Project Details	
Project Code	NMH27Ex Bernard
Title	Cracking the ribosome code of brain development
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	What if ribosomes carried a code that helps build the brain? Ribosomes are complex molecular structures that play active roles in protein synthesis. During development, progenitor cells generate a diverse pool of neurons that form the adult brain circuits, but the role of protein synthesis in this key developmental process is still poorly understood. Using zebrafish and mouse models, this project will compare ribosomes in progenitors and newly born neurons, combining developmental neuroscience with structural biology imaging. This research will uncover fundamental mechanisms of brain development and provide insight into processes disrupted in neurodevelopmental disorders.
Description	The vertebrate brain contains a wide diversity of neurons, organised in highly specific circuits that control sensory processing, cognition and behaviour. Most neurons are generated during embryonic development from neural progenitors, through a temporally and spatially tightly regulated process that controls the generation of the correct numbers and types of neurons. Different progenitor populations generate different neuronal types, including excitatory projection neurons and inhibitory interneurons. Disruptions in this process are linked to neurodevelopmental conditions such as microcephaly, intellectual disability, autism spectrum disorder and neurodevelopmental forms of epilepsy. Most of our current understanding of neuronal differentiation focuses on transcription: how genes are switched on or off. However, gene expression does not stop there and to shape cell structure and function, post-transcriptional events such as translation play crucial roles in refining transcriptional information and contribute to cell-type-specific expression patterns. Ribosomes are the molecular machines that translate mRNA into protein. However, not all ribosomes are the same: once viewed as passive and indiscriminate, ribosomes are now recognised as dynamic complexes with a composition and structure that can vary with the metabolic and differentiation state of the cell. Recent works have shown that translation is a key regulator of neuronal differentiation and that ribosomes change as stem cells differentiate. However, we still lack a cell-type-resolved, cross-species and structural understanding of whether the ribosome machinery adopts different states and structures when progenitors differentiate into different neuronal types. The project proposes to investigate whether neuronal differentiation in vertebrates is underpinned by ribosome structural and molecular complexity. We will address this using two complementary in vivo models of vertebrate brain development, zebrafish and mouse, through the following objectives: - Build a cell-type-resolved map of ribosome states during neuronal differentiation

	The student will use transgenic reporter lines and cell-sorting approaches to isolate cells from developing mouse and zebrafish brains (co-supervision Bernard and Nikolaou), together with a multimodal approach to study ribosome molecular and structural complexity. The ribosomes will be isolated using the RAPPL method. The student will then employ ribosome profiling and mass spectrometry proteomics to examine the molecular compositions of the ribosomes. The structures of the ribosomes will be solved via single-particle cryo-electron microscopy (cryo-EM) followed by atomic model building using cutting-edge AI-guided approaches (co-supervision Daum). To identify any changes in the in situ structure and sub-cellular organisation of the ribosomes to the near atomic scale, the student will culture primary cells on grids and use Focused Ion Beam Scanning Electron Microscopy (FIB-SEM, co-supervision Sharp) and cryo-electron tomography (cryo-ET, co-supervision Daum). Combining the information from single particle cryoEM and cryoET will provide a scale-spanning picture of how ribosomes develop as the cells differentiate. - Identify conserved and species-specific ribosome states By comparing zebrafish and mouse, the project will distinguish core vertebrate features of ribosome regulation from species-specific aspects. - Test the disease relevance Several neurodevelopmental conditions have been associated with defects in translation (including Fragile X syndrome, Tuberous Sclerosis Complex, autism- and epilepsy-associated EEF1A2 mutations). The project will be extended to a model of one of these disorders, to test whether ribosome composition and structure are altered. The student will be encouraged to steer the project from the outset and throughout the PhD. They will help refine key decisions, including the neuronal cell types to study, the developmental stages to prioritise and the neurodevelopmental disorder model to take forward, depending on their interests, the available tools and emerging data. The project also includes several experimental and analytical routes, allowing the student to shape its direction as it progresses. They will also be encouraged to identify and engage with additional internal and external collaborators where this would strengthen the project. This will be supported by the unique interdisciplinary team and environment and will develop the student's independence and network. Overall, this project will provide new insight into ribosome complexity during vertebrate brain development. It will also address whether ribosome composition and structure are disrupted in neurodevelopmental disorders linked to altered translation, potentially identifying new biological processes for future therapeutics strategies.
Can be completed part time?	No
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