Name	SILA ULTANIR
Position	Group Leader (2nd 6)
Year joined *(Crick or founder institute)*	2013

Career History

2004 - Columbia University, USA PhD, Neurobiology and Behavior
2004 - 2006 - University of California San Diego, USA Postdoc, Neuroscience
2006 – 2013 - University of California San Francisco, USA Postdoc, Neuroscience
2013 - The Francis Crick Institute (Previously Medical Research Council (MRC) – National Institute of Medical Research (NIMR)) Group Leader, current Developmental Neurobiology

Major Awards, Honours and Prizes

Loulou foundation for CDKL5 Research: Lab of the year award 2018. 50,000 USD.

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

Member of CDKL5 Forum Advisory Board for LouLou Foundation since 2018

Lab Name	***Kinases and Brain Development Laboratory***

Research programme and achievements

Formation of the neuronal circuitry relies on a large repertoire of signalling mechanisms that play roles in formation of neuronal dendrites, axons and synapses. My lab studies how kinases and protein phosphorylation regulate neuronal development and brain and may contribute to the disease of the nervous system. Numerous kinases are expressed in the nervous system and several are genetically associated with neurological diseases. My lab has a unique combination of expertise in kinase biology and cellular neuroscience. We strive to bridge large gaps in our knowledge of kinase functions with a focus on neurological disease-linked kinases.

In the past five years my lab worked on kinases with known genetic associations to human neurological disorders, and the hippo kinase signalling pathway, which has conserved roles in animal models of neuronal differentiation.

A large part of my lab now studies the kinase called CDKL5. Mutations in CDKL5 cause a severe neurodevelopmental disorder with seizures. We used chemical genetics to identify direct substrates of CDKL5, and via these substrates we revealed a role for CDKL5 in

regulating microtubule dynamics. Our findings opened up a new research area that we are actively working on. Reflecting the timeliness of our discovery, the phosphospecific antibodies we generated are widely used in CDKL5 research, particularly for preclinical studies by companies looking to restore CDKL5 function.

We also revealed a novel regulatory mechanism downstream of GAK, a kinase implicated in Parkinson's Disease. We discovered that GAK phosphorylates the alpha subunit of the Na+/K+ pump and showed that this phosphorylation regulates its trafficking.

In our hippo kinase research strand, we showed that LATS1/LATS2 kinases and their substrate, the transcription factor YAP1, are essential for preventing hyperproliferation and ependymoma-like tumour formation in mouse models. This study also revealed HOPX to be a novel factor present in a YAP1-fusion subtype of ependymoma, indicating that HOPX can be a marker for classifying ependymoma.

We also investigated NDR1/2 kinases, also thought to be downstream of the hippo pathway, using neuronal conditional NDR1/2 knockout mice. We revealed that NDR1/2 is critical for membrane trafficking and efficient autophagy-mediated protein clearance and that loss of NDR1/2 leads to neurodegeneration in the forebrain in mice.

Future Plans:

1. We will determine the function of CDKL5 signalling at molecular, cellular and behavioural levels using a wide array of interdisciplinary approaches. The Crick's many technology platforms are enabling us to conduct this research programme; we use light microscopy, proteomics, advanced sequencing, structural biology, electron microscopy, histopathology, genetic engineering in mouse models and BRF. At the end of a 3 year programme, I hope to have revealed novel kinase signalling mechanisms critical for brain development and plasticity.
2. I aim to expand my lab in the direction of kinase signalling that impacts neurodegeneration/ neuronal protein homeostasis.

Where possible, I would like to have our findings be translated to preclinical research. Antibody reagents that we generated are being used by several USA companies developing gene therapies for CDKL5 Deficiency Disorder, as preclinical markers of CDKL5 activity. While these antibodies are effective, better antibodies can be generated using rabbit monoclonal antibody technology, which is also very costly. It is one of my aims to initiate a pipeline of producing better versions of our antibodies (perhaps in collaboration with Abcam), where we see a clear value for research and therapeutic purposes.

Research outputs

Eder N., Roncaroli F., Domart, MC., Horswell, S., Andreiuolo F., Flynn, H.R., Lopes, A.T., Claxton, S., Kilday, J-P., Collinson, L., Mao, J-H., Pietsch, T.,Thompson, B., Snijders, A.P., Ultanir, S.K. (2020*). YAP1/TAZ drives ependymoma-like tumour formation in mice*. Nature Commun 11, 2380. DOI: 10.1038/s41467-020-16167-y
We showed that active YAP1 in radial glia derived neural precursor cells induces ependymoma-like tumours in mice. We demonstrated that YAP1 is necessary and sufficient using mouse models. We found that transcription coactivator HOPX, a factor consistently suppressed in malignancies, is highly expressed in our mouse models and in YAP1-fusion human ependymoma. HOPX differentiates YAP1-fusion subtype from the highly malignant

RELA-fusion human ependymomas. This supports the notion for subtype-specific care for ependymoma.

Lin, A.W., Gill, K.K., Castaneda, M.S., Matucci, I., Eder, N., Claxton, S., Flynn, H., Snijders, A.P., George, R., and Ultanir, S.K. (2018). ***Chemical genetic identification of GAK substrates reveals its role in regulating Na(+)/K(+)-ATPase*****. Life Sci Alliance 1(6):e201800118. DOI: 10.26508/lsa.201800118**
GAK is a serine/threonine kinase implicated in Parkinson's by GWAS. In this paper we identify GAK's direct substrates, and validated ATP1a3 as a substrate in cells. The role of the kinase domain of GAK was unknown, and we show that it enables recycling of Na+/K+ pump from early endosomes back to the plasma membrane. ATP1a3 is also implicated in movement disorders, including rapid onset dystonia. The ATP1a3 T705 phosphomutant is lethal in mice, indicating the significance of this phosphorylation site.

Baltussen, L.L., Negraes, P.D., Silvestre, M., Claxton, S., Moeskops, M., Christodoulou, E., Flynn, H.R., Snijders, A.P., Muotri, A.R., and Ultanir, S.K. (2018). ***Chemical genetic identification of CDKL5 substrates reveals its role in neuronal microtubule dynamics*****. EMBO J 37 37(24):e99763. DOI: 10.15252/embj.201899763**
We identified novel physiological substrates of CDKL5, a kinase linked to a severe neurodevelopmental disorder in humans. This study is important as it revealed for the first time that CDKL5 was a regulator of neuronal microtubules, thus identifying a new mechanism by which it regulates neuronal development and function. Our phospho-specific antibodies met the immediate need for a preclinical biomarker for studies in areas such as gene therapy.