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NDCil

Neurodevelopmental ciliopathies: a multimodel approach from molecular mechanisms to patients variant interpretation and treatment strategies

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Nervous system malformation and neurodevelopmental defects (ND) are common hallmark features of genetically inherited diseases called ciliopathies. All ciliopathies are caused by abnormalities in tiny hair-like extensions called primary cilia (Cil), which are found on the surface of most cell types, including neuronal and glial cells. These cilia act as antennae that allow cells to communicate with each other so that they can coordinate their behaviours to form fully functional tissues and organs. Whilst much progress has been made in understanding cilia biology, surprisingly, we know very little about how they build and maintain the nervous system, and there are no therapeutic strategies to resolve the neurodevelopmental features of disease. Furthermore, how mutations in ciliopathy patients specifically affect underlying cilia genes are poorly understood.

To address these shortfalls, the NDCil project focusses on the most prominent neurodevelopmental ciliopathy called Joubert Syndrome (JS). Patients with this disease are born with malformation of cerebellar and brainstem structures, resulting in debilitating brain dysfunction. Research thus far has found that JS disease disrupts processes at the base of the ciliary rod called the transition zone. The objectives of NDCil are to: i) uncover new fundamental knowledge of how JS affects the brain at different levels of scale (cilia/TZ, neuronal and glial cells, whole brain); ii) establish how mutations found in JS patients disrupt cilia genes and cell-cell communication; and iii) discover new drugs that alleviate JS symptoms. These objectives will be achieved using well-established and novel cell and animal models that mimic the JS disease state, including pluripotent stem cells from patients, mouse stem cells, zebrafish and the invertebrate animal C. elegans, together

with state-of-the-art techniques such as gene editing (CRISPR-Cas9), advanced imaging, automated drug screening and proteomics.

Altogether, our interdisciplinary consortium of five partners across five countries provides an integrated platform for determining precisely how JS affects neurons and the brain, and how mutations found in JS patients affect underlying genes. The project also strives to discover new potential lead compounds for JS resolution. We expect the project to have direct benefit to patient diagnosis, prognosis, counselling, and therapy. Also, we anticipate that many aspects of the research will be applicable to the wider group of neurodevelopmental disorders beyond JS.