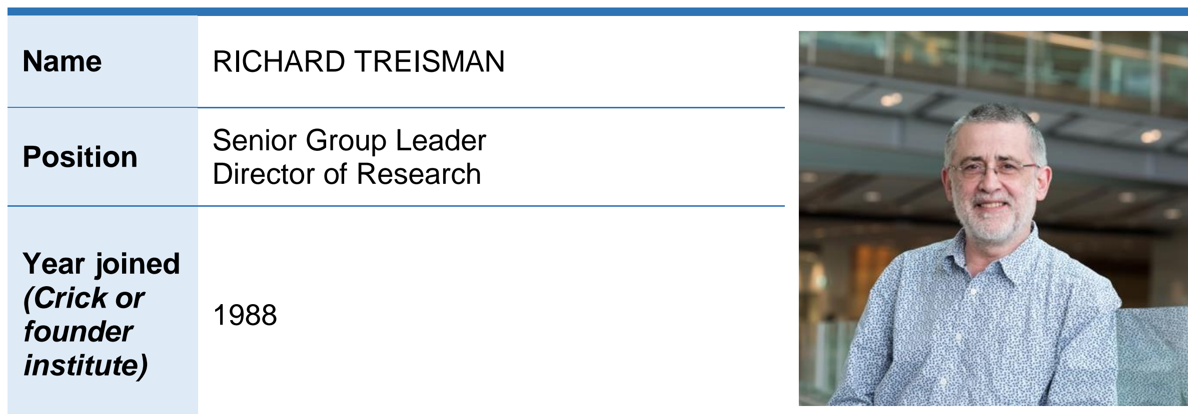

Name	RICHARD TREISMAN
Position	Senior Group Leader Director of Research
Year joined *(Crick or founder institute)*	1988

Career History

1981: Ph.D. ICRF / University College London
1981- 1984: Postdoctoral Fellow, Harvard University, USA
1984- 1988: Scientific Staff, MRC Laboratory of Molecular Biology, Cambridge
1988- present: ICRF, London Research institute, Francis Crick Institute
1999- 2002: Director of Laboratory Research, ICRF
2002- 2015: Director, CRUK London Research Institute
2015- present: Director of Research, Francis Crick Institute

Major Awards, Honours and Prizes

1987: Elected member of European Molecular Biology Organisation.
1992: International Research Scholar, Howard Hughes Medical Institute
1994: Elected to fellowship of the Royal Society
1995: EMBO Medal
1999: Member, Academia Europea
2000: Elected to fellowship of the Academy of Medical Sciences
2002: Louis Jeantet Prize for Medicine
2009: Elected to European Academy of Cancer Sciences
2012: Fellow of the AAAS
2016: Knighthood for service to biomedical science and cancer research
2018: Honorary Fellow, Christ's College Cambridge

Membership of external committees, editorial boards, review panels, SABs etc

2015- Member, CRUK Institute Directors Committee
2015- present: Chair, SAB, Nordic Centre for Molecular Medicine, Oslo, Norway
2017- present: CRUK Science Committee member
2018- present: CRUK City of London Centre executive member
2016- 2018 Royal Society Council
to 2017 Chair, ERC Advanced Grant panel LS1
2019: Member of review panel, IRCM Montreal, 2019
2019- present: SAB Member, Fritz Lipmann Institute, Jena, Germany

Lab Name	***Signalling and Transcription Laboratory***

Research programme and achievements

My group has a long-term interest in transcriptional regulation by extracellular signals, with a central focus transcription factor SRF and its partners, the TCFs and MRTFs, which are regulated by ras-ERK and rho-actin signalling respectively. The MRTFs are RPEL proteins, which bind G-actin, and RPEL protein biology isour second focus.

The SRF network

Our work on SRF has centred on genomic analysis of the SRF network and its role *in vivo.* We study proliferative and migratory responses in cancer and immune models.
We extended our previous genomic studies of the MRTF-SRF signalling to examine the role of TCF-SRF signalling in the fibroblast response to ERK activation. We found that most ERK-induced chromatin modification is TCF-dependent, as is the majority of ERK-induced transcription, consistent with a transcription cascade model. We also showed that phosphorylation acts both positively and negatively in control of the TCFs and MRTFs. We also established that TCF-MRTF competition is an important determinant of cell contractility in normal fibroblasts.
Our recent studies indicate that MRTF-SRF signalling is essential to prevent senescence in fibroblasts, and we are investigating the relationship of this to cytoskeletal dynamics and the target genes involved. We showed that cancer-associated fibroblasts (CAFs) exhibit heightened sensitivity of MRTF-SRF signalling to mechanical stress, and that in this system MRTF-SRF and YAP-TEAD signalling are mutually dependent. Future work will seek to identify the contribution of MRTF-SRF signalling to CAFs' pro-tumorigenic activity. We are will examine the role of the SRF network in melanoma, in which senescence, Ras-ERK signalling, and Rac signalling are implicated.
We demonstrated that MRTF-SRF signalling is required for the proliferative response of peripheral CD8 T cells to infection. We are currently testing the idea that it is required for the homotypic T-T cell interactions that mediate cytokine signalling. We have also found that SRF-null HSCs cannot colonise bone as a result of MRTF-SRF dependent cell migration defects.

Rho-actin signalling and RPEL proteins

We have explored our understanding of G-actin/RPEL interaction to develop a new class of FRET-based G-actin sensors, which at last allow us to visualise rho-actin signalling directly. We are developing sensors targeted to different subcellular locations, and sensor transgenes, which we will use to evaluate rho-actin signalling dynamics in rgw various biological contexts that under investigation, and make them available to the community of the study of actin dynamics more generally.
We continue to work on the molecular mechanisms of RPEL protein regulation by G-actin. We have found that G-actin negatively regulates recruitment of MRTFs to DNA via SRF, and have also shown that G-actin/MRTF interaction inhibits productive transcription, apparently promoting recruitment of the RNA exosome to nascent transcripts. Current work aims to understand the phenomena at the molecular level.
We demonstrated that the Phactr1/PP1 complex is a sequence-specific PP1 holoenzyme. Using proteomics, we have identified candidate dephosphorylation targets in fibroblasts and neurons, many of which are cytoskeletal regulators, and can now ask questions about the biology of the Phactr proteins. We are also developing Phactr1/PP1 inhibitory tool compounds.

We used structural and biochemical approaches to demonstrate that the ArhGAP12 and ArhGAP32 families of rhoGAPs are RPEL proteins controlled by rho-actin signalling. RPEL proteins. We are working to establish the role of G-actin binding in control of their functions, particularly in the control of phagocytosis and cell junction dynamics.

Research outputs

Gualdrini, F., *Esnault, C., Horswell, S., Stewart, A., Mathews, N., and Treisman, R. (2016)** ***SRF Co-factors Control the Balance between Cell Proliferation and Contractility**. Mol Cell. 64,1048-1061. DOI: 10.1016/j.molcel.2016.10.016**
The TCFs were the first transcription factors to be identified as targets for ERK signalling, but their contribution to the transcriptional response to ERK signalling has remained unclear. We used MEFs from animals lacking all three TCFs to show that TCF inactivation significantly inhibits over 60% of TPA-inducible gene transcription. Using an integrated ChIPseq/Hi-C approach, we distinguished direct and indirect targets of TCF signalling. The TCFs and MRTFs compete for a common surface on SRF, and this antagonism controls the efficiency of MRTF signalling: cells lacking the TCFs exhibit elevated MRTF/SRF signalling, and enhanced contractility and adhesiveness.

Esnault, C., *Gualdrini, F., Horswell, S., Kelly, G., Stewart, A., Mathews, N., East, P., and Treisman, R. (2017)** ***ERK-induced activation of TCF family of SRF cofactors initiates a chromatin modification cascade required for transcription**. Mol. Cell 65, (6):1081-1095. DOI: 10.1016/j.molcel.2017.02.005**
The relation between signalling to chromatin and transcriptional activation is poorly understood. In parallel with the above study, we investigated the relationship between ERK signalling, histone modifications, and transcription factor activity, focusing on the ERK-regulated ternary complex factor family of SRF partner proteins. We showed much ERK-induced chromatin modification at TSS regions is TCF-dependent. At direct TCF-SRF targets, we used reconstitution of TKO MEFs with Elk-1 mutants to show that signalling induced chromatin modification requires both Elk-1 phosphorylation and recruitment of the transcription machinery. Induction of histone modifications following ERK stimulation is thus directed by transcription factor activation and transcription.

Foster, C., Gualdrini, F., Treisman, R. (2017) ***Mutual dependence of the MRTF-SRF and YAP-TEAD pathways in cancer-associated fibroblasts is indirect and mediated by cytoskeletal dynamics*****. Genes Dev 31, 2361-2375. DOI: 10.1101/gad.304501.117**
The MRTF-SRF and the YAP-TEAD transcriptional regulatory networks both respond to extracellular signals and mechanical stimuli: the MRTFs are controlled directly by G-actin, while YAP activity is somehow potentiated by F-actin. Cancer-associated fibroblasts play an important pro-invasive role in stimulating cancer progression, and previous studies have shown that this involves YAP-TEAD signalling. This paper shows that CAFs also exhibit mechanically-dependent MRTF activation, which is also required for their contractile and pro-invasive activity. The two pathways are mutually dependent, requiring recruitment of MRTF and YAP to DNA via their respective DNA-binding partners, and reflecting their ability to control cytoskeletal gene expression.

Diring, J., Mouilleron, S., McDonald, N.Q. and Treisman, R. (2019) ***RPEL family rhoGAPs link Rac/Cdc42 GTP loading to G-actin availability*****. Nat Cell Biol. 2019 Jul;21(7):845-855. DOI: 10.1038/s41556-019-0337-y**
This paper shows that the ArhGAP9/12/15/27 and ArhGAP32/33 families of rhoGAPs are RPEL proteins whose activity is coupled to G-actin concentration. G-actin forms a 1:1 complex with these ArhGAPs, interacting with an RPEL motif located between the PH and GAP domains, thereby inhibiting their GAP activity. Mutations that block G-actin binding exhibit elevated GAP activity towards their substrate GTPases Rac and Cdc42. Strikingly, treatment of cells with drugs enhancing or inhibiting G-actin/ArhGAP interaction has

corresponding effects on Rac GTP loading. These results establish a novel homeostatic feedback loop, in which ArhGAP12-family (and presumably ArhGAP32-family) GAP activity increases when G-actin levels become limiting.

Fedoryshchak*, R.O., Přechová*, M., Butler, A., Lee, R., O'Reilly, N., Flynn, H., Snijders, A.P, Eder, N., Ultanir, S., Mouilleron, S. Treisman, R. (2020) *Molecular basis for substrate specificity of the Phactr1/PP1 phosphatase holoenzyme*. ELife 9:e61509. DOI: 10.7554/eLife.61509
Unlike kinases, PPP-family phosphatases such as PP1 have little intrinsic specificity. PP1 acts in partnership with over 200 different PP1-interacting proteins, but it has remained unclear how they might confer sequence-specificity on PP1. We used proteomics to identify dozens of candidate Phactr1/PP1 substrates, and used structural and biochemical approaches to show that the Phactr1/PP1 holoenzyme is sequence-specific. Phactr1 binding reshapes the PP1 hydrophobic groove, thereby creating a novel composite hydrophobic surface for substrate recognition. This study explains how cofactors can enhance the reactivity of PP1 toward specific substrates, and suggests a way forward for the development of PP1 holoenzyme-specific inhibitors.