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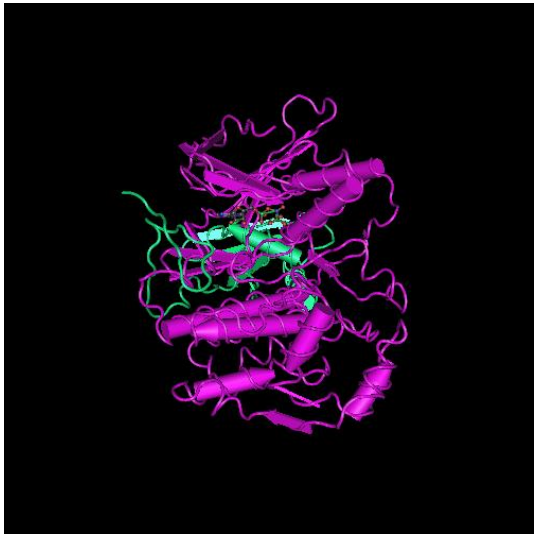
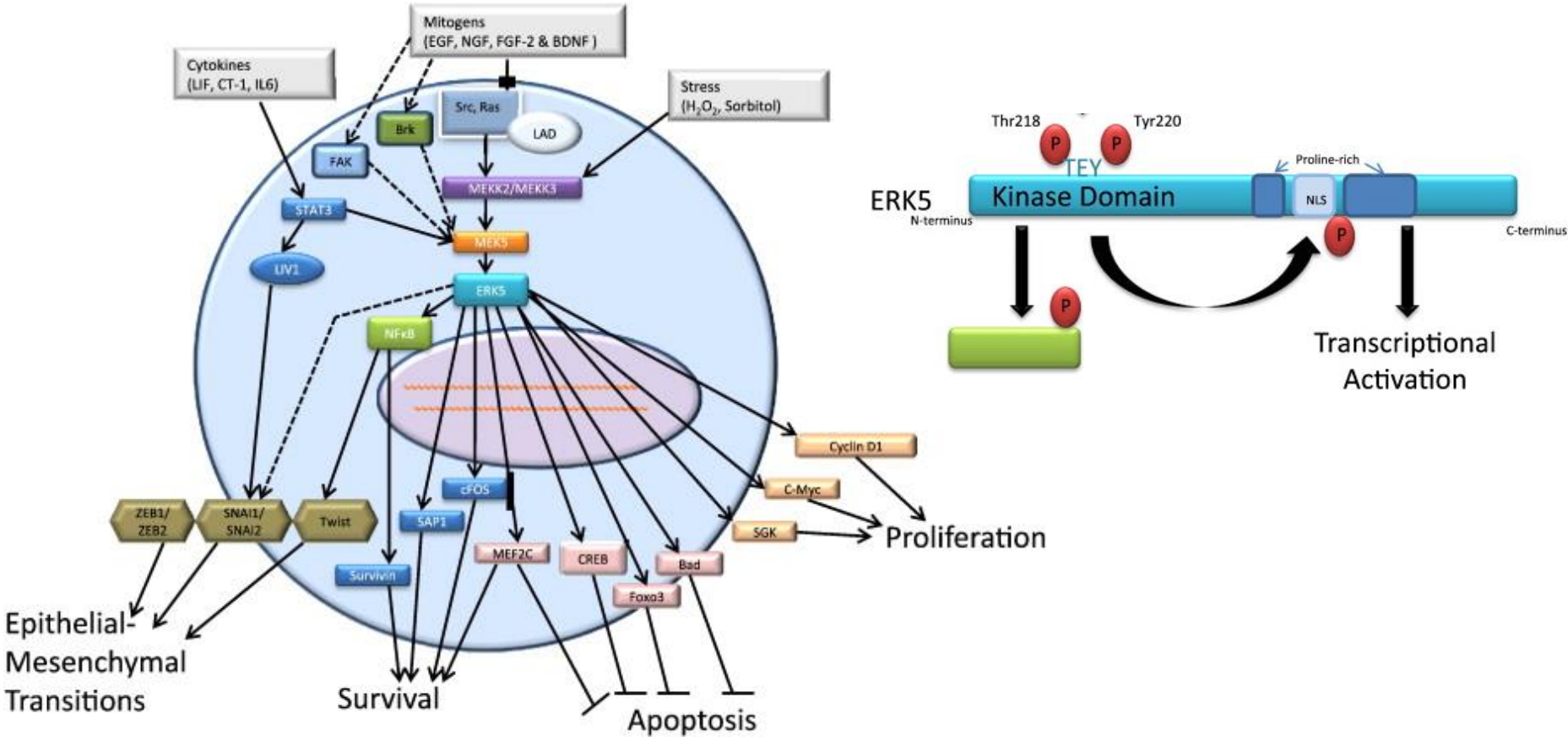
ERK5 and osteosarcoma



Dr Katie Finegan

University of Manchester

ERK5 is a signalling protein



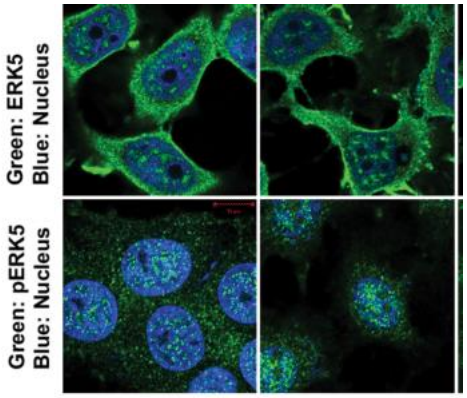
MEK5/ERK5 pathway: The first fifteen years Barbara A. Drew, Matthew E.Burow and Barbara S.Beckman

ERK5 and osteosarcoma

Pre-clinical evidence

Silencing ERK5 in osteosarcoma cell lines affects:

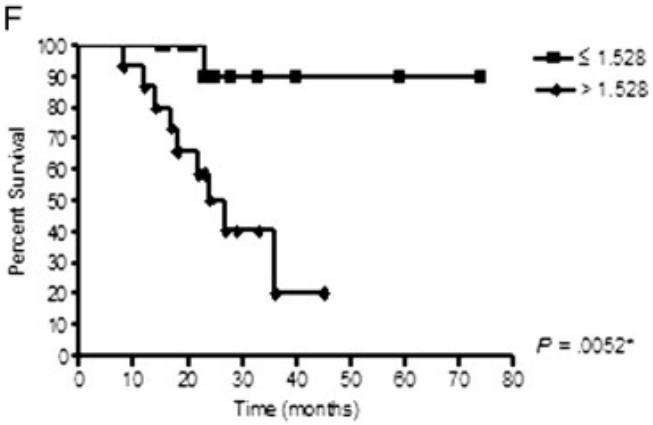
- invasiveness *in vitro*
- Slug/MMP9 expression *in vitro*



Clinical evidence

Overexpression of ERK5 (MAPK7) associated with

- poorer response to treatment (chemotherapy)
- tumour progression (metastases)
- worse overall survival



Yue B1, Ren QX, Su T, Wang LN, Zhang L. ERK5 silencing inhibits invasion of human osteosarcoma cell via modulating the Slug/MMP-9 pathway.

Tesser-Gamba F1, Petrilli AS, de Seixas Alves MT, Filho RJ, Juliano Y, Toledo SR. MAPK7 and MAP2K4 as prognostic markers in osteosarcoma. Hum Pathol. 2012 Jul;43(7):994-1002.

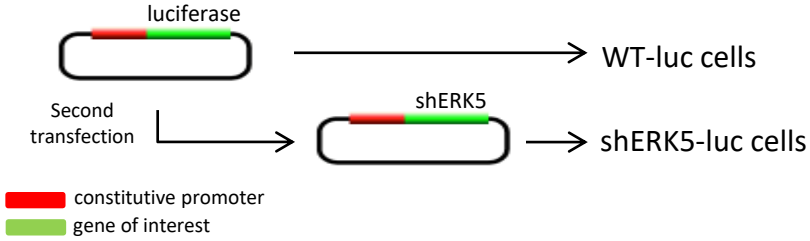
ERK5 and osteosarcoma

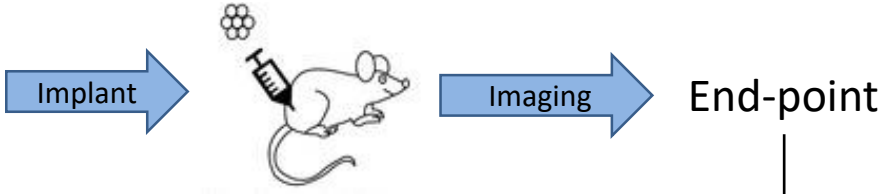
1. How does ERK5 regulate osteosarcoma?
2. Can we target ERK5 for therapeutic gain in osteosarcoma?

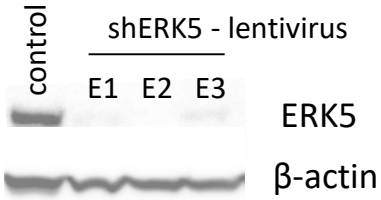
Preclinical model of osteosarcoma

IF injection of 143-B cells, metastatic to the lung

Experimental design



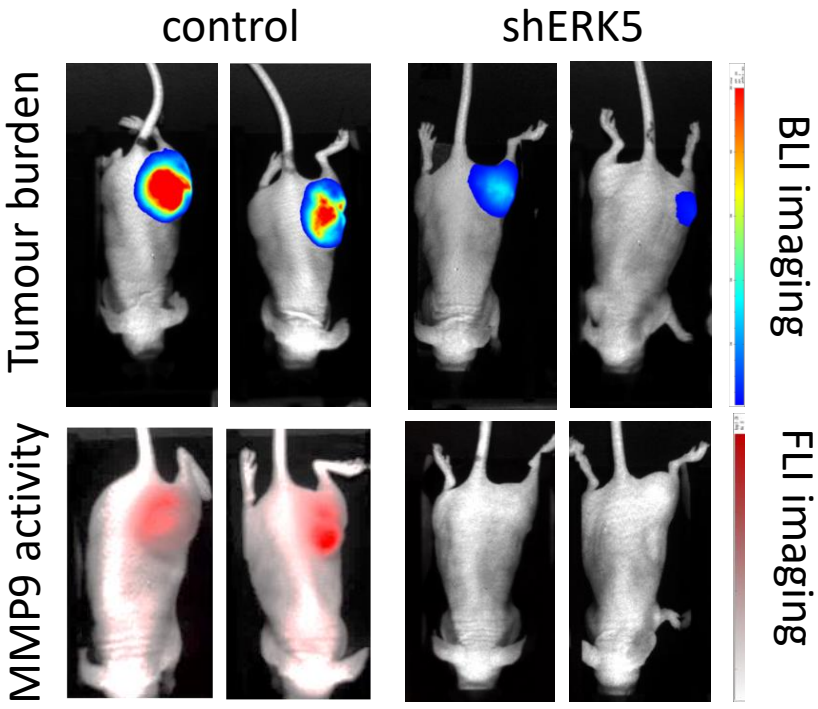


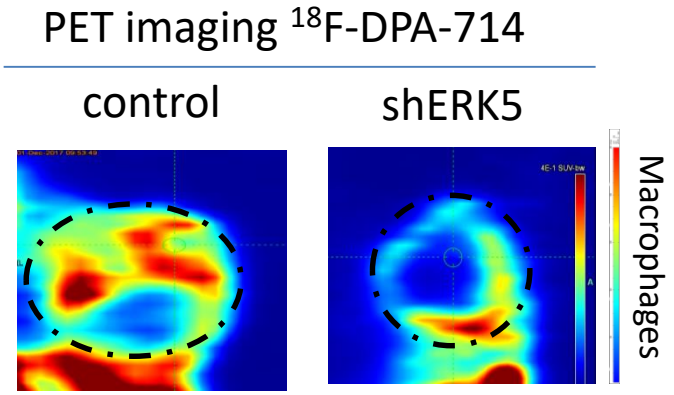


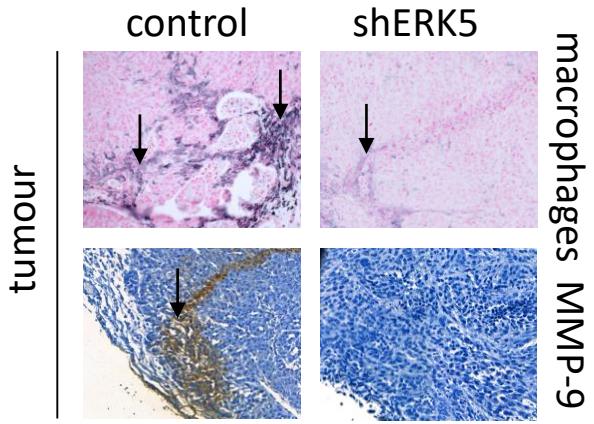
ANALYSIS

Imaging signal
FACS
qRT-PCR
ELISA
Lung clonogenicity
Histopathology

Loss of ERK5 impairs osteosarcoma growth





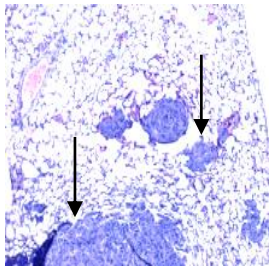


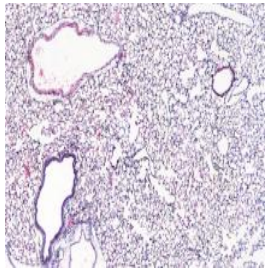
ERK5 is required for the metastatic spread of osteosarcoma

	Number of colonies/mg of lung	SD
WT-luciferase	4.43	± 0.46
shERK5-luciferase	0.092	± 0.082

control shERK5

lung

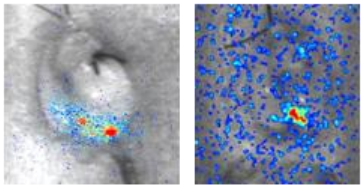




H and E

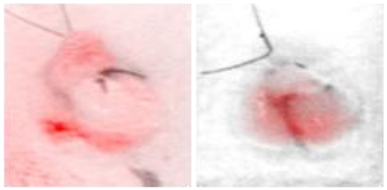
***Ex-vivo* imaging, excised lung, control mice**

Tumour burden



BLI imaging

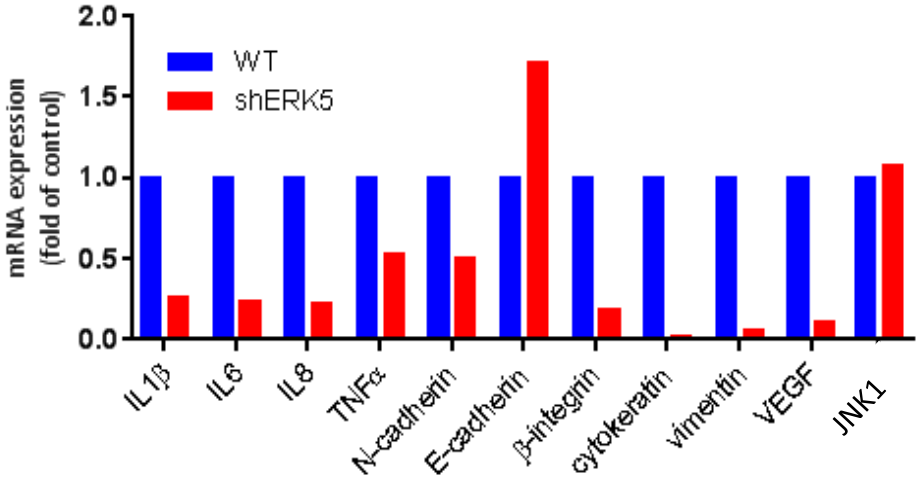
MMP9 activity



FLI imaging

No signal detected in shERK5 lungs

Underpinning mechanism



Loss of EKR5 in 143B cells

- Down-regulation of EMT genes
- Upregulation of E-cadherin
- Decreased pro-angiogenic signals
- Reduction in cytokine production

Corroboration in *ex vivo* samples

- IHC
- FACS analysis of immune cell composition
- Isolation tumour cells and macrophages (FACS)
  - ELISA
  - qRT-PCR

***In vivo* phenotype of EKR5 loss**

- Prevention of metastatic spread
- Decrease in macrophage residency
- Slower primary tumour growth

Translation

ERK5 kinase activity is dispensable for cellular immune response and proliferation

Emme C. K. Lin[a,1], Christopher M. Amantea[a], Tyzoon K. Nomanbhoy[a], Helge Weissig[a], Junichi Ishiyama[b], Yi Hu[a], Shyama Sidique[a], Bei Li[a], John W. Kozarich[a], and Jonathan S. Rosenblum[a,1]

[a]ActivX Biosciences, Inc., La Jolla, CA 92037; and [b]Watarase Research Center, Kyorin Pharmaceutical Co., Ltd., Tochigi 329-0114, Japan

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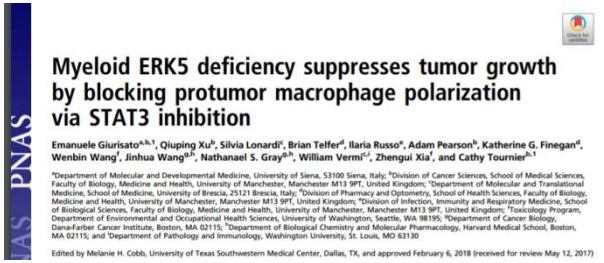
Tumor and Stem Cell Biology

Cancer Research

ERK5 Is a Critical Mediator of Inflammation-Driven Cancer

Katherine G. Finegan[1], Diana Perez-Madrigal[1], James R. Hitchin[2], Clare C. Davies[1], Allan M. Jordan[2], and Cathy Tournier[1]



Myeloid ERK5 deficiency suppresses tumor growth by blocking protumor macrophage polarization via STAT3 inhibition

Emanuele Giurisato[a,b,1], Qiuping Xu[b], Silvia Lonardi[c], Brian Telfer[d], Ilaria Russo[e], Adam Pearson[b], Katherine G. Finegan[d], Wenbin Wang[f], Jinhua Wang[g,h], Nathanael S. Gray[g,h], William Vermi[c,i], Zhengui Xia[f], and Cathy Tournier[b,1]

[a]Department of Molecular and Developmental Medicine, University of Siena, 53100 Siena, Italy; [b]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PT, United Kingdom; [c]Department of Molecular and Translational Medicine, School of Medicine, University of Brescia, 25121 Brescia, Italy; [d]Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PT, United Kingdom; [e]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PT, United Kingdom; [f]Toxicology Program, Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA 98195; [g]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115; [h]Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115; and [i]Department of Pathology and Immunology, Washington University, St. Louis, MO 63130

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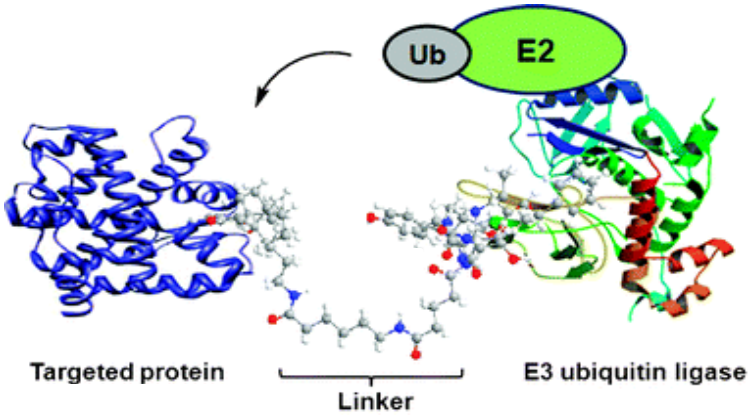
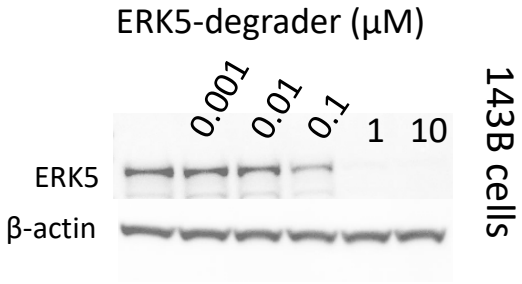
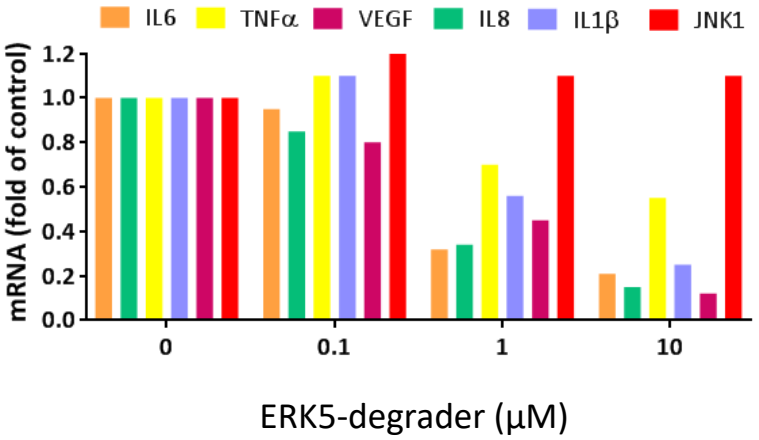




- Small molecule degrader of ERK5
- Should target ALL the functions of ERK5
- Mimics the phenotype of ERK5 knockdown



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Adam McMahon
Tracy Hussell

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