The role of cyclin F in Motor Neurone Disease

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Motor Neurone Disease (MND) is characterised by the loss of motor neurons in the brain and spinal cord. Most patients with MND develop proteinaceous inclusions within affected neurons of the central nervous system, suggesting overall dysregulation of protein degradation systems. Our team identified mutations in *CCNF*, the gene encoding cyclin F. Cyclin F is a substrate binding component of a multi-protein ubiquitin ligase (denoted $SCF^{cyclin\ F}$), which mediates the ubiquitylation of substrates in order to influence the cell cycle.

Overarching aims of this thesis concern the impact of *CCNF* mutations on the ubiquitin ligase activity of $SCF^{cyclin\ F}$ and the downstream impact within cells. Addressing these aims involved using a series of biochemical assays (including *in vitro* ubiquitylation assays, immunoprecipitations, proximity-ligation assays and mass spectrometry). Results demonstrate that an MND-linked mutation in cyclin F leads to defective ubiquitylation activity, ultimately leading to the accumulation of proteins tagged for degradation.

Overall, the work provides insight into how the precise control of cyclin F ligase activity is dysregulated when cyclin F carries a disease-causing mutation. Furthermore, outcomes from this work provide novel links between cyclin F (a cell cycle regulator) and a devastating disease involving the degeneration of post-mitotic neurons.

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Belief change without compactness

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One of the main goals of Artificial Intelligence (AI) is to build rational agents that are capable of taking rational decisions autonomously. For this, it is essential to devise mechanisms to properly represent knowledge, and reason about the knowledge that an agent has about the world. However, an agent's knowledge is not static — it gets updated as the agent acquires new information. One of the big challenges involving knowledge representation is how an agent ought to change its own knowledge and