Structure and small molecule interactions of pathogenic C9orf72 RNA

Acronym: SM- RNA

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Summary of the research project

A mistake in the C9orf72 gene was found in 2011 to be the most common cause of amyotrophic lateral sclerosis (ALS); but it is not known how this mistake gives rise to ALS.
The type of mistake in the gene is very unusual, it involves a small string of DNA letters at the beginning of the gene, which expand massively, from being a few copies with the code GGGGCC to many copies of this six letter code. In fact, expansions of thousands of copies of this six letter code lead directly to both ALS and a related disorder frontotemporal dementia (FTD).
DNA sequences that are rich in the letter G can form highly stable chemical structures called 'G-quadruplexes'. These unusual structures can be involved in many processes including those to make a related chemical called RNA, which is needed to make proteins and those to process that RNA in various different ways to help the cell function normally.
In 2012, we showed that the RNA, not just the DNA, which is made from these GGGGCC copies forms RNA G-quadruplexes itself. This has profound implications for how ALS may be occurring, through having these strange chemical structures in the cell
Here we propose to look further at the C9orf72 G-quadruplex, in the RNA, to see how it behaves in cells. We will use our investigation of the C9orf72 RNA structure to identify small molecules that bind to the C9orf72 mutant RNA. This will provide the basis for investigating the use of small molecules as a therapeutic approach to modulate and interfere with the toxicity of this RNA species
By collaborating with the UCL School of Pharmacy, we aim to identify molecules that bind to these specific RNA G-quadruplexes.

Adrian Isaacs, PhD, is since 2010 a Lecturer in the Department of Neurodegenerative Disease, Institute of Neurology at UCL. From 2006 to 2010 he was in the same institute, a senior Post-Doctoral Fellow in the MRC Prion Unit. He did his Post Doc at Harvard Medical School. He graduated (PhD) from the University of Oxford, UK

Dr Isaacs' five recent publications relevant to this research:

1) Fratta P, et al. C9orf72 hexanucleotide repeat associated with amyotrophic lateral sclerosis and frontotemporal dementia forms RNA G-quadruplexes. Sci Rep. 2012; 2:1016.

(2) Ghazi-Noori S, et al. Progressive neuronal inclusion formation and axonal degeneration in CHMP2B mutant transgenic mice. Brain. 2012; 135(3):819-32.

(3) Urwin H, et al. FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. Acta Neuropathologica. 2010; 120(1):33-41.

(4) Urwin H, et al. Disruption of Endocytic Trafficking in Frontotemporal Dementia with CHMP2B Mutations. Hum Mol Genet. 2010; 19(11):2228-38.

(5) Filimonenko M, et al. Functional multivesicular bodies are required for autophagic clearance of protein aggregates associated with neurodegenerative disease. J Cell Biol. 2007; 179(3):485-500