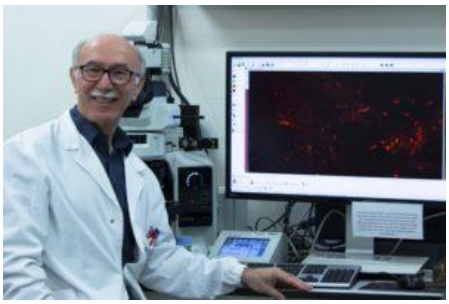
Functional and metabolomic analysis of iPSC-derived Purkinje neurons from A-T patients



SCIENTIFIC LEAD: Dr Marco Foiani & Dr Domenico Delia: FIRC Institute of Molecular Oncology, Milan, Italy

LENGTH: Due to conclude 2022

COSTS: £80,000

STUDY: This project really is cutting-edge science. We know that the cells of people with AT are missing the ATM protein. What we don't know, is why some brain-cells die off in the absence of the ATM protein, particularly the Purkinje cells and granule neurons. This is arguably the biggest question in AT research. Purkinje cells are large neurons with many branching extensions found in the cortex of the cerebellum of the brain and they play a fundamental role in controlling motor skills. Before answering the question, as it is impossible to remove Purkinje cells from the brains of living people, the scientists first had to focus on growing Purkinje cells in the laboratory from induced pluripotent stem cells, developed from the cells of people with AT, and turn them into Purkinje cells. Once achieved, they will carry out a series of analyses of the metabolic processes at work in the cells, to determine what factors and alterations make these cells hypersensitive to the absence of ATM.

PROGRESS: The team have succeeded in creating the first ATM-deficient Purkinje cells, a significant development in itself. They have obtained mature Purkinje neurons without needing to involve coculture with mouse cerebellar granule cells. It is the first time this has ever been achieved with cells from people with AT. The cells are now being produced in sufficient numbers so they can then be used to screen potential drugs and in further experiments to understand why it is that these cells die off when other neurons don't. So far, imaging analysis has been performed in order to compare the mitochondrial content, structure and activity, and an analysis undertaken to determine the response to drugs that induce metabolic stress by targeting the glycolysis pathway. Mitochondria are the powerhouse of the cell. They produce the energy required for the cell's function but can produce by-products that can damage cellular components. An assessment of the expression of certain mitochondrial proteins which are defective as a consequence of ATM-deficiency, on cerebellar biopsies from AT patients, is also being undertaken.