Project Details	
Project Code	MRCNMH26Ex Schrader
Title	Exploiting novel lipid binding proteins to tackle neurological disorders
Research Theme	NMH
Project Type	Wet lab
Summary	Successful applicants will join a dynamic, multi-disciplinary research project at the forefront of molecular cell biology, neurobiology, and lipid biochemistry. This cutting-edge project aims to uncover novel connections between organelle membrane proteins, lipid metabolism, and neurodegenerative diseases. Through innovative approaches—including advanced lipid analysis and the study of newly identified lipid-binding proteins—you will help reveal fundamental biological and biomedical principles. The findings are expected to open new pathways for improving lipid uptake and developing potential therapeutic strategies for neurodegenerative disorders.
Description	Adrenoleukodystophy (ALD, X-ALD) is a severe neurodegenerative disease, a hereditary condition which results in damage to the membranes that insulate nerve cells in the brain. The birth incidence of ALD is estimated at 1:14,000 and patients suffer from a variety of debilitating symptoms including progressive demyelination and adrenal insufficiency. This can lead to chronic fatigue, hearing and visual impairment, and seizures with rapid degeneration to a vegetative state. The severity and onset of symptoms can vary and the disease, despite being X-linked, can also manifest in carrier females in later life. ALD is caused by mutations in the ALDP gene which encodes a lipid transporter on peroxisomes, which are sub-cellular organelles with key functions in the processing of a range of lipid species including those required for proper function of neuronal membranes. Mutations in ALDP affect transport of lipids into peroxisomes, compromising lipid processing. The pathophysiology of ALD is complex but can be attributed to: 1) reduced lipid transport into peroxisomes resulting in insufficient processed lipids at the neuronal membrane and 2) accumulation of the unprocessed lipids in the cytoplasm leading to toxic effects. Currently therapeutic options are limited or in their infancy, and mostly aim at reducing accumulation of unprocessed lipids to limit toxicity. Surprisingly, the ALDP protein itself has no intrinsic affinity for lipids (Baker et al., 2015 Biochem Soc Trans. 43:959). We recently discovered a novel lipid binding protein, ACBD5, at peroxisomes, which appears to act as an ALDP cofactor, allowing increased lipid channelling to the transporter (Costello et al., 2017 J Cell Biol 216:331; Islinger et al., 2020 BBA 1867:118675; Kors et al., 2022 J Cell Biol 221(3):e202003143; Costello et al., 2023 J Biol Chem 299:105013; Kors et al., 2024 BBA-Mol Cell Res 1871:119843). In cooperation with the Amsterdam Medical Centre, we also identified first patients with loss-of-function mutations in ACBD5 (Ferdinandusse et al., 2017, J Med Genet 54:330; Schrader et al., 2020, J Inherit Metab Dis. 43:71; Dawes et al., 2025, Frontiers Mol Neurosci 18:1602343). Removal of ACBD5 results in the accumulation of the same lipid species which are evident in ALD patients. Our findings now enable us to further explore the properties and functions of ACBD5 in lipid metabolism, neuronal function and neurodegeneration. Our exciting discovery of ACBD5 (and related proteins) as a novel peroxisomal membrane protein with lipid-

	binding properties and a role in transport/uptake of lipids into peroxisomes opens new avenues for the treatment of neurodegenerative disorders, which the student will explore. Modulation of ACBD5 may be exploited to overcome defects in ALDP and improve lipid uptake in ALD, and possibly other neurodegenerative diseases with aberrant lipid metabolism. The student will be integrated in a multi-disciplinary project combining molecular and biochemical studies (M Schrader, Biosciences, Exeter) with neurobiological approaches/in vivo models (GA Smith, Dementia Research Institute, Cardiff) and expertise in lipid metabolism and lipidomics (V O'Donnell, School of Medicine, Cardiff; S Kemp, Amsterdam Medical Centre, NL). The student will combine molecular cell biology and biochemical approaches to further characterise the properties and functions of ACBD5 in lipid binding and as a cofactor for lipid transport. Cellular approaches will be combined with organismal models (fly, mouse) and mass spectrometry/lipidomics to determine the impact of ACBD5 on neuronal development, lipid composition and neurodegeneration. With this multi-disciplinary approach, we aim to unravel new basic biological and biomedical principles, to understand the properties and functions of ACBD5, and to explore approaches to improve lipid uptake into peroxisomes to combat neurodegenerative disorders such as ALD.

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