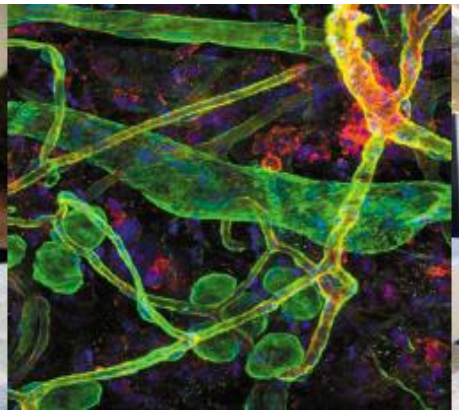
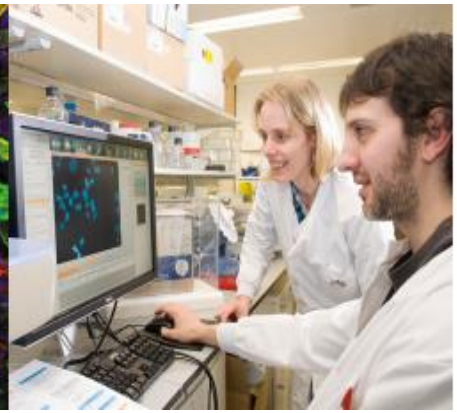
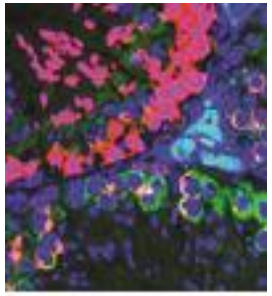
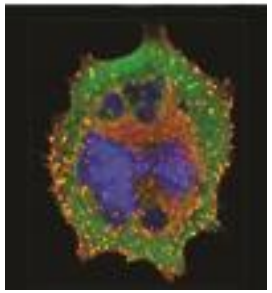
CANCER RESEARCH UK | BEATSON INSTITUTE



Cancer Research UK Beatson Institute





Our Mission

Cancer discovery for patient benefit

Objectives

- Establish an outstanding basic research programme into the mechanisms of cancer biology
- Use our discoveries to identify new therapeutic targets
- Develop strong clinical links to translate our research into novel therapeutic strategies

Key Research Themes

- Regulation of invasion & metastasis
- Regulation of cancer metabolism, growth & survival

CANCER RESEARCH UK | BEATSON INSTITUTE

The Beatson Institute for Cancer Research

- Named after Sir George Beatson- pioneer of endocrine therapy for cancer
  - Established in 1912
- The BICR is an independent organisation
  - Board of Governors: Chair Nic Jones (Harpal Kumar to March 2013)
  - Director accountable to the board for the management
- One of 5 core funded CR-UK Institutes
- Moved into new building in 2008
- 14+3 Group Leaders plus Drug Discovery Programme

CANCER RESEARCH UK | BEATSON INSTITUTE

Two coordinated aims

Develop strength within the Beatson Institute

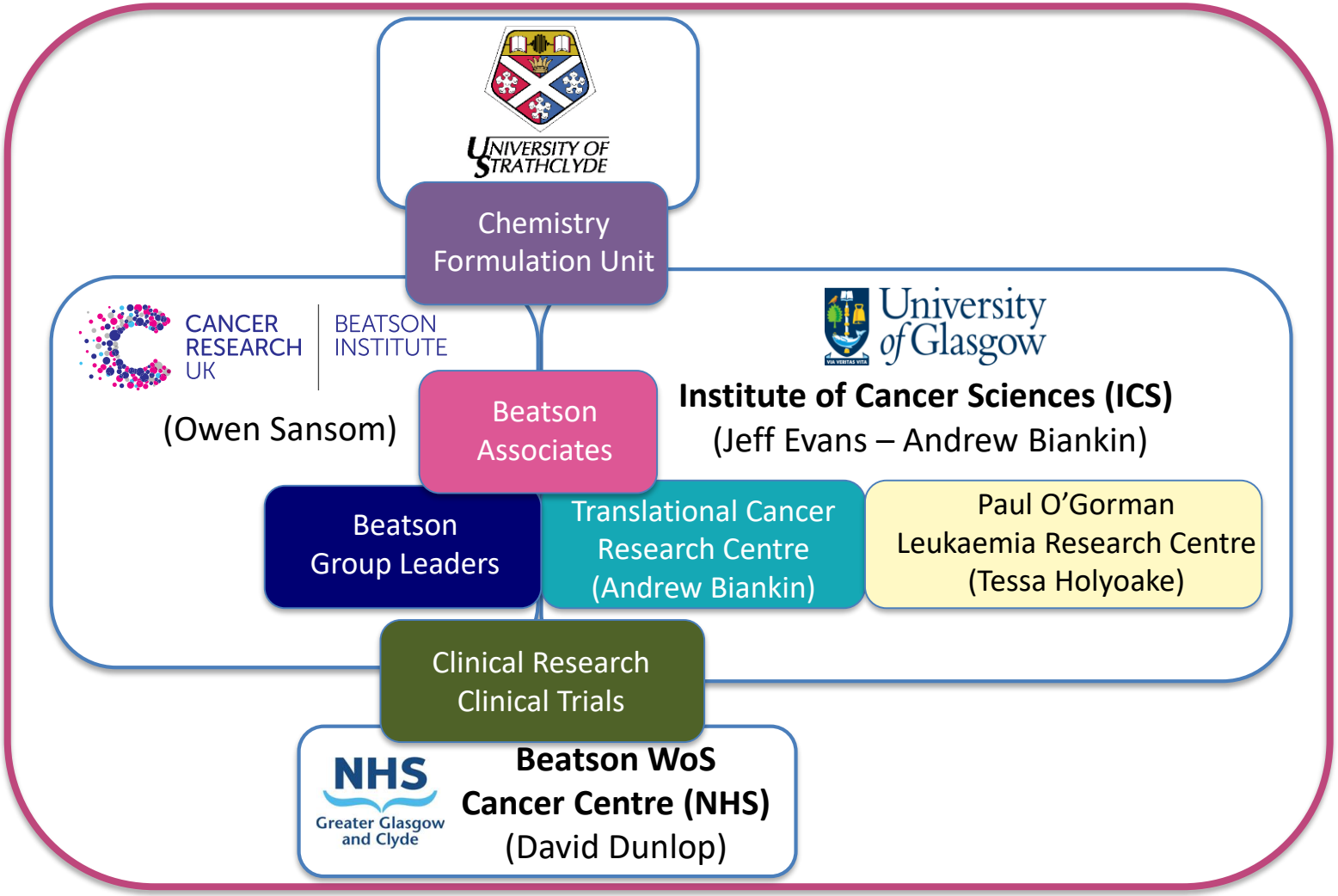
- Basic Science
- Advanced Technologies
- Drug Discovery

Build interactions outside the Beatson Institute

- Translational Cancer Research
- Clinical Cancer Research

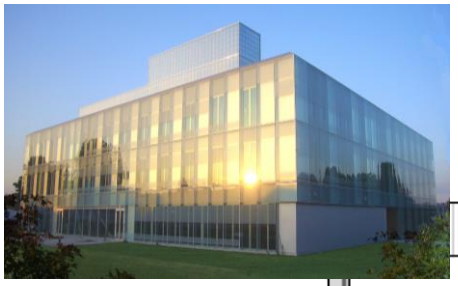
CANCER RESEARCH UK | BEATSON INSTITUTE

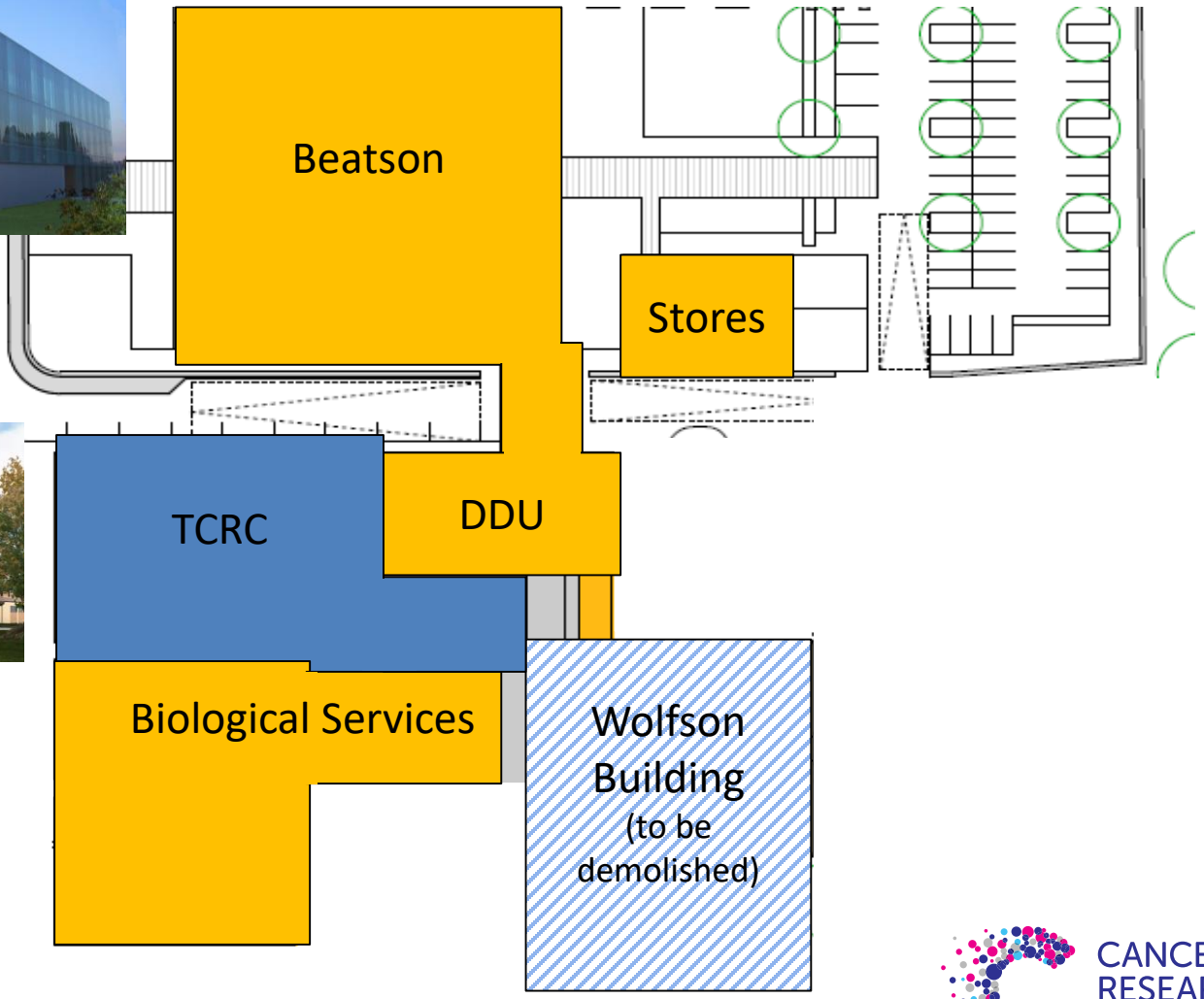
Cancer Research in Glasgow



CR-UK West of Scotland Cancer Centre (WeCan)

Cancer Research Facilities at Garscube





CANCER RESEARCH UK | BEATSON INSTITUTE

The Beatson West of Scotland Cancer Centre

Clinical Director: Dr David Dunlop

- £105 million building opened 2007 - 22,000m^2, 1000 rooms
- Serves population of 2.8 million (60% of Scottish population)
- Busiest cancer centre in UK

  8,000 new patients/year

  20,000 courses chemotherapy

  6,500 courses radiotherapy

- 14% patients enter a clinical trial
- 11 radiotherapy machines

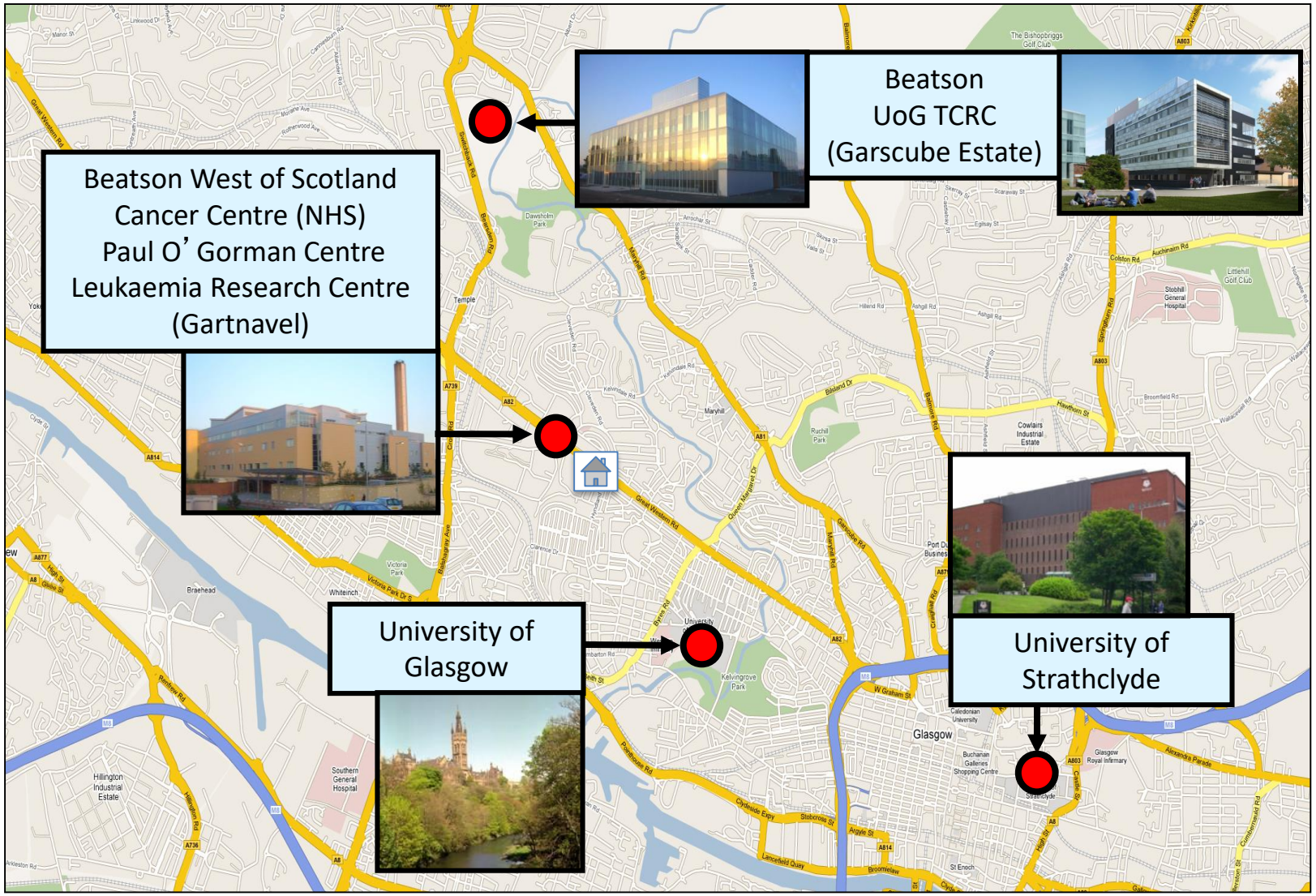
  3 with image guided radiotherapy (on board CT)

  1 stereotactic radiotherapy

  Cyclotron on site

THE beatson
WEST OF SCOTLAND CANCER CENTRE

NHS
Greater Glasgow and Clyde


Beatson
UoG TCRC
(Garscube Estate)
Beatson West of Scotland
Cancer Centre (NHS)
Paul O' Gorman Centre
Leukaemia Research Centre
(Gartnavel)
University of
Glasgow
University of
Strathclyde
1 mile

Pancreas Cancer Studies in Glasgow

Beatson Institute- Owen Sansom, Jennifer Morton, Mike Olson, Laura Machesky
Mouse models of pancreatic cancer and cell models, preclinical trials

West of Scotland Cancer Centre- Jeff Evans- clinical trials, Andrew Biankin- Precision Panc

Jeff Evans
Consultant Oncologist
Beatson GL
Head of ICS

Jen Morton
Preclinical Mouse Studies

Owen Sansom
Beatson Director
Preclinical studies

Andrew Biankin
Director TCRC
Pancreatic Cancer Genetics

Beatson Groups- Invasion and Metastasis

Laura Machesky

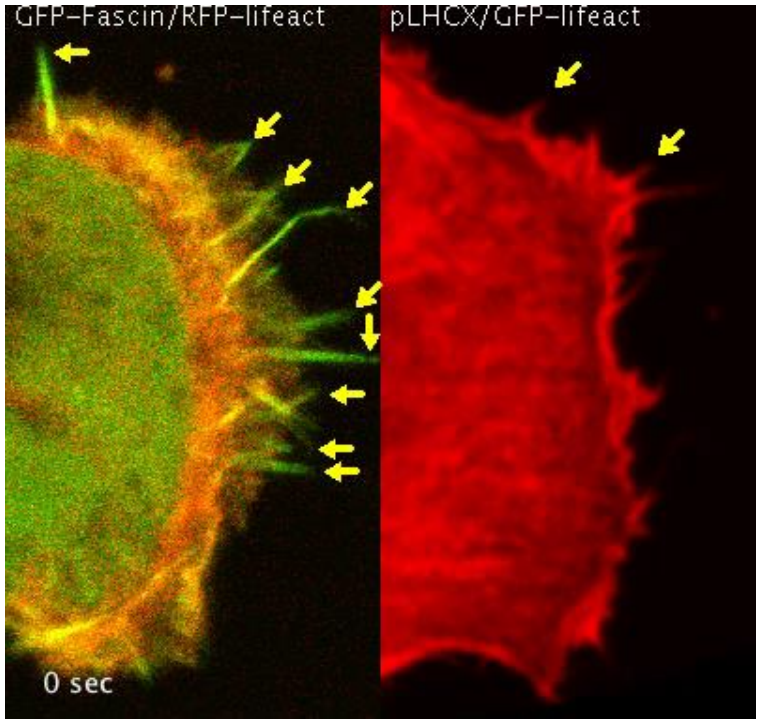
Robert Insall

Mike Olson

Jim Norman

- Cell Migration- invasion, chemotaxis
- Cancer stromal remodeling and tumour microenvironment
- Mouse models of cancer

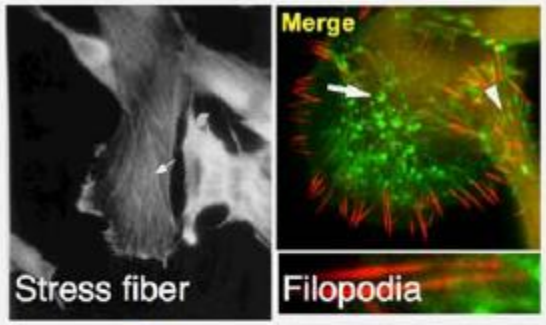
Fascin is not expressed in normal epithelium but upregulated in many epithelial cancer types

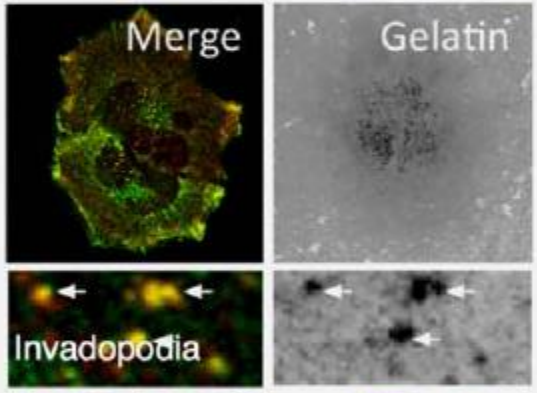


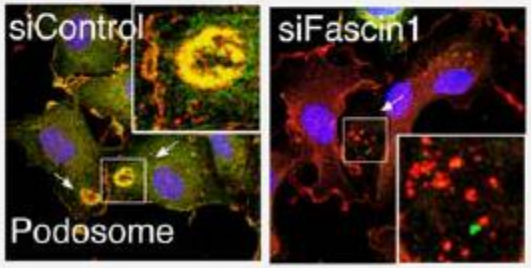
Fascin bundles actin and induces filopodia, migration and invasion (Pancreatic cancer cells, Ang Li)

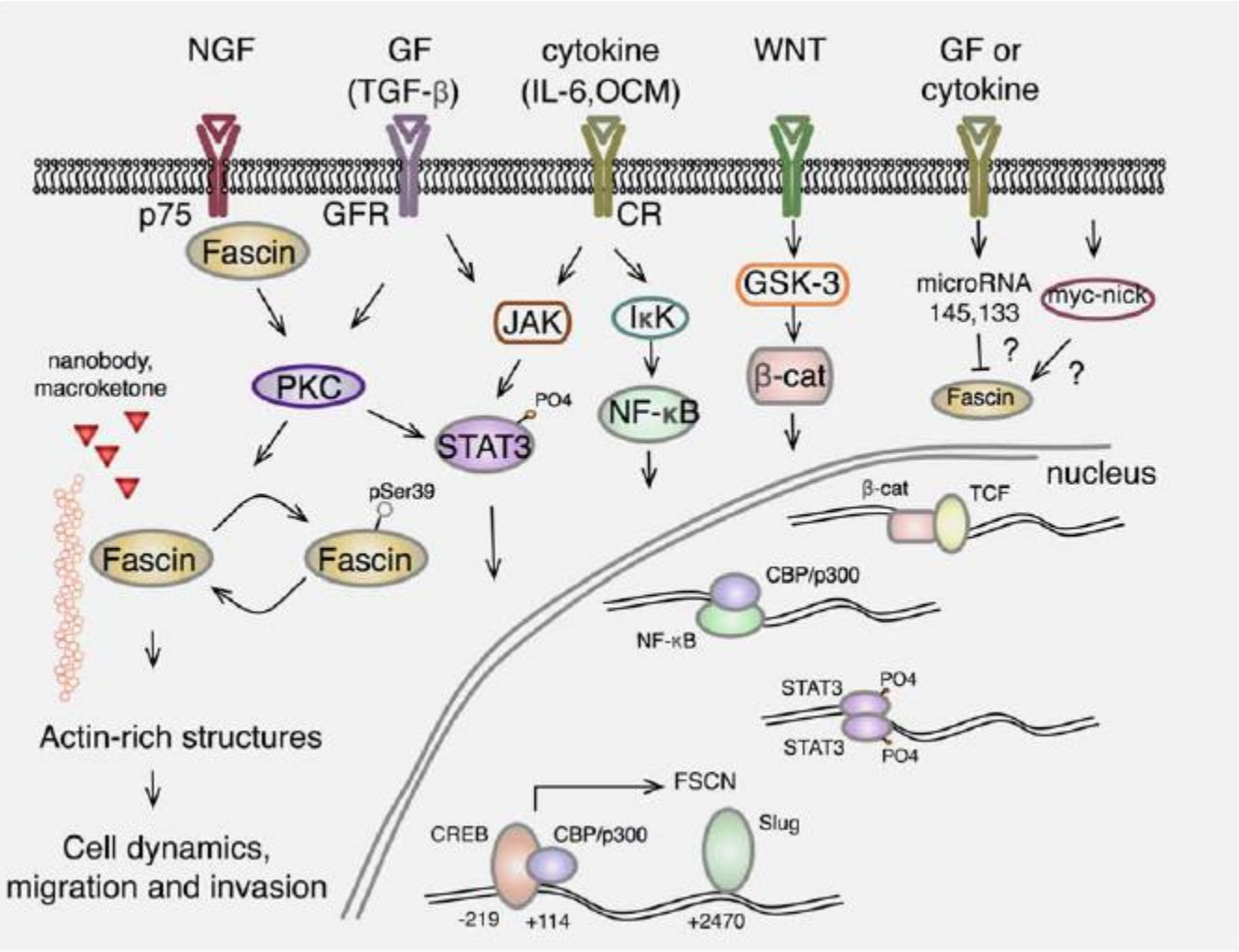
- Fascin enhances cell motility
- Embryonic cells express fascin when they become motile
- Fascin is not expressed in epithelia
- Increased fascin expression is associated with multiple epithelial cancer types- e.g. breast, head and neck, pancreatic, colorectal

Fascin is a target of multiple pathways in cancer progression



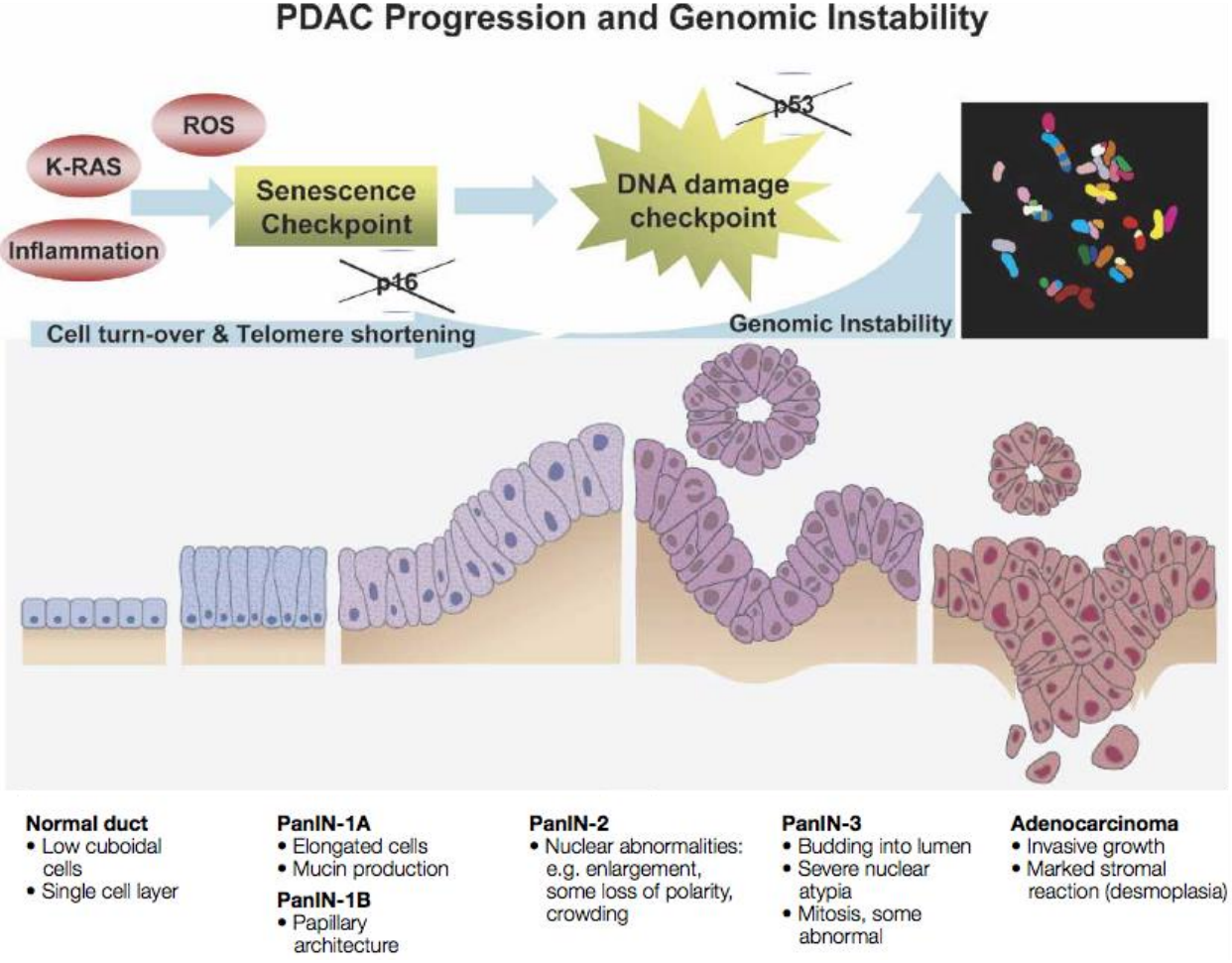






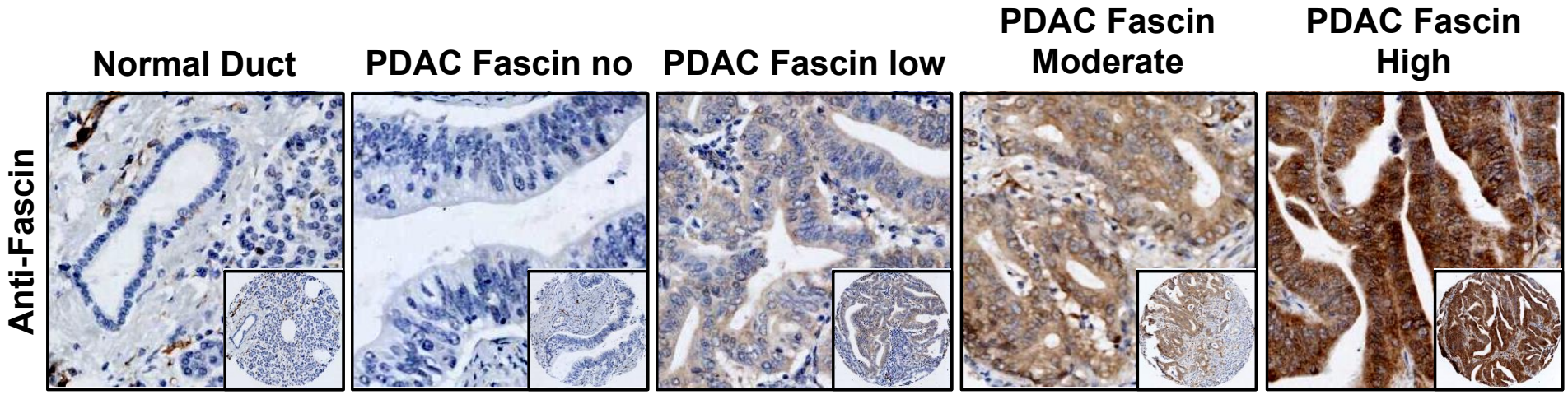
Pancreatic Cancer Outlook and Progression

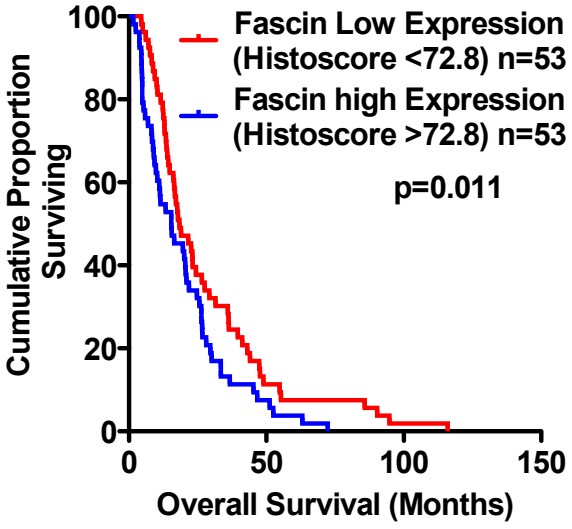
- 5-year survival rate for PDAC is only around 5% and hasn't improved in decades
- Only 10-20% of diagnosed can have surgery
- Usually presents late and has often spread

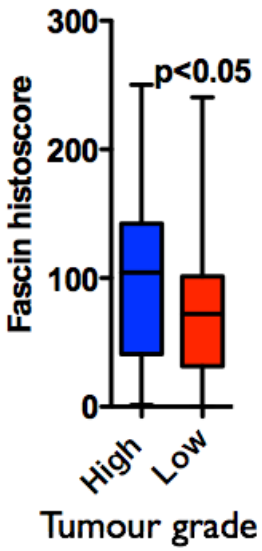


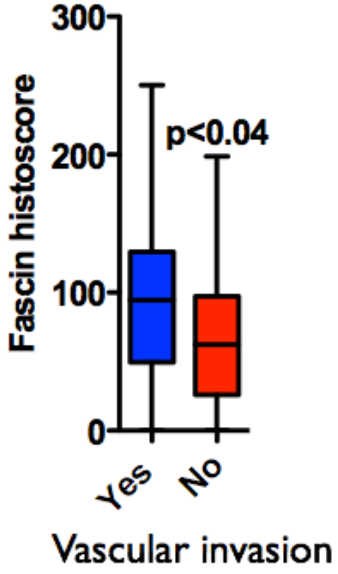
High Fascin Correlated Negatively with Survival in Human PDAC 122 cases

Nigel Jamieson, Colin MacKay, Ross Carter- Dept of Surgery
West of Scotland pancreatic Unit



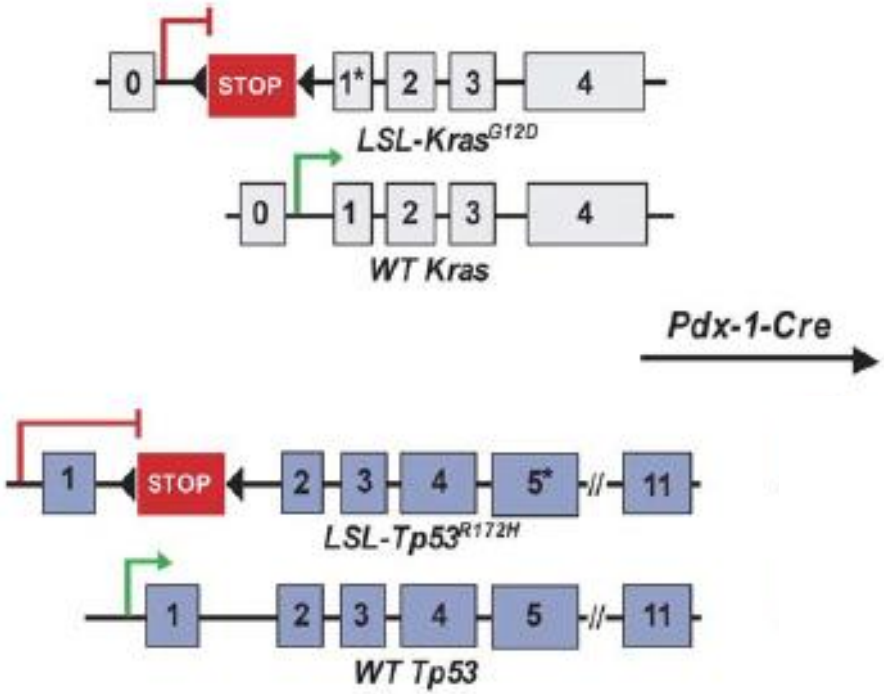




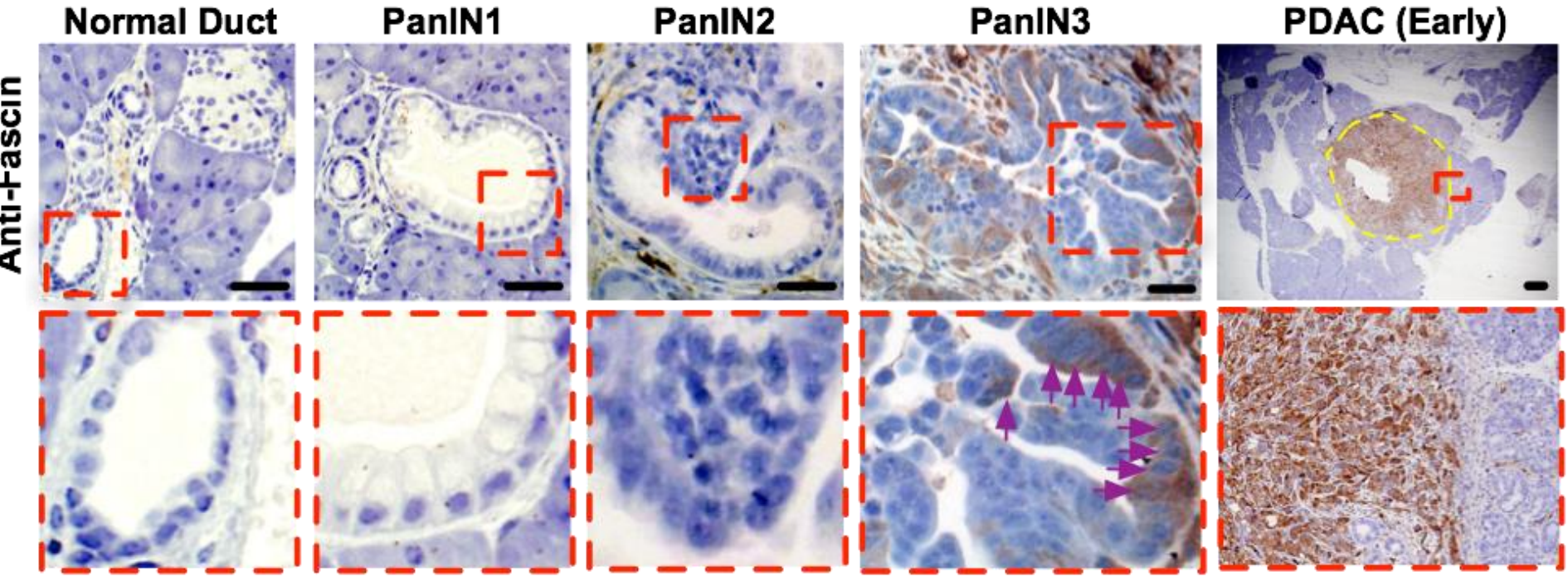


Trp53^{R172H} and *Kras*^{G12D} cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice

Sunil R. Hingorani,[1,2,*] Lifu Wang,[2] Asha S. Multani,[4] Chelsea Combs,[2] Therese B. Deramaudt,[1,3] Ralph H. Hruban,[5] Anil K. Rustgi,[1,3] Sandy Chang,[4] and David A. Tuveson[1,2,*]

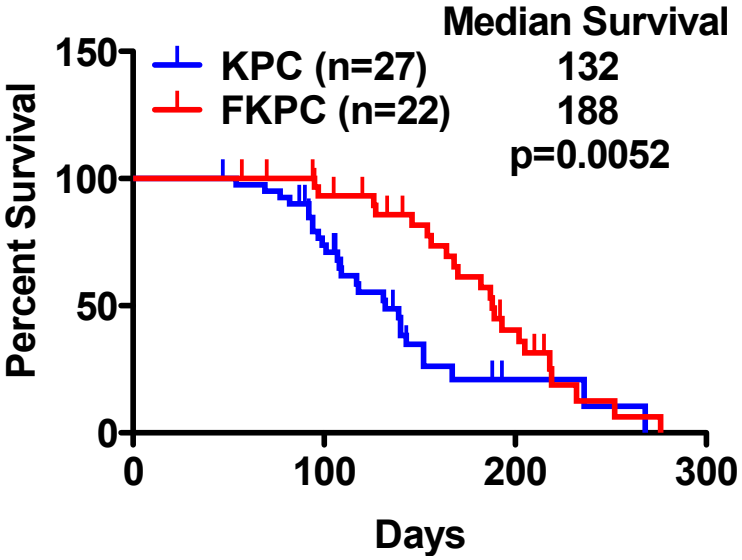


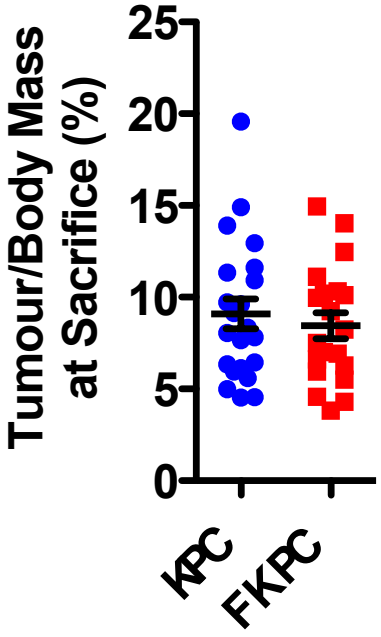
PDAC Mouse Model shows progression through PanIN to PDAC and metastasis



Progression from normal to pre-neoplastic to early cancer shows fascin expression around the transition to carcinoma but not in early PanIN lesions.

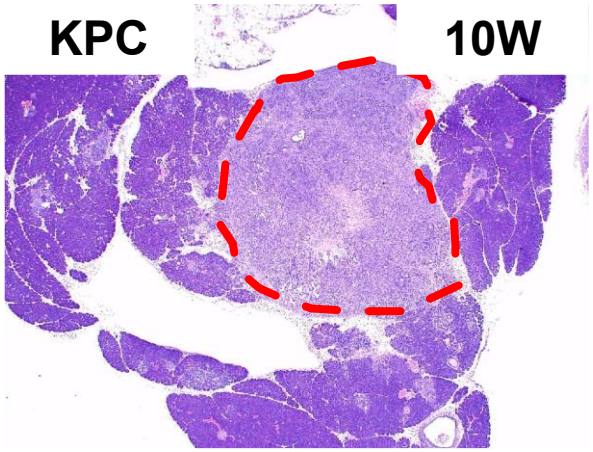
Loss of fascin enhanced survival but did not affect tumour growth properties

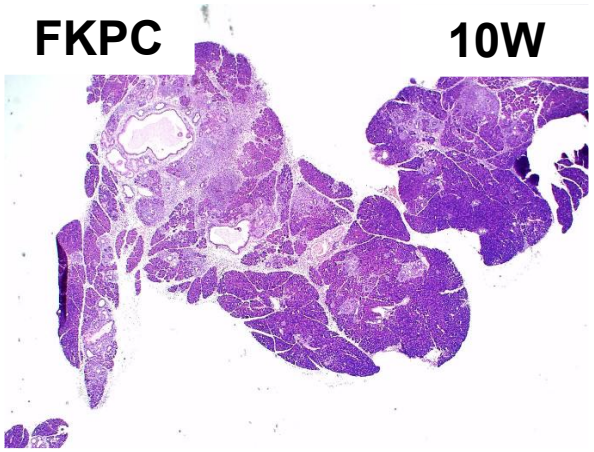


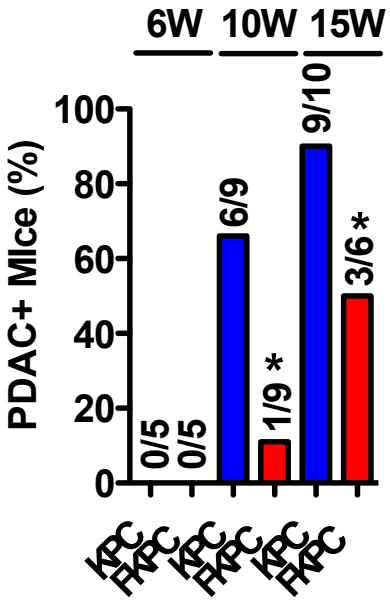


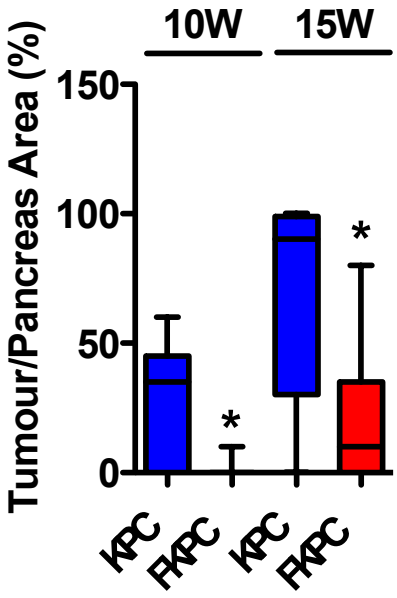
Markers for cell death (cleaved caspase 3), cell growth (Ki67, BrDu) and cell cycle (PH3) were not affected by loss of fascin

Fascin loss reduces tumour burden at early times



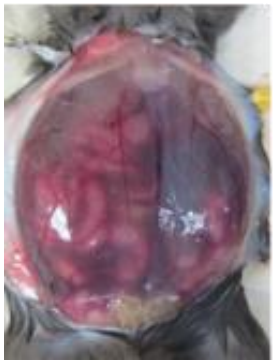


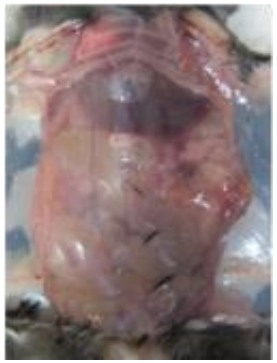


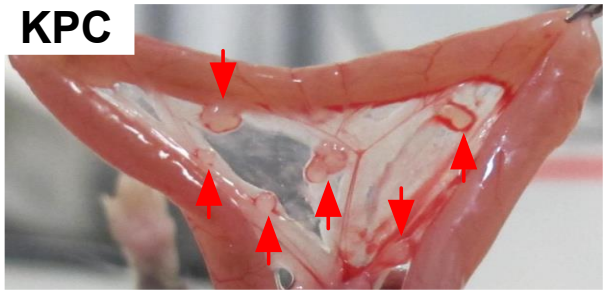


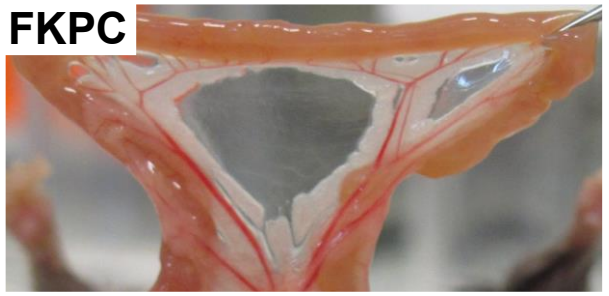
Fascin KO mice have fewer and smaller tumours at 10w and 15w

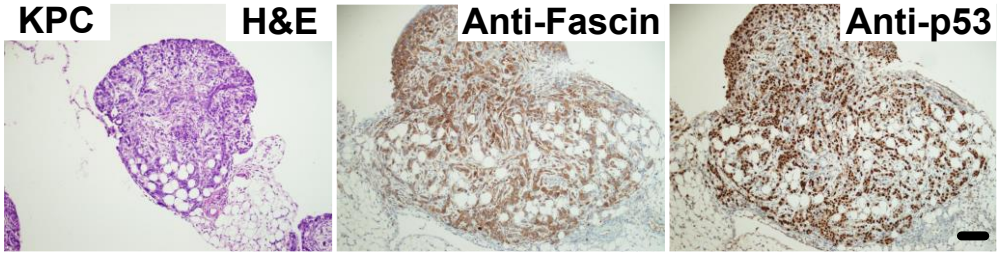
Fascin KO have less ascites and peritoneal metastasis

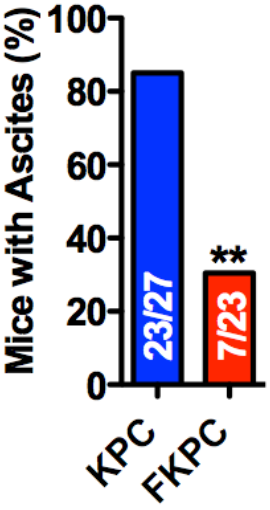


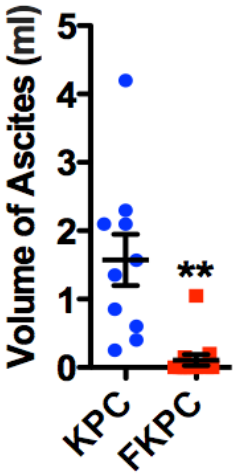


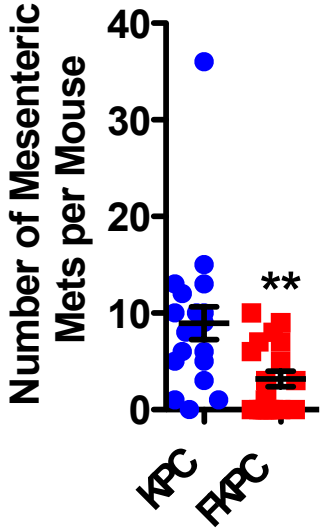






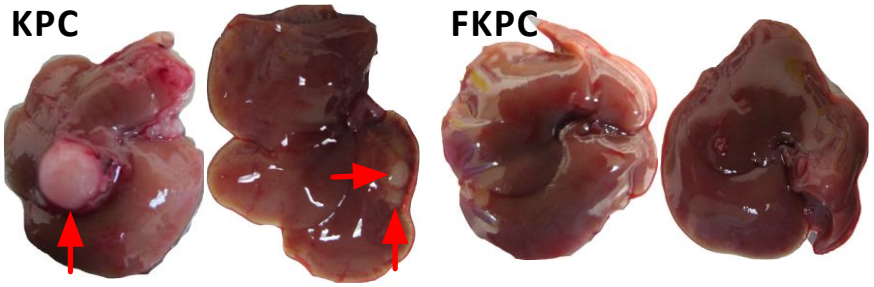


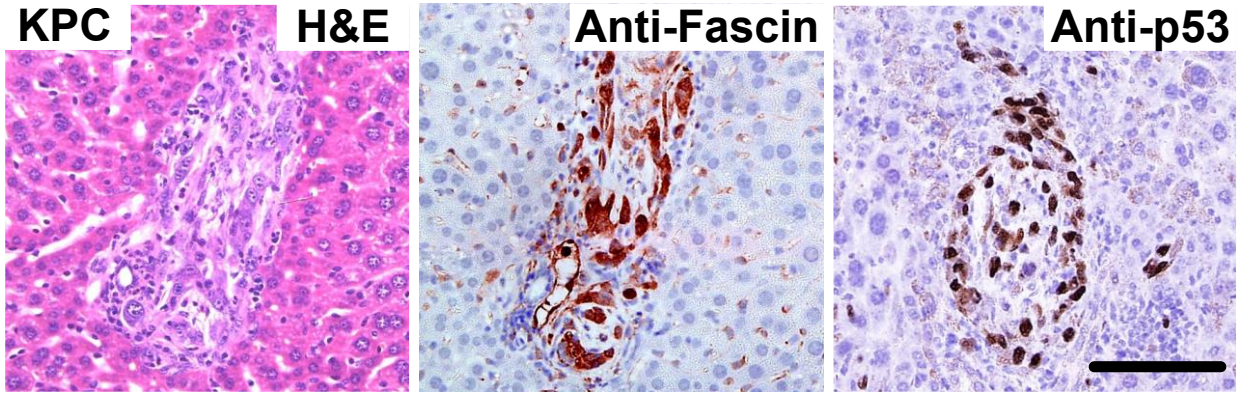


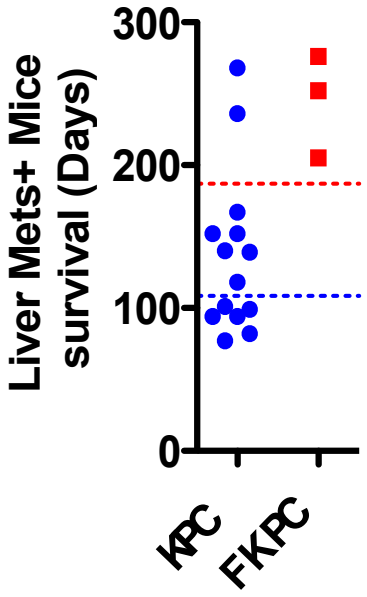


Ang Li et al., 2014

Loss of fascin reduces liver metastasis



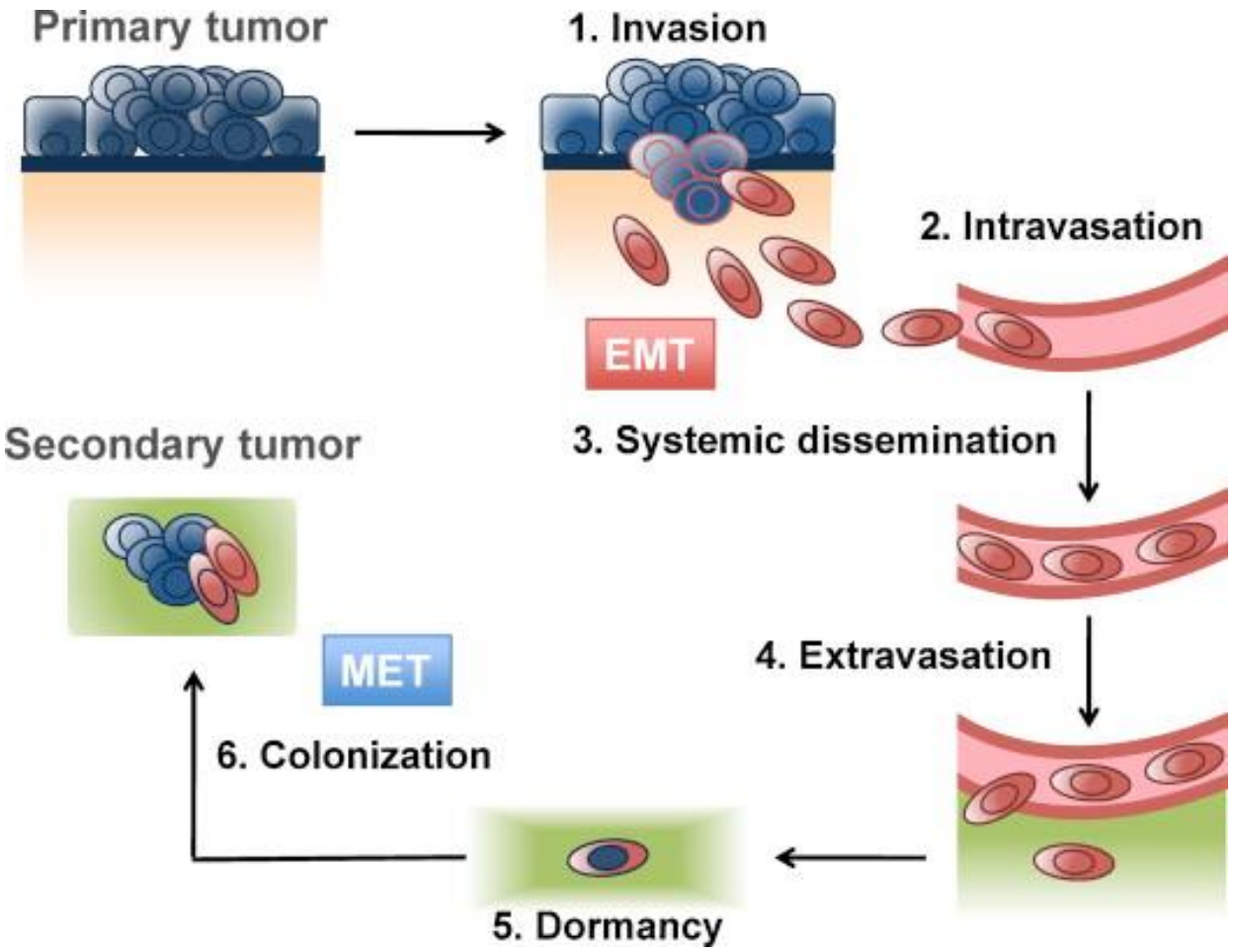




Overall metastasis summary

	Metastasis Index	Mesenteric Mets	Diaphragm Mets	Liver Mets
KPC	24/27 (88%)	19/20 (95%)	12/27 (44%)	14/27 (52%)
FKPC	13/23 (57%)**	12/22 (55%)**	3/23 (13%)*	3/23 (13%)**

Fascin is a part of EMT
Epithelial to mesenchymal transition



Scheel and Weinberg 2012

ARTICLE

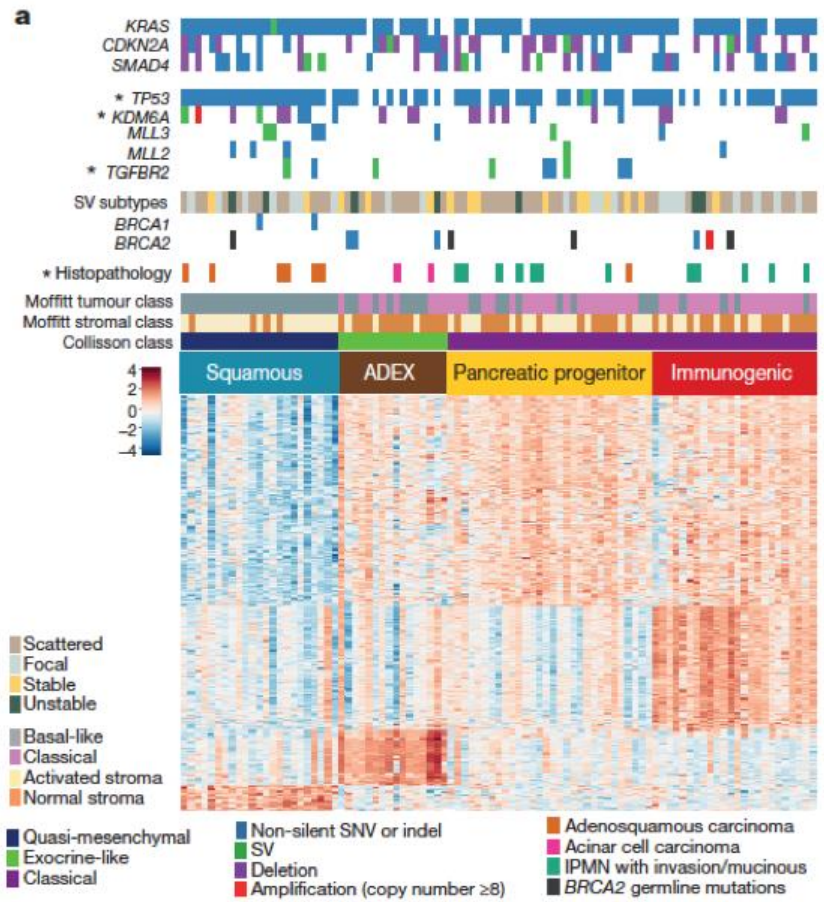
doi:10.1038/nature16965

Genomic analyses identify molecular subtypes of pancreatic cancer

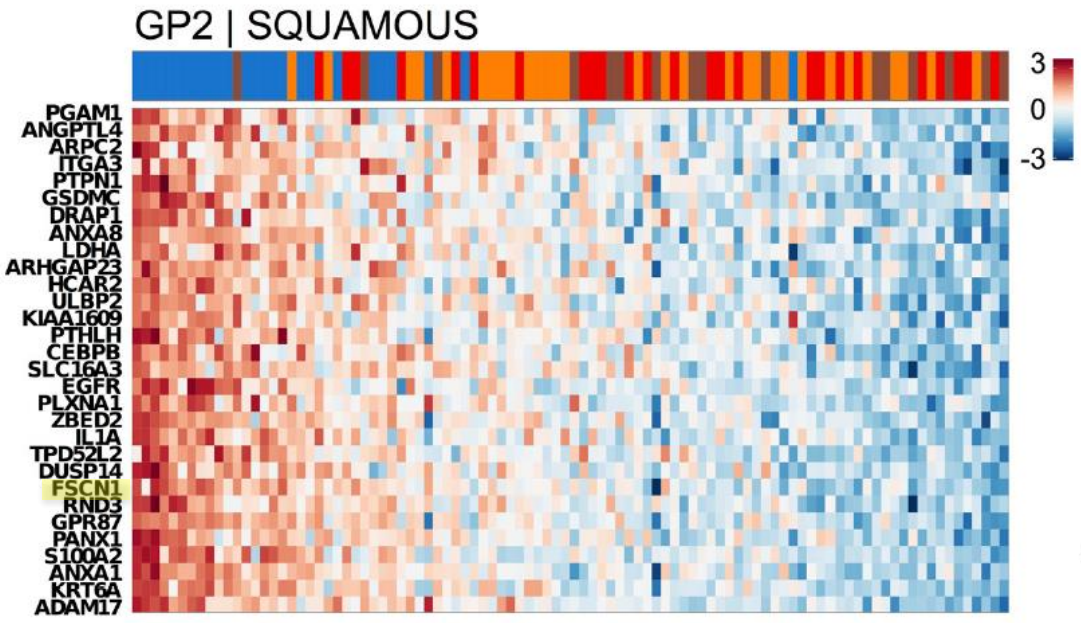
Peter Bailey[1,2], David K. Chang[2,3,4,5], Katia Nones[1,6], Amber L. Johns[3], Ann-Marie Patch[1,6], Marie-Claude Gingras[7,8,9],

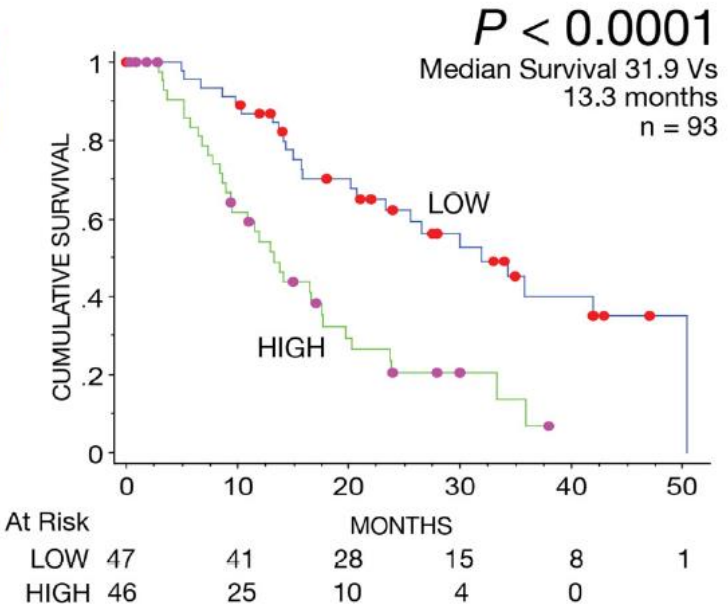
Sequence analysis of 456 Human PDAC
Identifies 4 main sub-types

- Squamous
- ADEX
- Pancreatic Progenitor
- Immunogenic



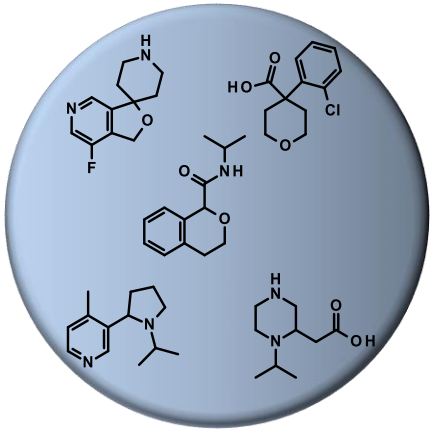
Fascin is one of the highest expressed genes in squamous subtype



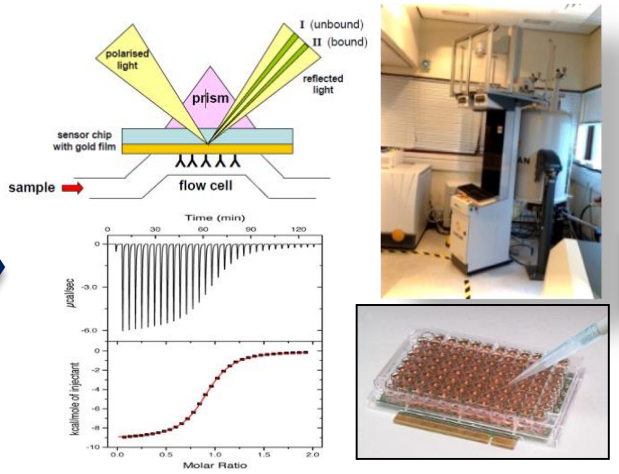


Beatson Drug Discovery Team- Fragment Screening- Fascin Binding Compounds

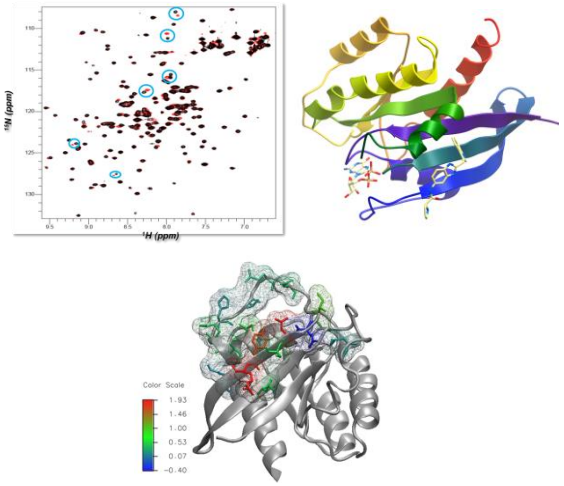
- Set of ~1000 high quality Beatson fragments (shape, solubility, stability)
- Biophysical screening (SPR, NMR etc) allows detection of weak hits , the challenge (as in all FBHI campaigns) is understanding how to develop them
- Crystallography is critical, Follow-up by mining commercial compound collections



Fragment library



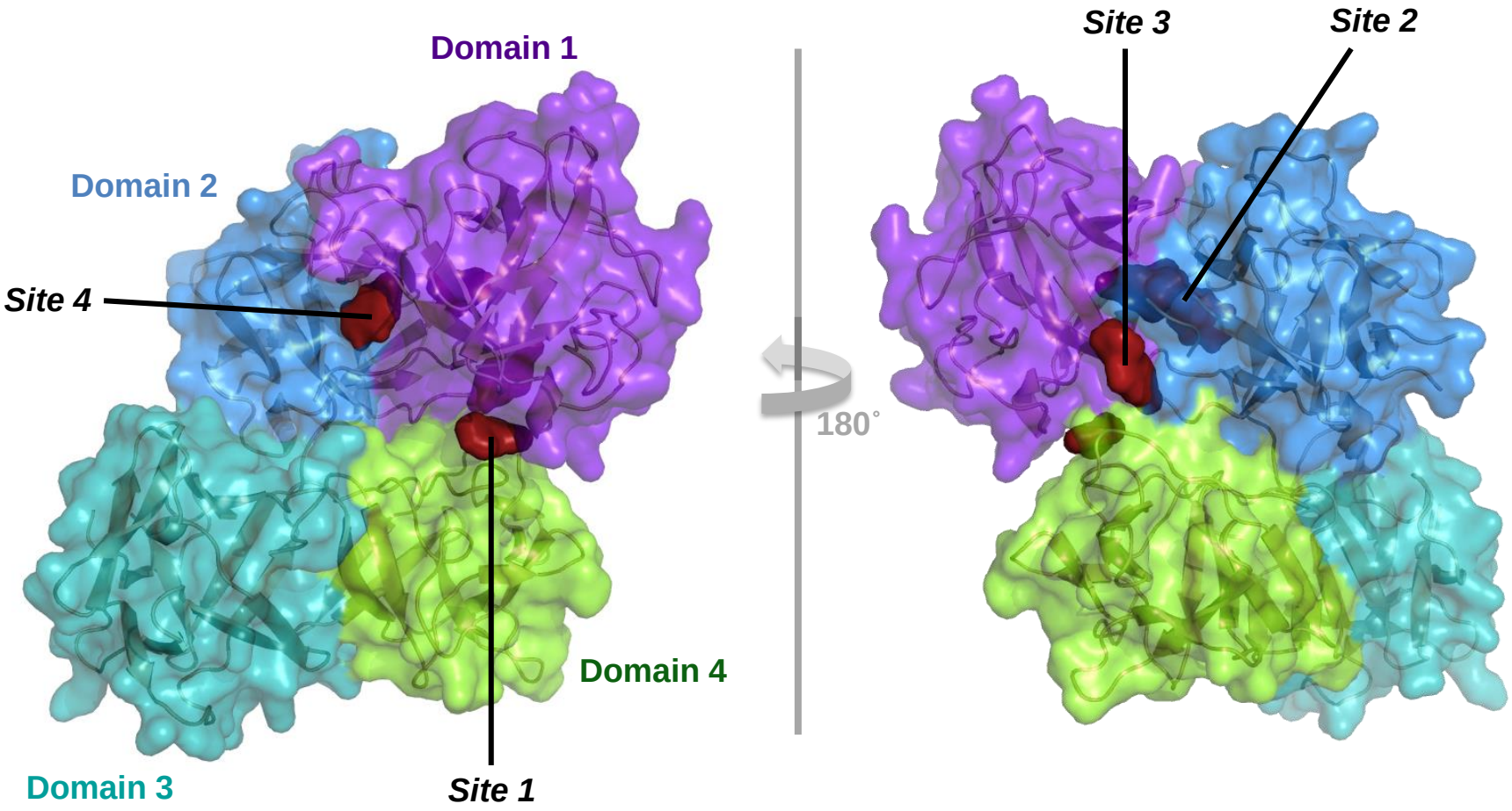
Multiple orthogonal screening/validation technologies



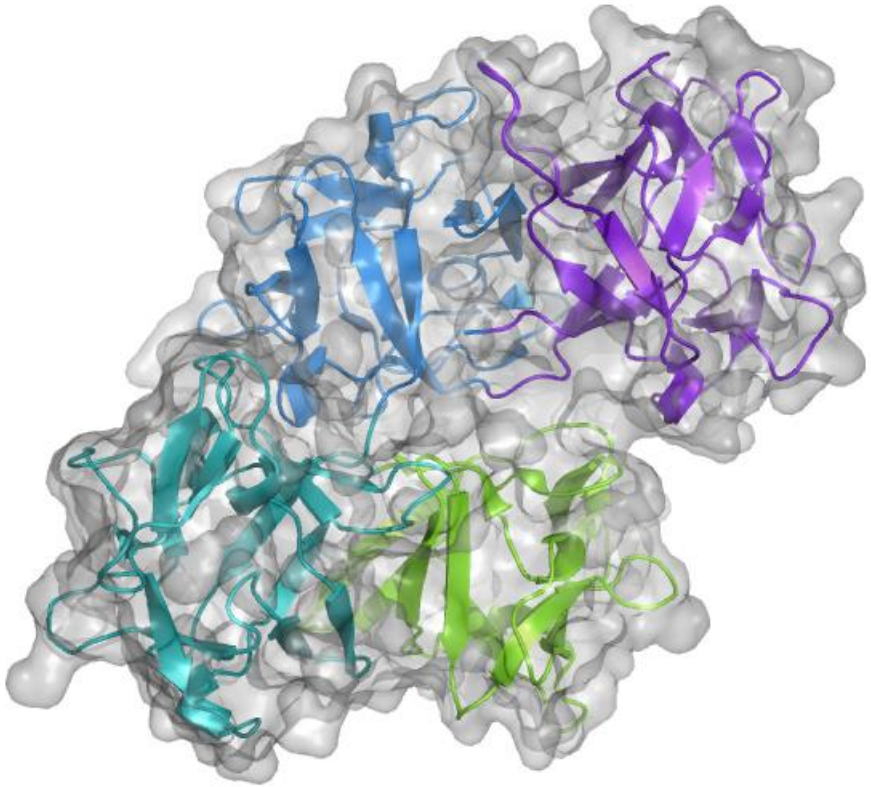
Structure generation to inform design

Fragment Binding Sites

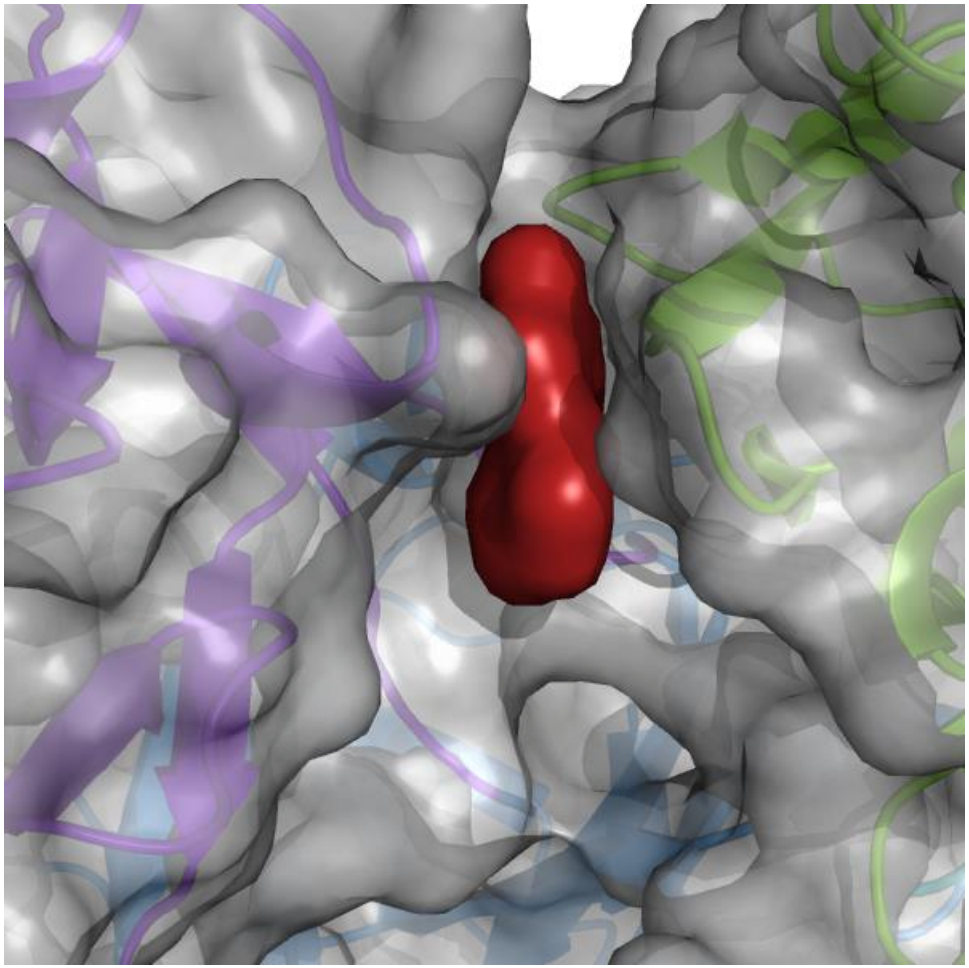
- 53/1000 confirmed hits
- Multiple fragment-complex structures solved
- Four distinct fragment binding sites



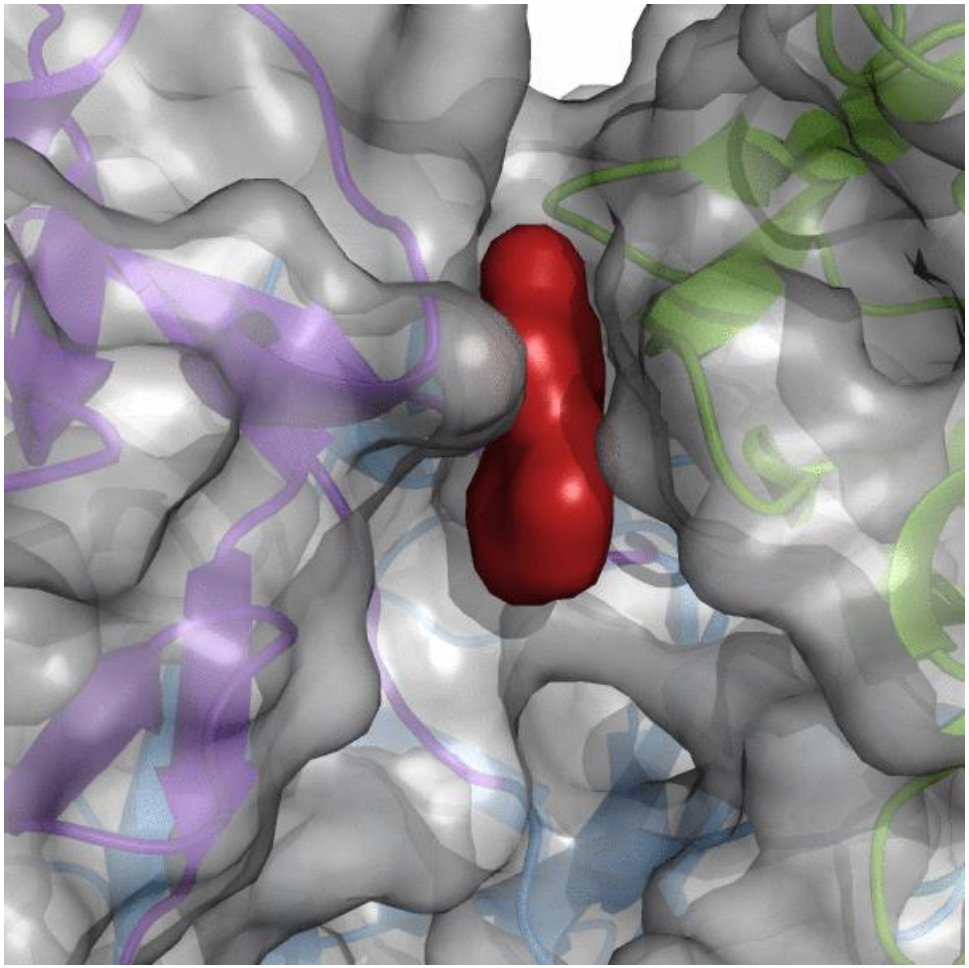
Functional Effect of Binding



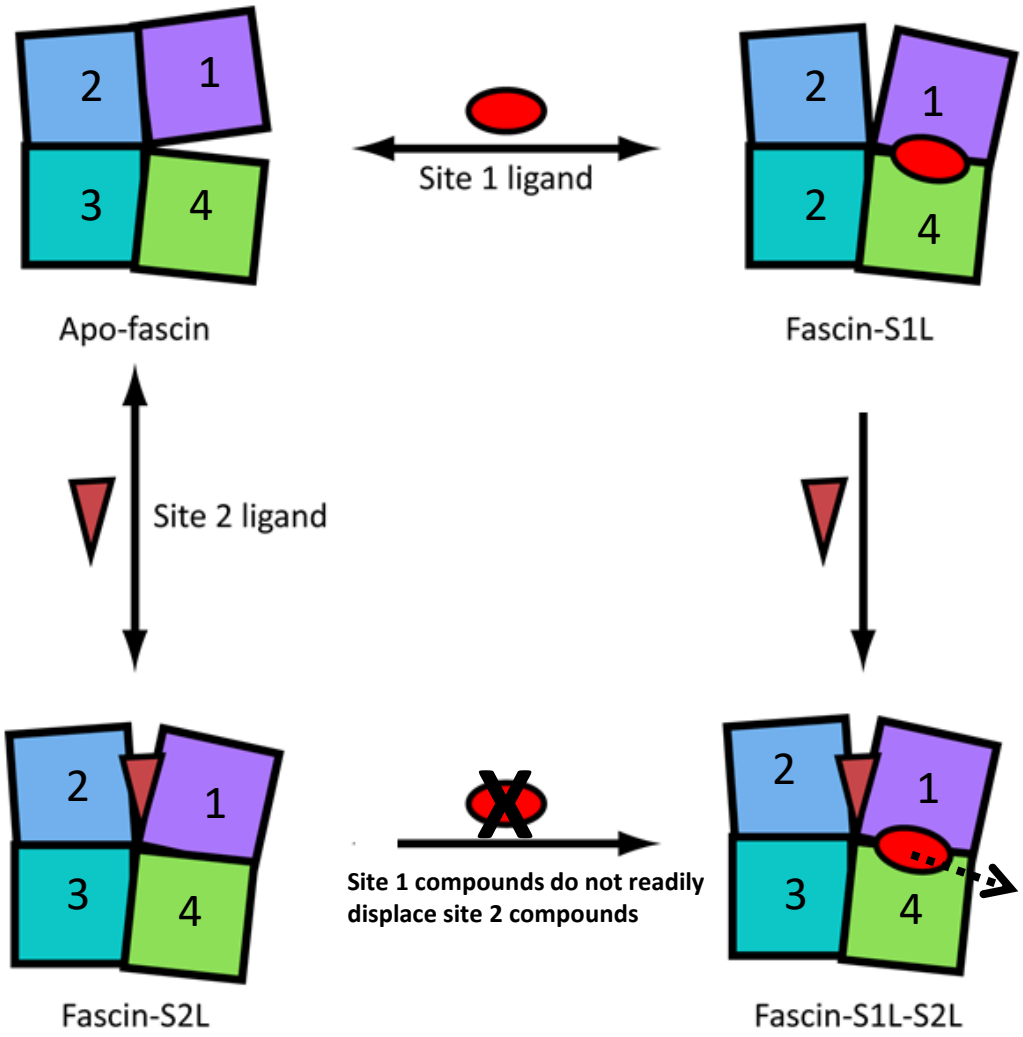
Functional Effect of Binding



Functional Effect of Binding

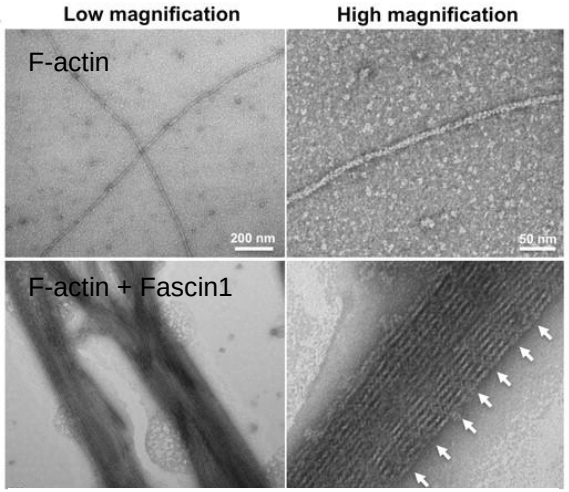


Functional Effect of Binding

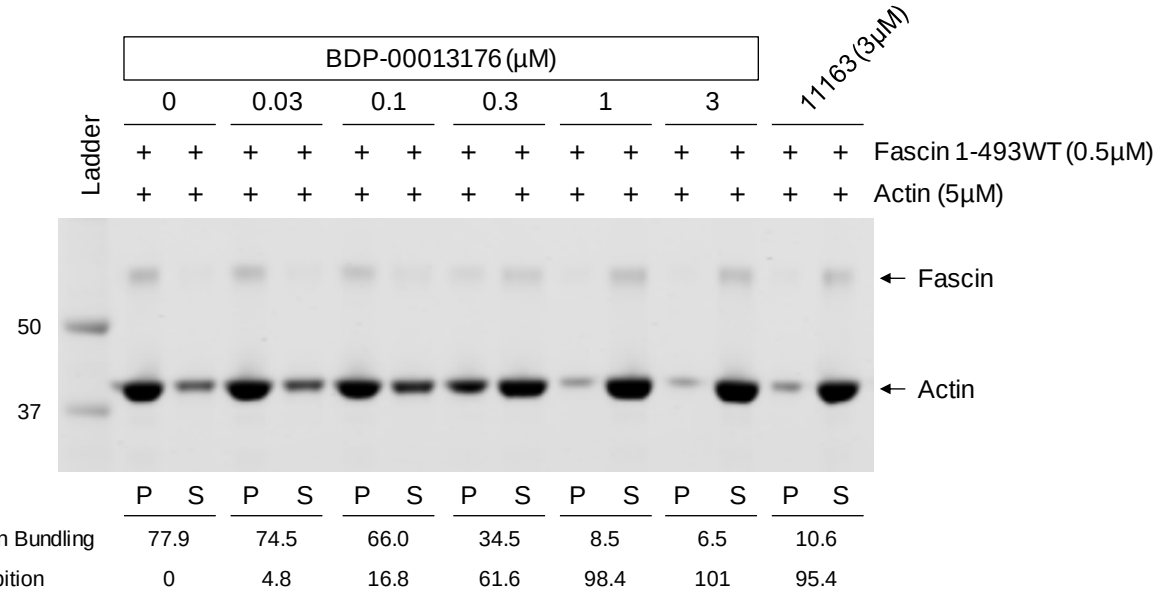


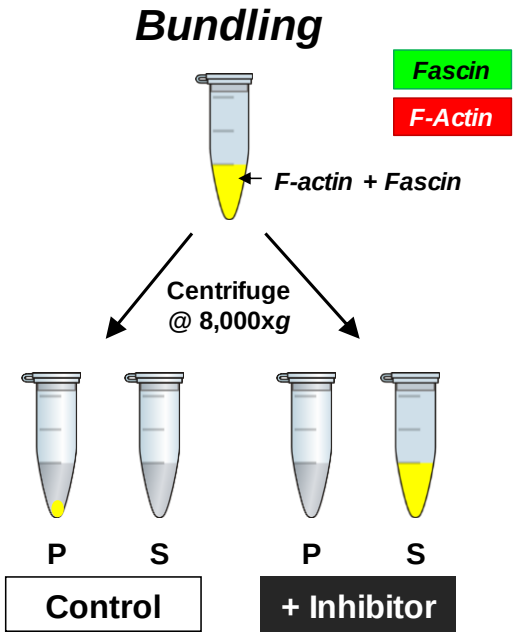
- Binding of site 1 and site 2 ligands inflict a similar motion of change to protein
- However, the amplitude of this change is larger for the site 2 compounds which “wedge open” a space between domain 2 and 1
- Site 1 compounds pull the domain towards themselves in a similar motion but their presence stops greater motion
- This manifests itself with a greater allosteric effect for site 2 compounds and hence a greater functional effect

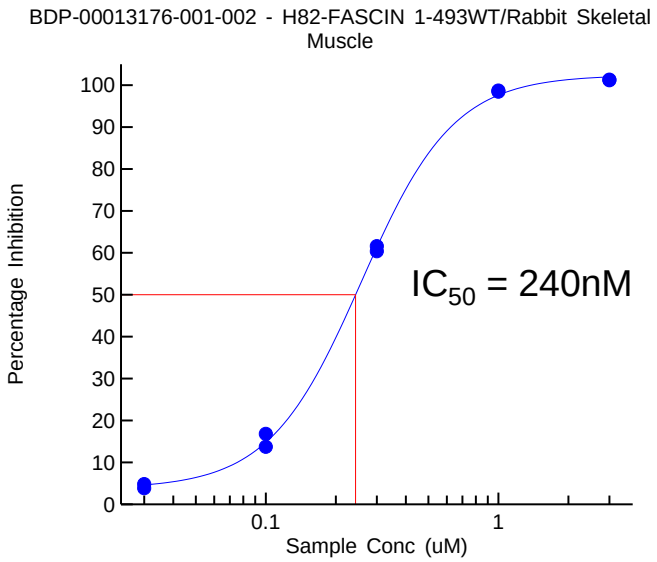
Functional biochemical assay – Bundling assay

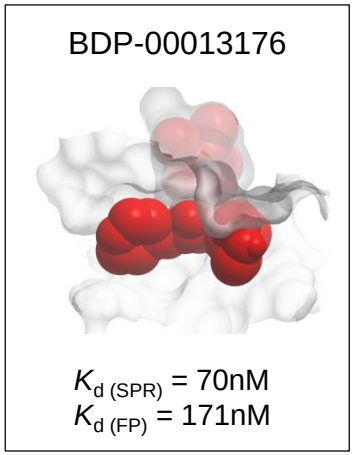


Jansen et al., 2011 JBC 286:30087-30096









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Future Plans

- Continue development of fascin inhibitors
- Explore more targets in PDAC
- Continue to develop our understanding of PDAC metastasis and the role of fascin

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