Name	SONIA GANDHI
Position	Seconded Group Leader (UCL)
Year joined *(Crick or founder institute)*	2017

Career History

2004 – 2007 - Wellcome Trust Clinical Research Training Fellow, UCL QS Institute of Neurology
2007 – 2009 - Neurology Specialist Registrar, Barts and the Royal London NHS Trust
2009 – 2013 - NIHR Clinical Lecturer Neurology, Imperial College London
2013 – 2018 - Honorary Consultant Neurologist, National Hospital for Neurology & Neurosurgery
2013 – 2019 - Wellcome Trust Intermediate Clinical Fellow, UCL Institute of Neurology & The Francis Crick Institute
2017 – 2023 - Group Leader, The Francis Crick Institute, Laboratory Secondment
2020 – 2025 - MRC Senior Clinical Fellow, UCL Queen Square Institute of Neurology & The Francis Crick Institute

Major Awards, Honours and Prizes

2004: Wellcome Clinical Research Training Fellowship
2012: Wellcome Intermediate Clinical Fellowship
2019: MRC Senior Clinical Fellowship

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

Member, Swedish Research Council Neuroscience Panel 2017-2020
Member, Grant Assessment Panel for Parkinson's UK 2016 – present
Member, Faculty of Brain Sciences Equality and Diversity Committee 2017- present
Member, Athena Swan Committee, UCL Institute of Neurology 2017- 2019
Member, Wellcome Diversity and Inclusion Panel 2018
Member, Lancet Advancing Women in Science Panel 2019
Advisory Board, EBioMedicine 2019 – present

Lab Name	***Neurodegeneration Biology Laboratory***

Research programme and achievements

Since 2015, my research program has focussed on understanding the molecular and cellular mechanisms that cause neurodegenerative diseases, in particular Parkinson's disease. The accumulation of abnormal insoluble misfolded protein and progressive neuronal death are the key hallmarks of neurodegeneration, although it is not known how protein misfolding and aggregation leads to neuronal dysfunction and death in the human brain. To investigate this, my laboratory has:

(i) developed biophysical tools based on highly sensitive single molecule and super resolution approaches that can resolve the process of protein aggregation. Applying these tools to complex biological systems such as human biofluids and human cells, we have shown that during protein aggregation there is a range of intermediates with different structural conformations and sizes. Importantly one of those intermediate species, an oligomer rich in beta sheet structure, is particularly toxic to neurons.

(ii) identified several mechanisms by which the toxic oligomer species of the misfolded protein causes toxicity: we reported an interaction between oligomers and the ATP synthase in mitochondria, that result in bioenergetic impairment, and opening of the mitochondrial permeability transition pore in disease states. We demonstrated how misfolded protein can induce neuronal death through an iron dependent lipid peroxidation pathway termed ferroptosis. We further showed that misfolded protein can activate pro-inflammatory states in astrocytes, inducing TLR4 mediated neuronal injury.

(iii) established a human iPSC-based discovery platform, with in house developed directed differentiation methods to generate region specific CNS cell types affected in disease to test and validate the disease mechanisms.

The future research program of the Neurodegeneration Biology Laboratory incorporates the following themes:

- The interactions between protein misfolding and mitochondrial function; and protein misfolding and lysosomal function; and mitochondrial-lysosomal interactions and signalling in health and disease states in human neurons. This will be explored using the human (patient derived) models based on mutations in the protein misfolding pathway, mitochondrial homeostasis pathway, and lysosomal pathway.
- The dissection of cell autonomous (neuron mediated) vs non cell autonomous processes (astrocyte induced neuronal dysfunction) in disease states. This will be investigated using longitudinal imaging, and transcriptional dynamics of enriched, and co-cultures of different cell types.
- Establishing a transcriptomic and functional cell framework of the inherited forms of Parkinson's disease and determining how the sporadic, or idiopathic forms of disease are related to these familial forms.
- Generating a map of the Parkinson's brain utilising the oligomer as the biomarker for early disease: this will integrate super resolution imaging of oligomers in brain, spatial transcriptomics, and single cell transcriptomic and genomic analyses in postmortem human brain to understand where, how and why protein aggregates form in situ in disease.
- Taking forward the discoveries from MapPD, we will adopt gene editing approaches in our iPSC models to determine how these targets influence protein aggregation, and neuronal pathophysiology.

Research outputs

Aitken, J., Ambrose, K., Barrell, S. et al. (2020) *Scalable and robust SARS-CoV-2 testing in an academic center*. Nat Biotechnol 38, 927–931. DOI: 10.1038/s41587-020-0588-y
This paper was driven by the Crick-Covid-19 Consortium in response to the Covid-19 pandemic, and describes how we were able to successfully repurpose the Crick to increase the capacity for Sars-CoV-2 testing in unprecedented times. I have led, and been responsible for many aspects of this work, which has dominated much of the past 6 months, and so I include this output here.

Angelova, P.R., Choi, M.L., Berezhnov, A.V. et al. (2020) *Alpha synuclein aggregation drives ferroptosis: an interplay of iron, calcium and lipid peroxidation*. Cell Death Differ 27, 2781–2796. 10.1038/s41418-020-0542-z
This work demonstrates how lipid peroxidation may a be a critical driver of neuronal toxicity in protein aggregation diseases such as Parkinson's.

Hughes, C.D., Choi, M.L., Ryten, M. et al. (2019) *Picomolar concentrations of oligomeric alpha-synuclein sensitizes TLR4 to play an initiating role in Parkinson's disease pathogenesis*. Acta Neuropathol 137, 103–120. 10.1007/s00401-018-1907-y
This work shows the importance of neuron-glial interactions and inflammatory pathways in Parkinson's.

Ludtmann, M.H.R., Angelova, P.R., Horrocks, M.H. et al. (2018) *α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson's disease*. *Nat Commun* 9, 2293 10.1038/s41467-018-04422-2
This work combines single molecule imaging and super resolution methods with mitochondrial imaging and electrophysiology to demonstrate the mechanism by which α-synuclein oligomers alter mitochondrial function.

Hall CE, Yao Z, Choi M, Tyzack GE, Serio A, Luisier R, Harley J, Preza E, Arber C, Crisp SJ, Watson PMD, Kullmann DM, Abramov AY, Wray S, Burley R, Loh SHY, Martins LM, Stevens MM, Luscombe NM, Sibley CR, Lakatos A, Ule J, Gandhi S*, Patani R. (2017) *Progressive Motor Neuron Pathology and the Role of Astrocytes in a Human Stem Cell Model of VCP-Related ALS*. Cell Rep 19(9):1739-1749. DOI: 10.1016/j.celrep.2017.05.024
I led the imaging methodology and functional phenotyping in iPS derived motor neurons and astrocytes.