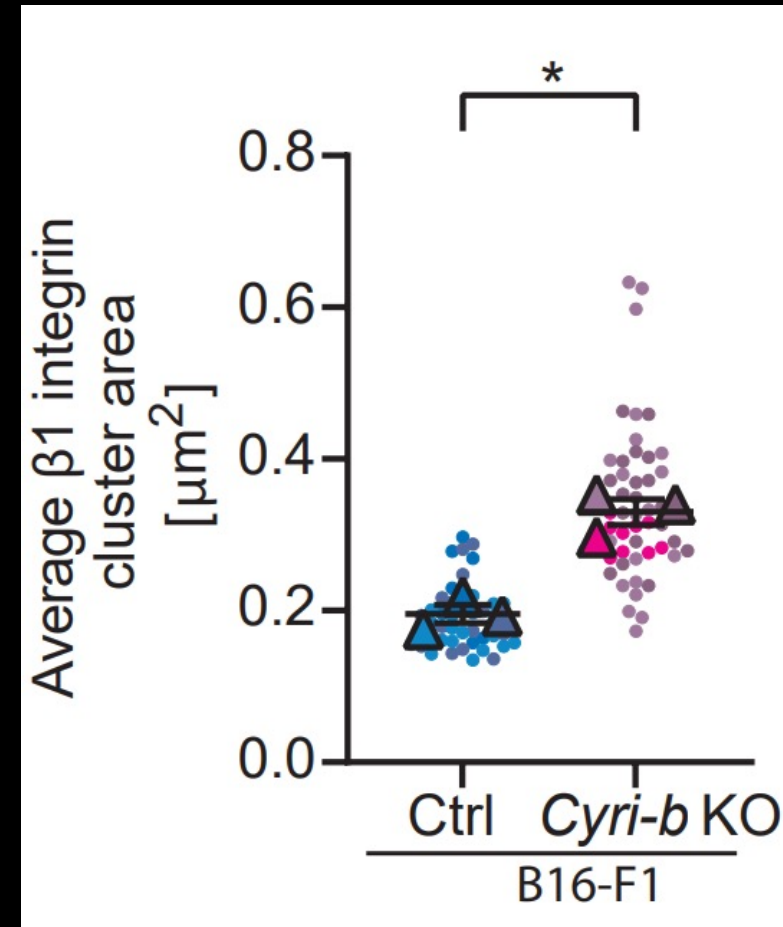
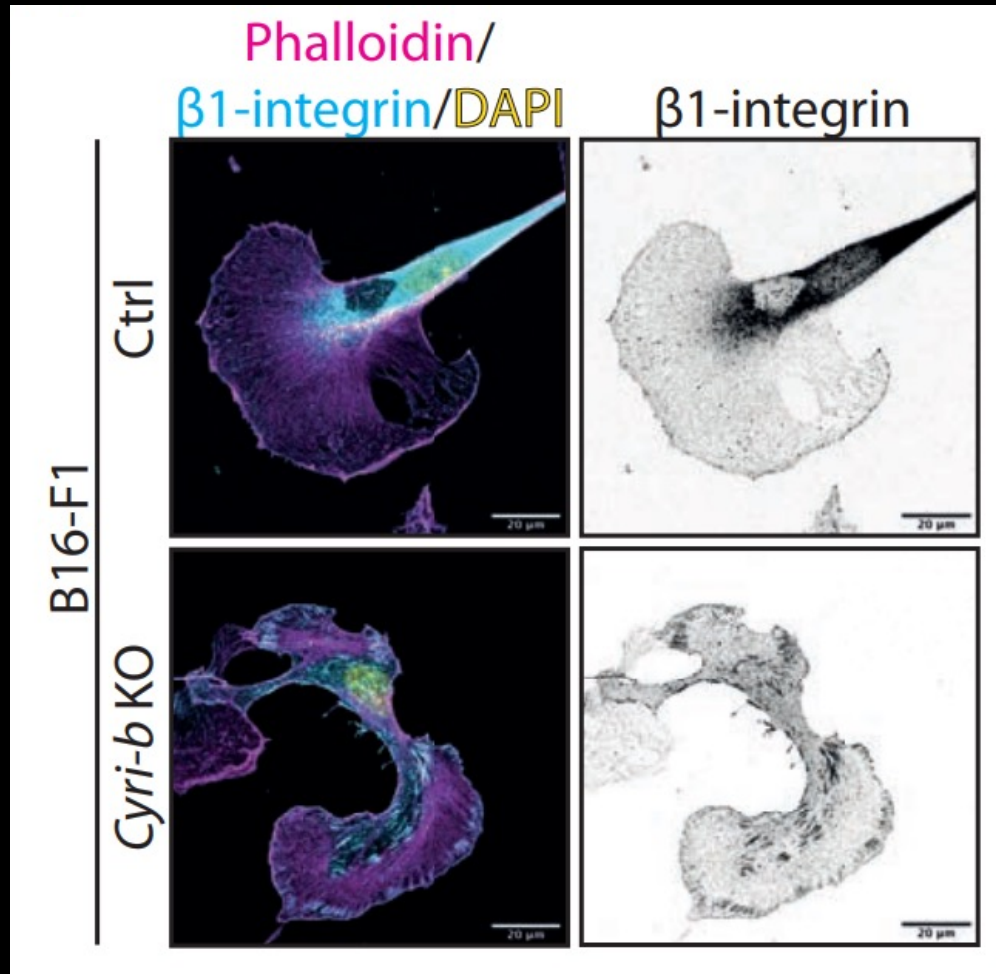
Cells become more migratory and invasive



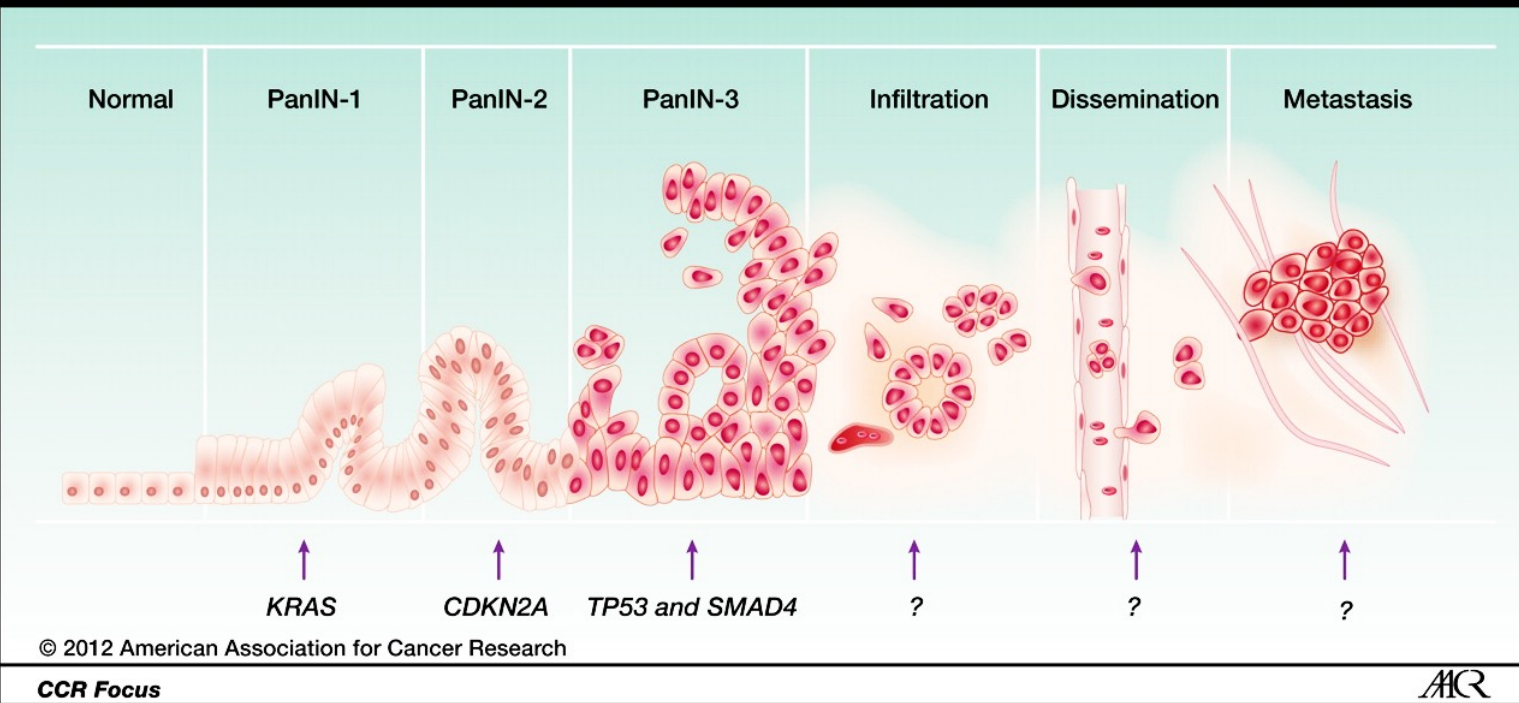
Cells gain anchorage-independent growth capabilities



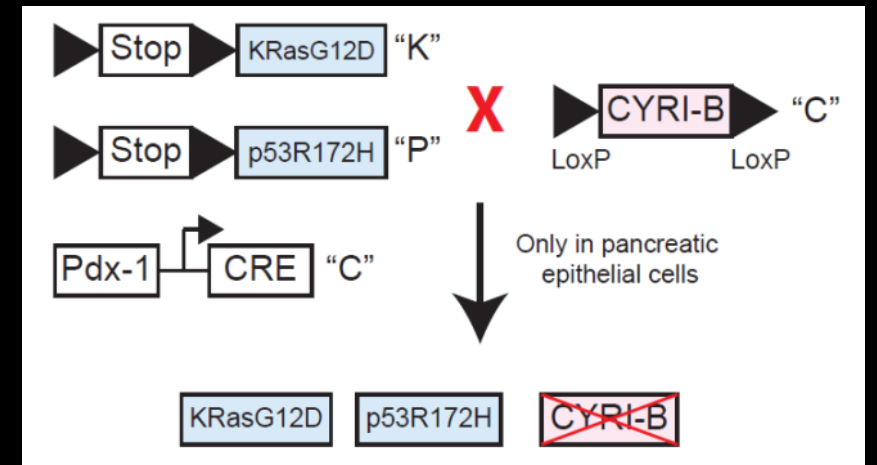
# CYRI-B knockout cells accumulate integrin adhesions



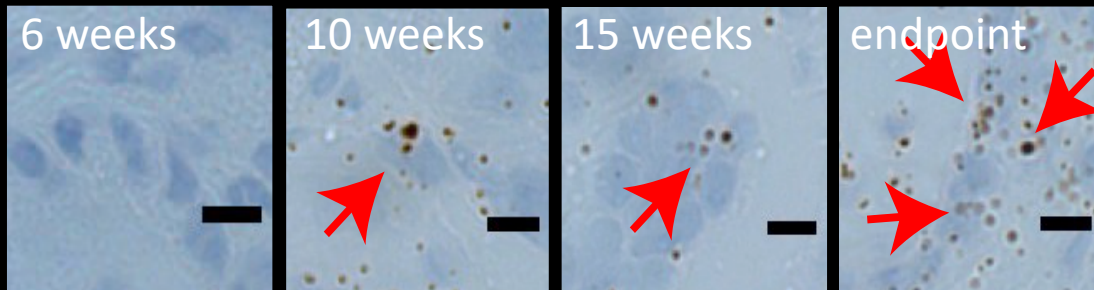
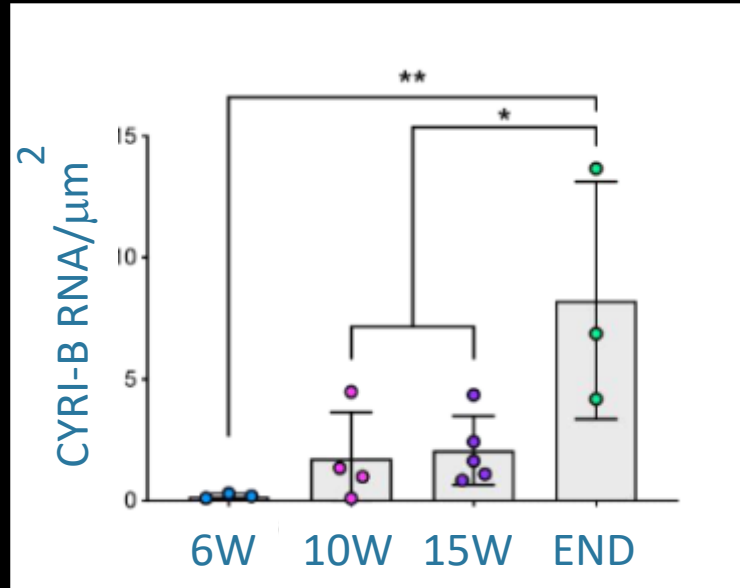
# Does CYRI-B have a role in PDAC progression?



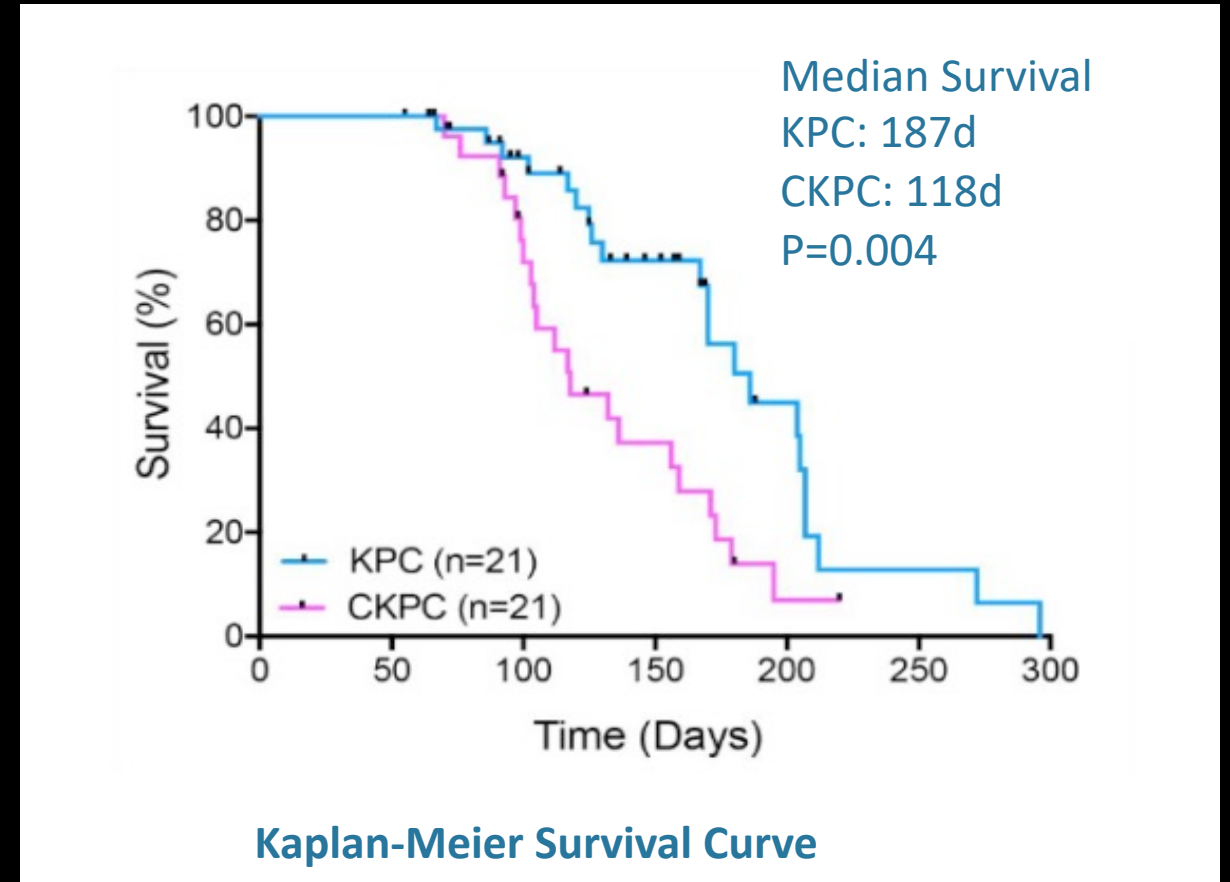
KPC model for metastatic PDAC



# CYRI-B increases during tumour progression

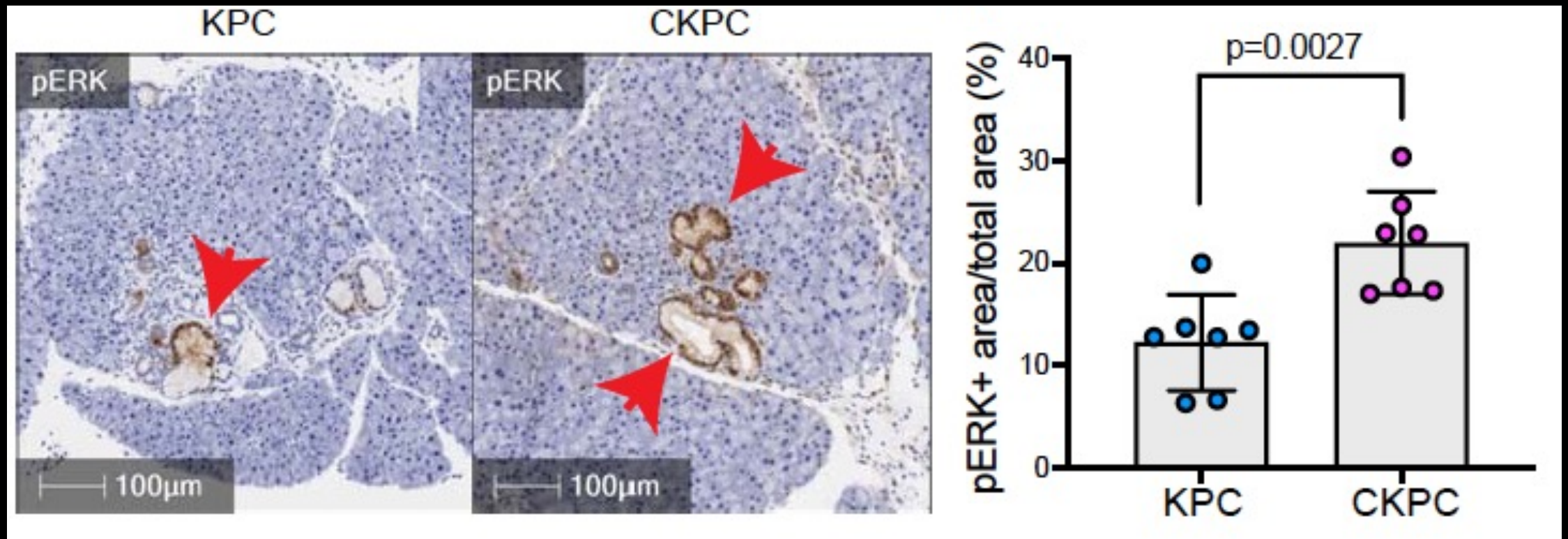


In situ hybridisation of CYRI-B RNA





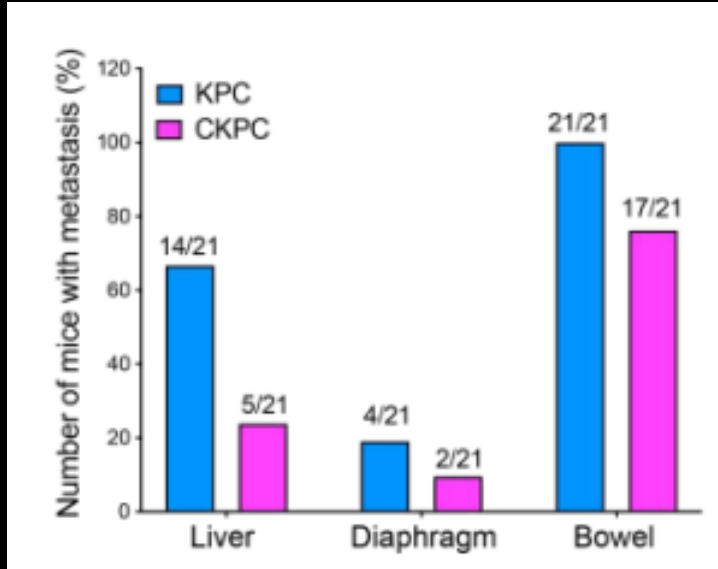
# CYRI-B loss accelerates PanIN at 15 weeks in KPC mice



CYRI-B KO show: Increased p-ERK, p-JNK, Ki67 (proliferation) and more Severe grades of PanIN at 15 weeks.

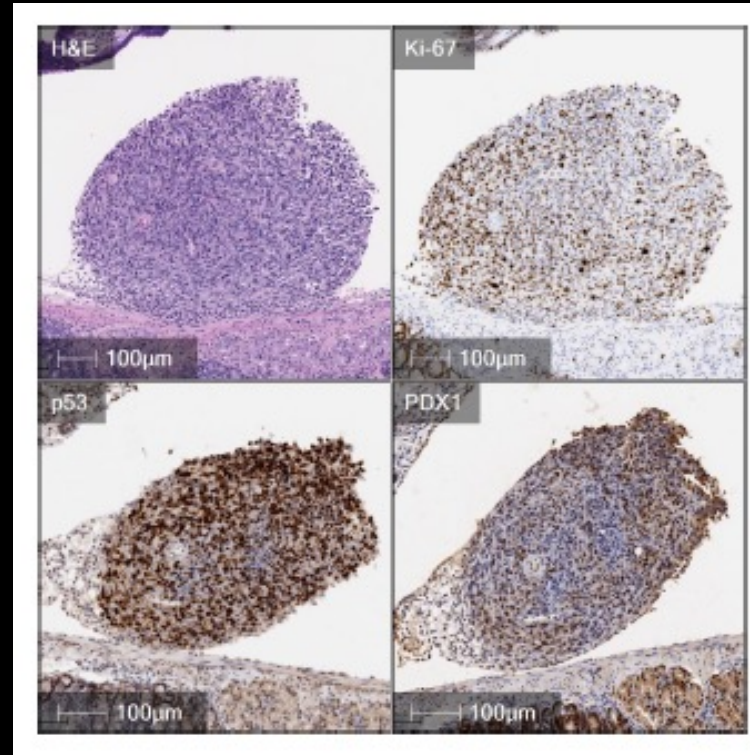
# Cyri-b KO tumours are less metastatic

## Metastasis from Primary

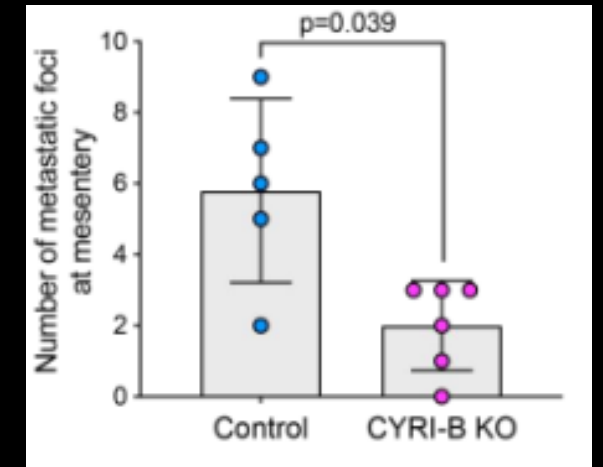


% Mice with metastasis

## Intraperitoneal seeding transplant model



Mesenteric mets

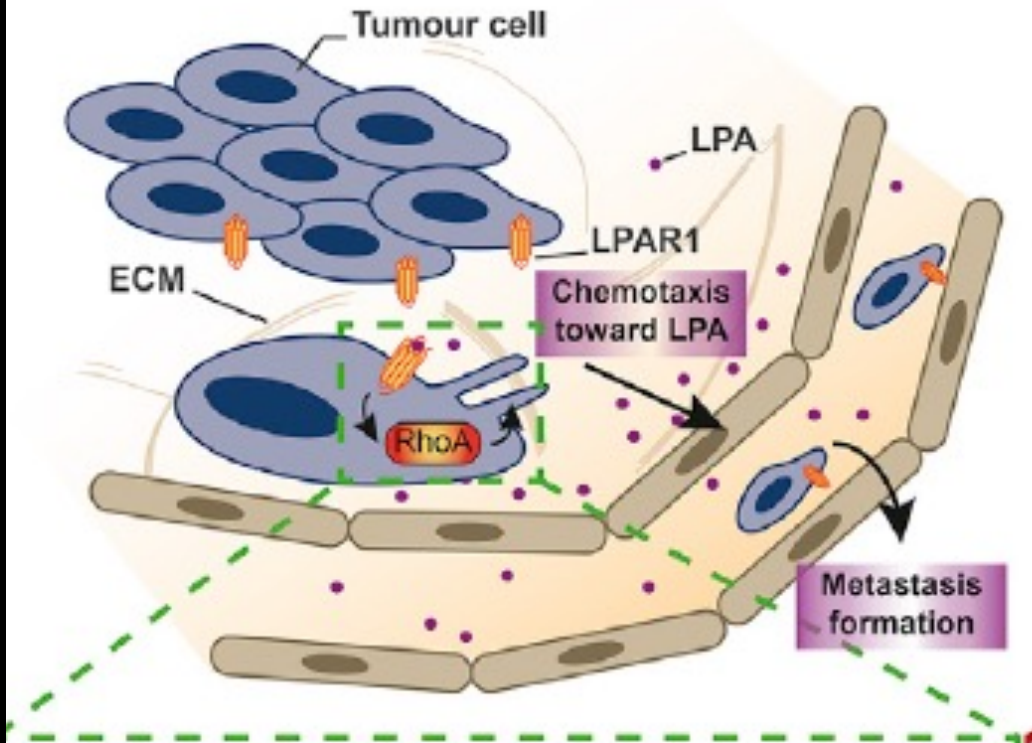


Number of mesenteric mets

# N-WASP Control of LPAR1 Trafficking Establishes Response to Self-Generated LPA Gradients to Promote Pancreatic Cancer Cell Metastasis

Juin et al., Dev. Cell 2019

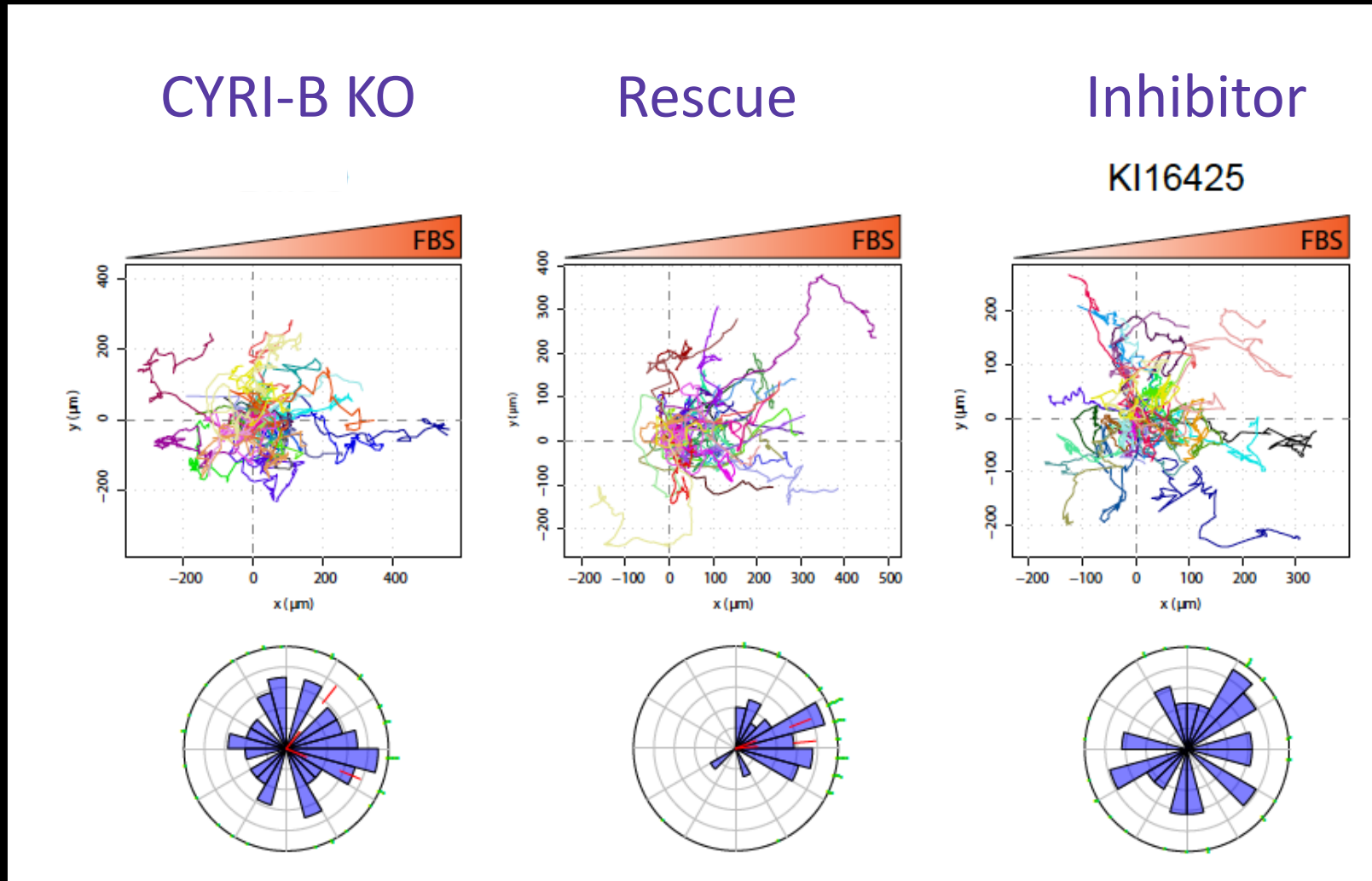
Lysophosphatidic acid-mediated chemotaxis drives metastasis



LPAR1 recycling mediates chemotaxis in PDAC cells- impacting metastasis



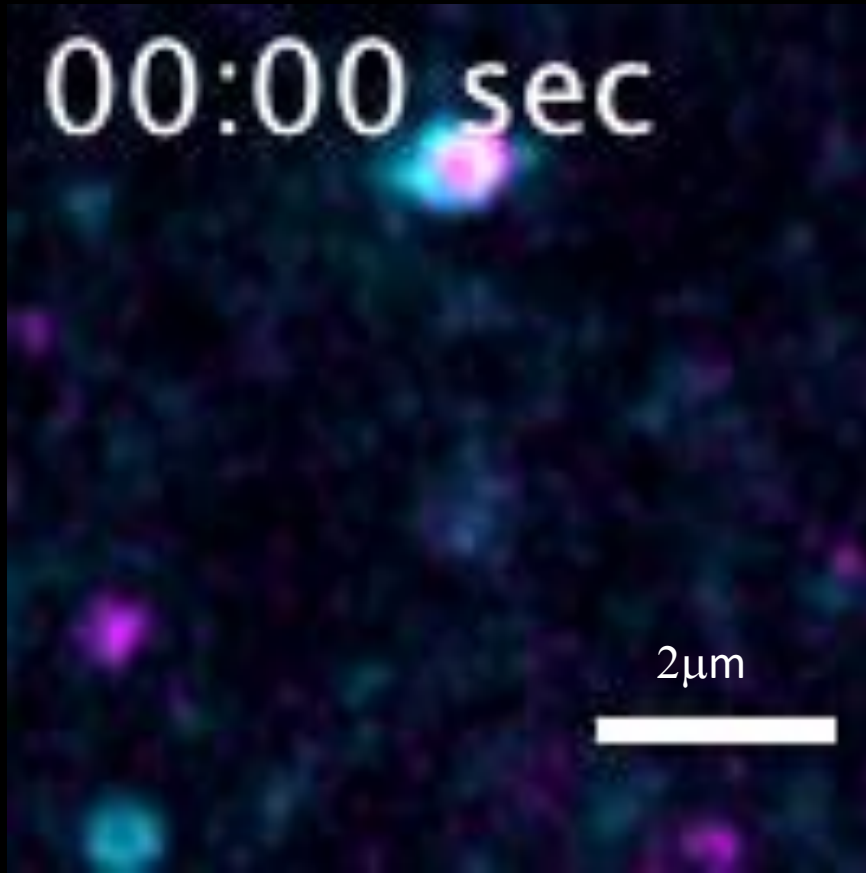
# *Cyri-b* KO cells fail to chemotax to LPA in serum



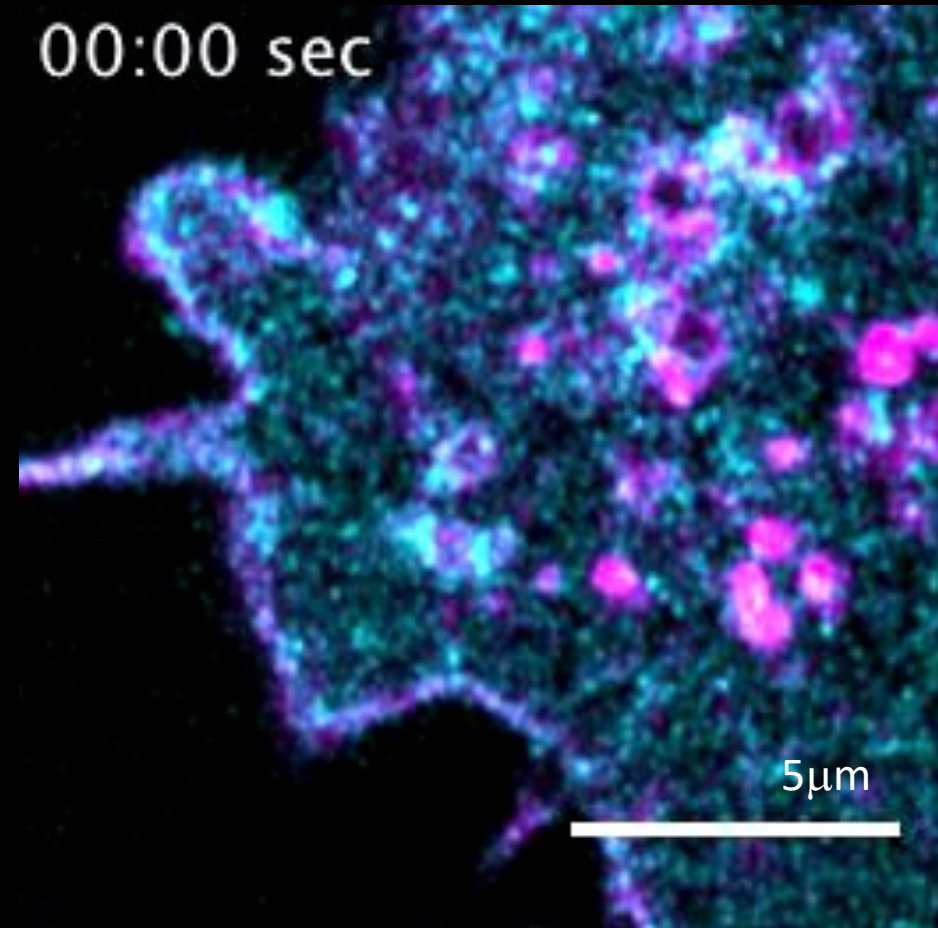
Motility is not reduced, but directionality is lost in *Cyri-b* KO

# CYRI co-localises with LPAR1 at Macropinocytic Events

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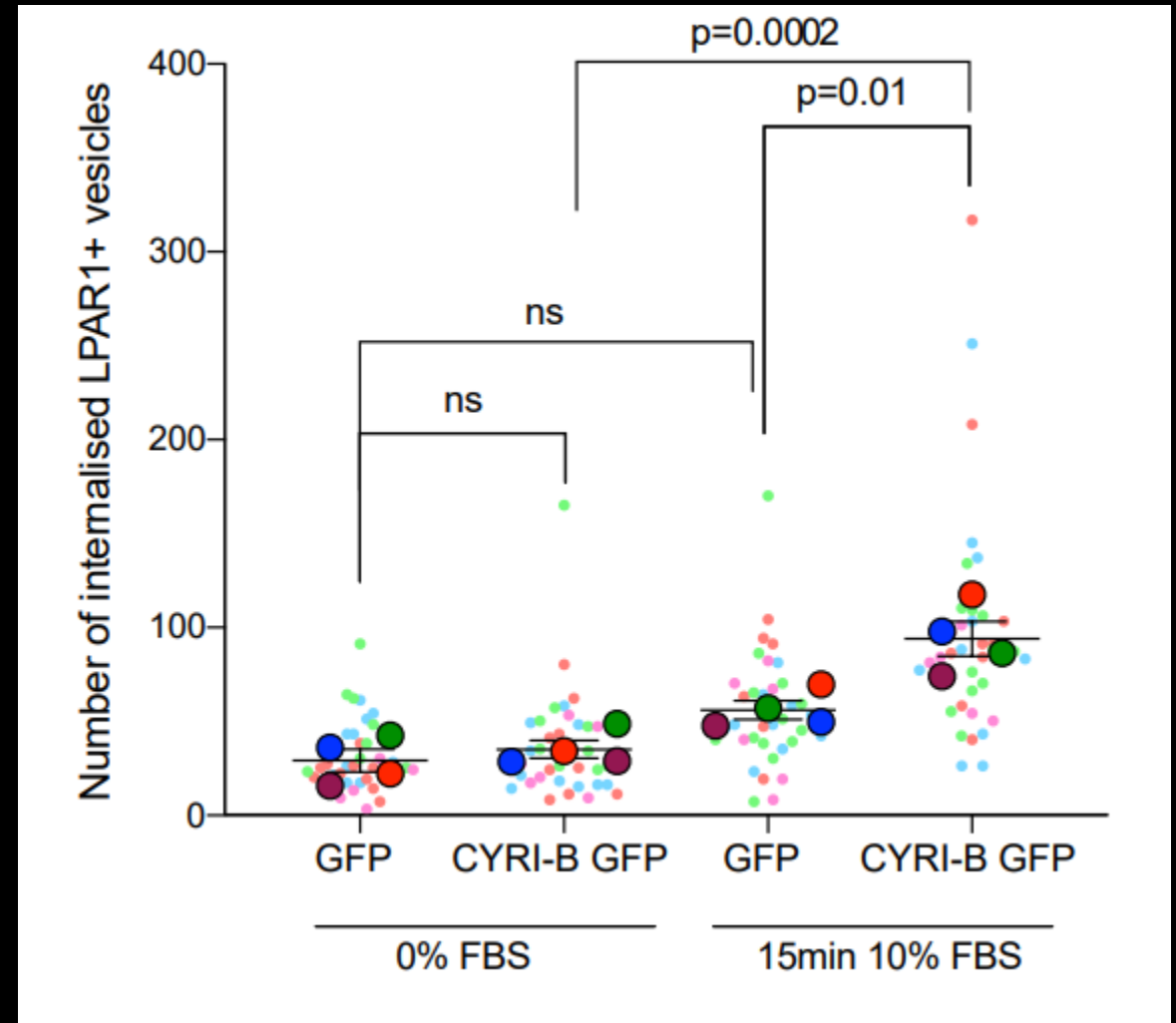
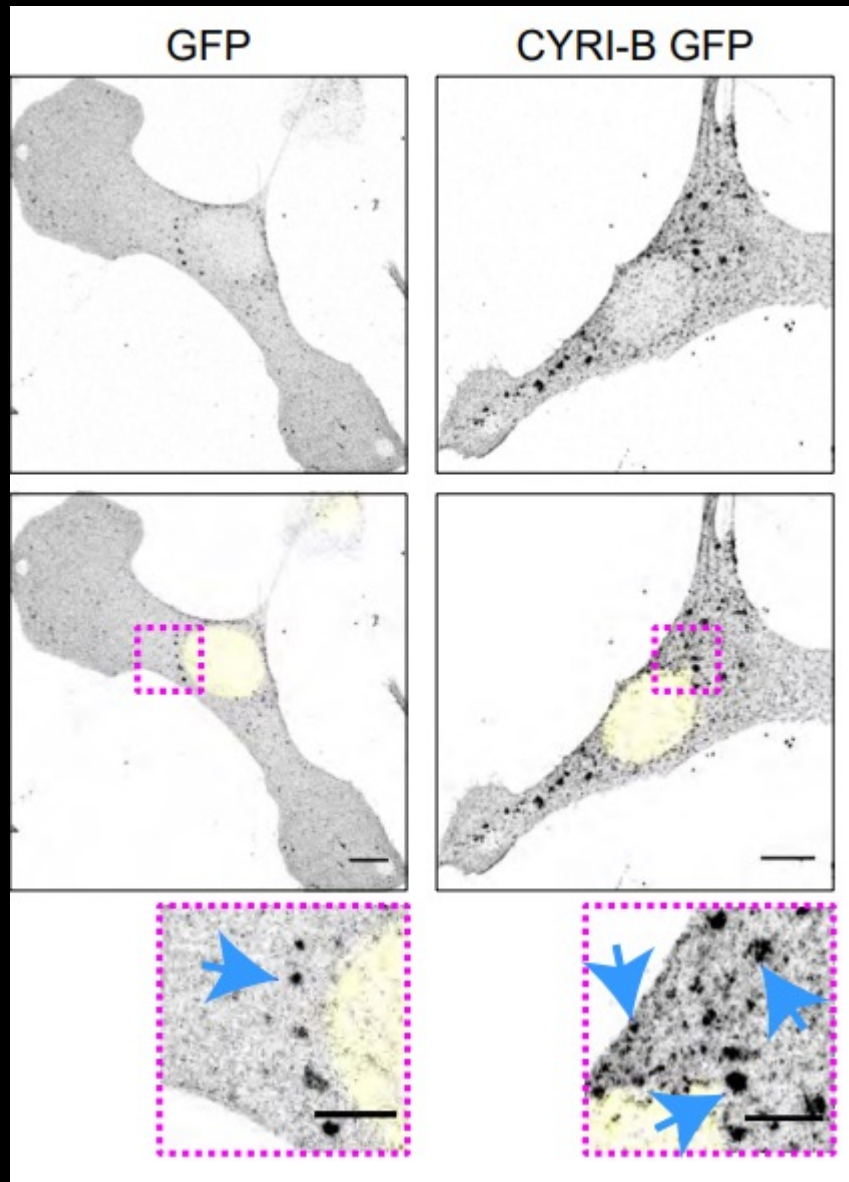


LPAR1 + 70kDa Dextran



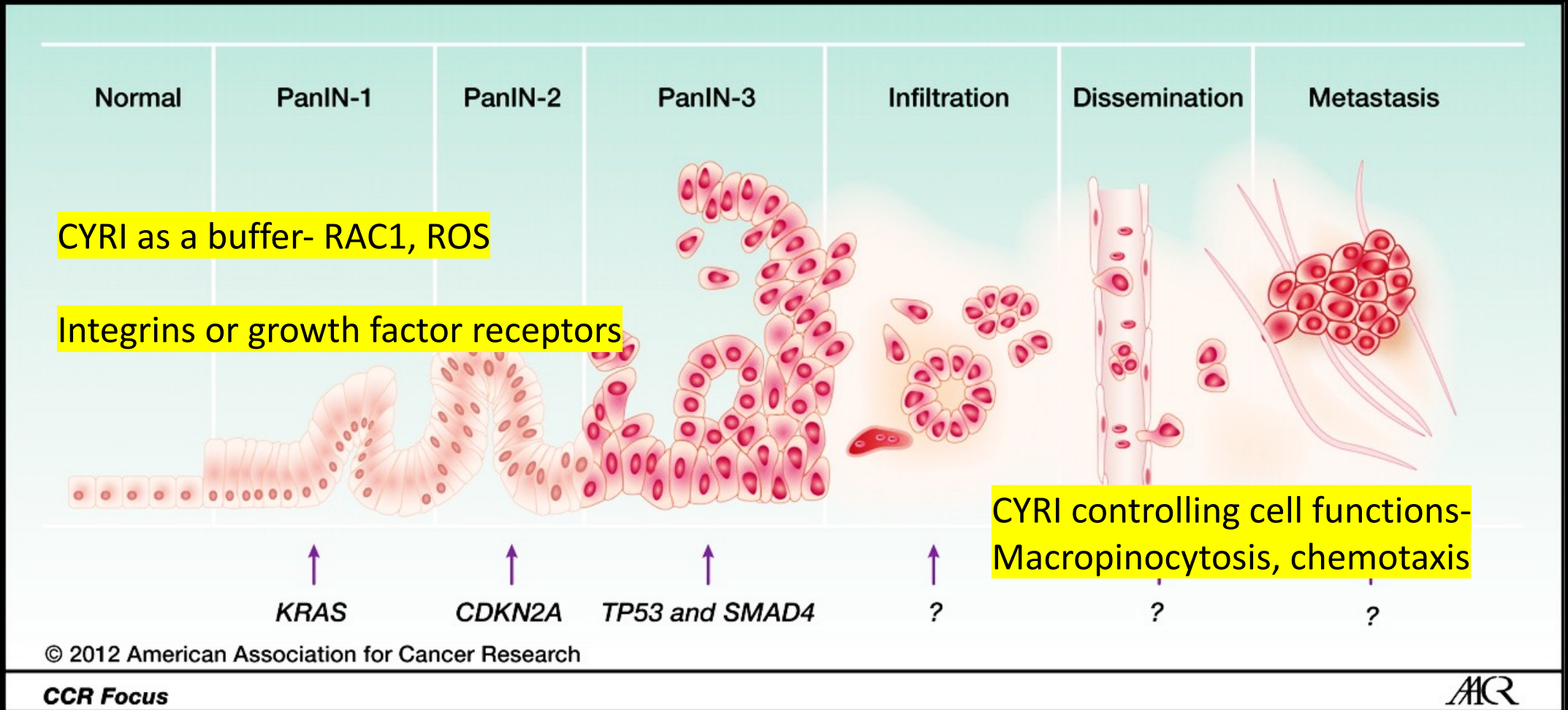
CYRI-B + LPAR1

# CYRI-B depleted cells show impaired LPAR1 internalisation

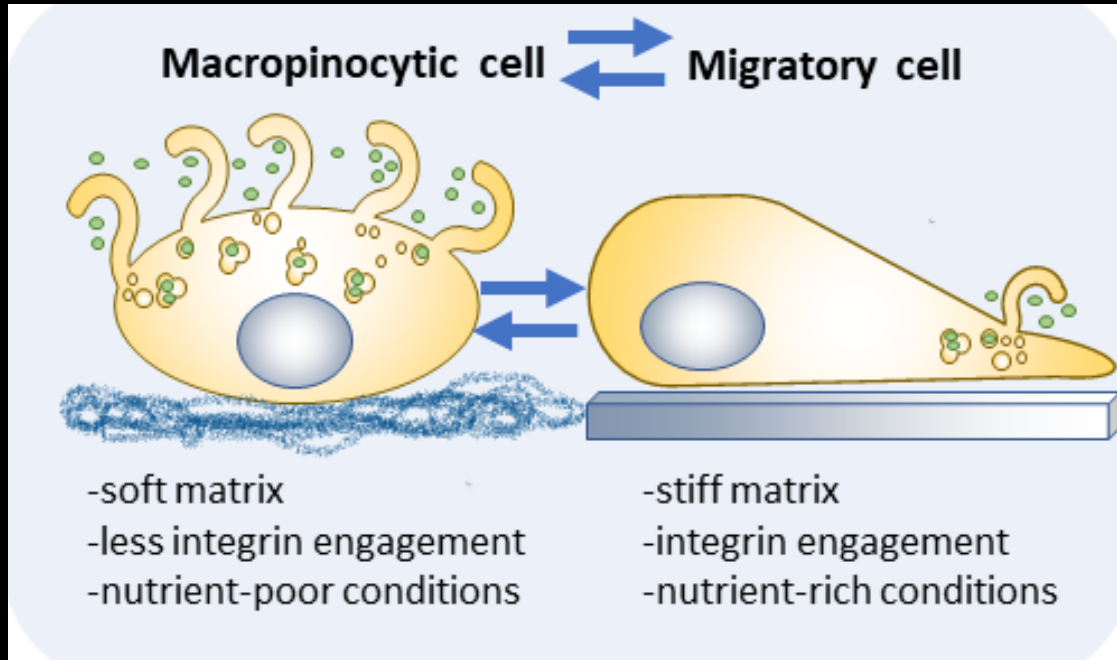




# CYRI-B in early and late PDAC progression

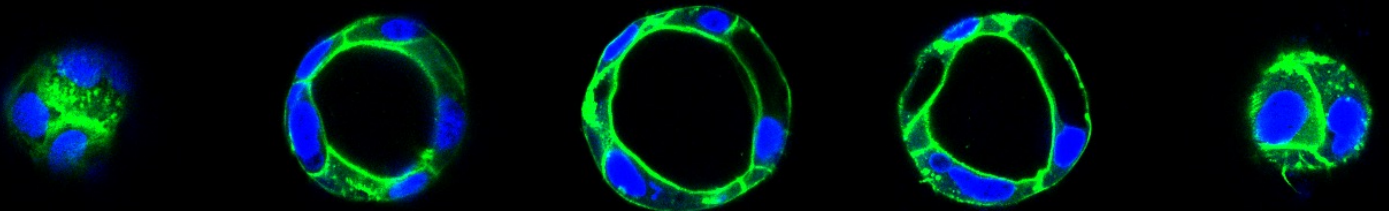


# How do cells balance macropinocytosis with migration?



Is macropinocytosis important for metastasis?

Can we alter macropinocytosis for therapeutic benefit?



# Thank You!

## Machesky Lab

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Eugenia Barros  
Wei Du  
Shatruhan Rajput

Osian Jones  
Li Ma  
Sayantkia Gosh



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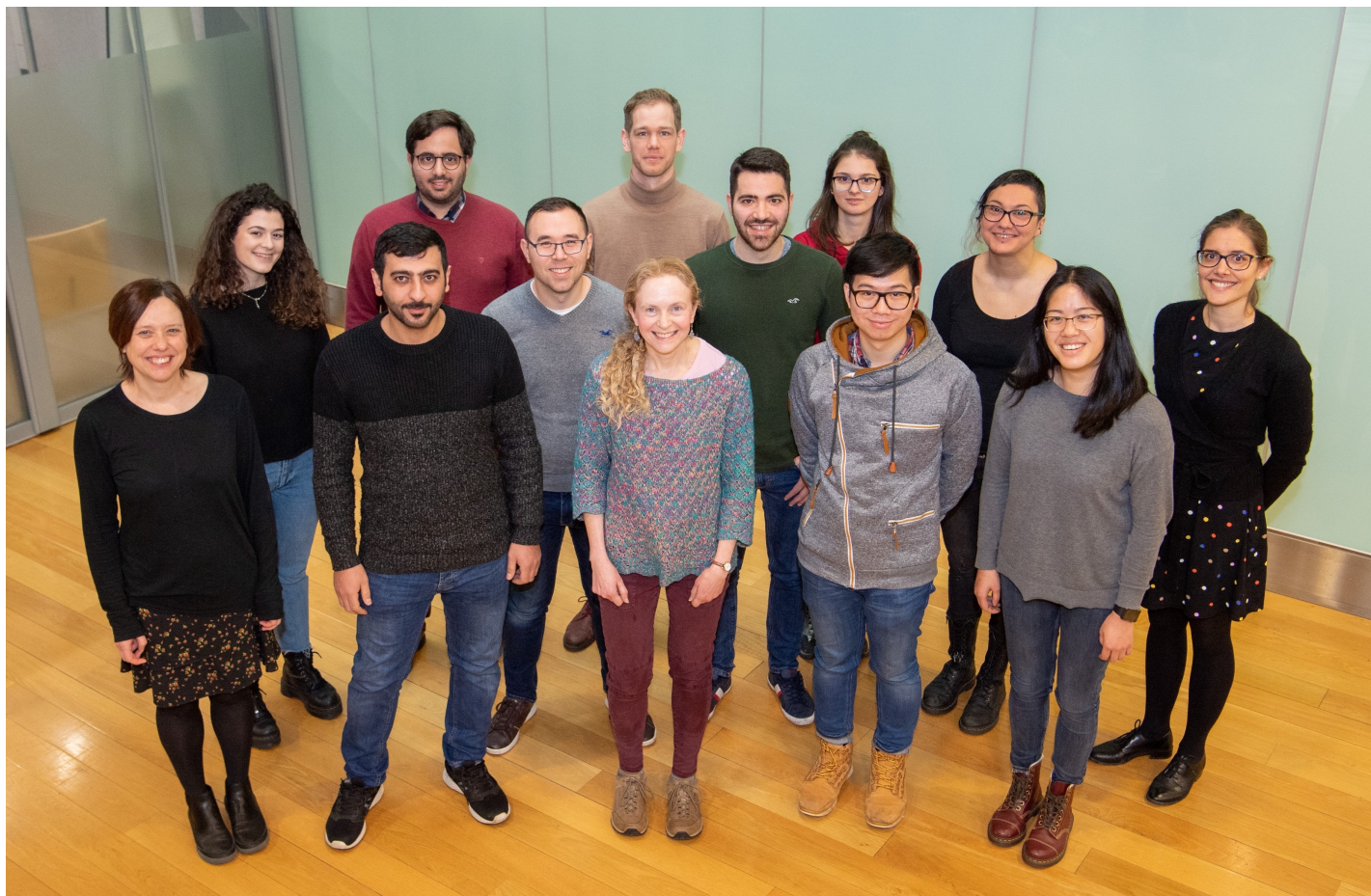
Elaine Wingsee Ma

Hakem Albilasi

Savvas Nikolau

James Drew

# Thank You!



Collaborations:

Robert Insall



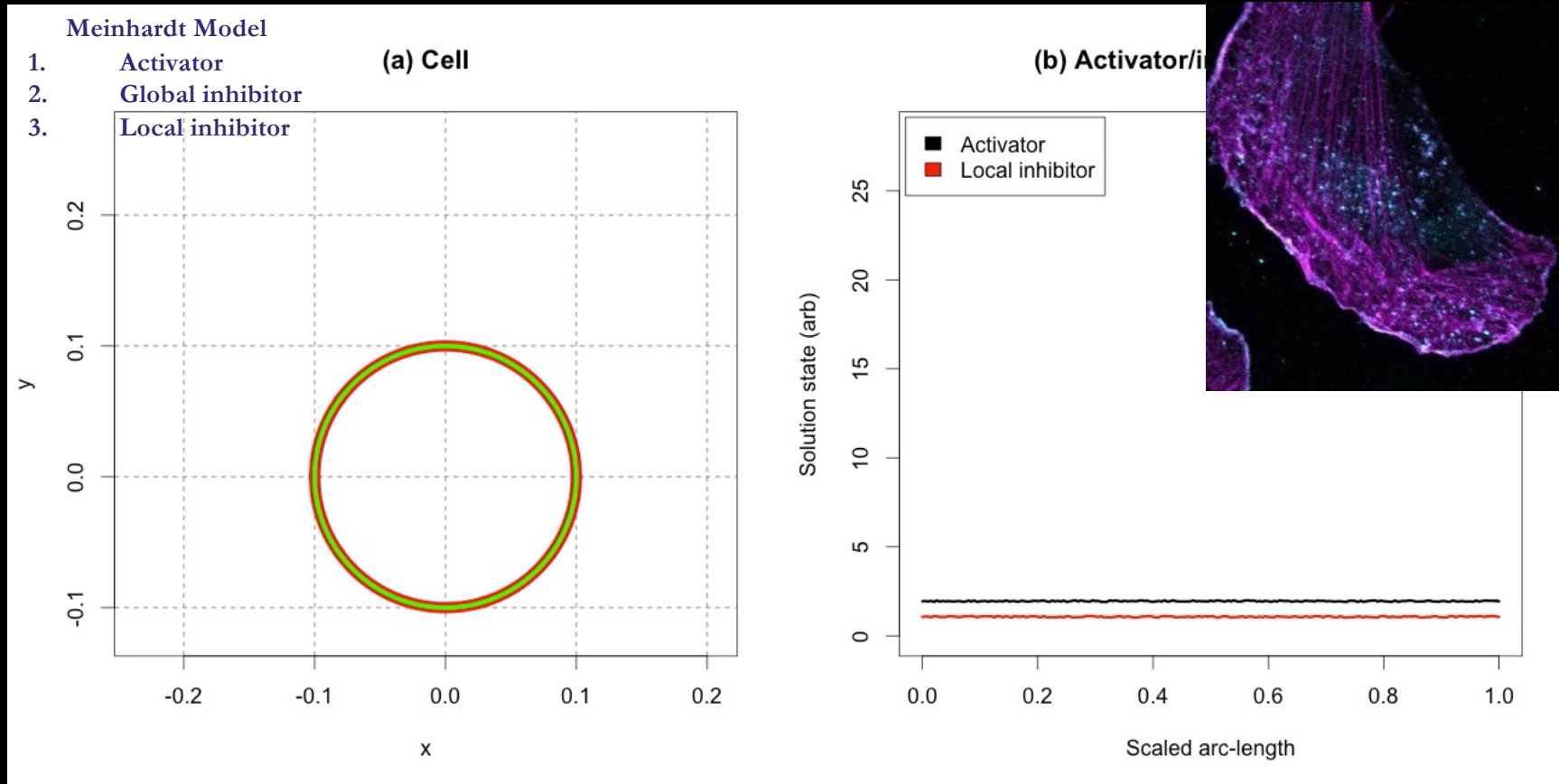
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RESEARCH  
UK

BEATSON  
INSTITUTE



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CAMBRIDGE

# CYRI-B is a “local inhibitor” of protrusions



“Activator” is Rac1 and WAVE Complex

Local inhibitor follows activator- builds up and results in splits