Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune and neurodegenerative disease of the central nervous system (CNS), characterized by pathological features as demyelination, axonal degeneration and inflammatory plaques. The treatment of MS today includes disease-modifying therapies, ameliorating the inflammatory response which is not able to prevent the progressive neurological decline, contributing to disability. This incomplete traditional framework of the understanding of the etiology and pathology of MS and the common comorbid condition, depression, indicates that the pathological pathways of MS and comorbidities remain unexplored and undiscovered. A new systemic framework of the understanding of MS originates from the dysfunction of the lipid metabolism. The brain energy homeostasis is maintained by a competing relationship between oxidation of glucose and fatty acids, depending on the energy demand of the tissue. Glucose is the primary energy substrate in the brain whereas fatty acids are used in β-oxidation as an alternative energy substrate. In the fatty acid metabolism, a carnitine shuttle with carnitine palmitoyl transferase 1 (CPT1) is required, as the outer mitochondrial membrane is impermeable to fatty-acyl CoA. Thereby, CPT1 serves as the regulatory rate-limiting step in the β-oxidation of fatty acids. Several human mutations for CPT1A are identified and the mutations CPT1A P479L and CPT1A G710E are of particular interest, since these are associated with low prevalences of MS and depression. Given that the lipid metabolism and thus CPT1 plays a pivotal role in the energy homeostasis, it is tempting to hypothesize that dysregulation of this may underlie diseases of the CNS. Therefore, the aim of the PhD thesis was to obtain a thorough understanding of the metabolism in health and disease, in order to clarify the etiology and pathology of MS and depression. The efficacy of lipid metabolism blockage has been evaluated, both pharmacologically by using etomoxir targeting CPT1 and genetically by generating Cpt1a P479L mice. In Manuscript I, the experimental autoimmune encephalomyelitis (EAE)-induced animals showed decreased clinical score, indicating amelioration of the disease. Moreover, the efficacy of etomoxir was superior to the standard treatment, interferon-β, of MS targeting T cell function. In Manuscript II, a pallet of autoantigens was modulated after etomoxir treatment in EAE-induced animals, showing that blockage of lipid metabolism causes alterations in the antibody response, thus targeting B cell function. In Manuscript III, the Cpt1a P479L mice showed resistance to EAE development compared to wild type mice. Moreover, high-fat diet, thought to exacerbate the disease course, affected the wild type EAE mice whilst the Cpt1a P479L EAE mice were unaffected. In Manuscript IV, the chronic mild stress-induced animals revealed reduced anhedonic behavior after etomoxir treatment compared to the standard treatment, escitalopram, of depression. In conclusion, the results presented in this PhD thesis provide knowledge supporting the new systemic framework for understanding the etiology and pathology of MS and depression. This indicates a change of paradigm towards development, progression and treatment of CNS diseases, in particular MS and depression, with lipid metabolism playing a central role, opening up a pathway to a new cure.
To fulfill the requirements for the PhD degree, Anne Skøttrup Mørkholt has submitted the thesis: The Central Role of CPT1A in Systemic Treatment of Multiple Sclerosis and Comorbidities; a Pathway to a New Cure, to the Faculty Council of Medicine at Aalborg University.

The Faculty Council has appointed the following adjudication committee to evaluate the thesis and the associated lecture:

- Associate Professor Simon Glerup
  Aarhus University
  Denmark

- Professor Jon Daniël Laman
  University Medical Center Groningen
  The Netherlands

Chairman:
Clinical Associate Professor Claudia Christina Hilt Pfleger
Aalborg University Hospital
Denmark

Moderator:
Associate Professor Jacek Lichota
Aalborg University
Denmark

The PhD lecture is public and will take place on:

**Program for PhD lecture on**

**Friday 26 April 2019**

**by**

**Anne Skøttrup Mørkholt**

The Central Role of CPT1A in Systemic Treatment of Multiple Sclerosis and Comorbidities; a Pathway to a New Cure.

Chairman: Clinical Associate Professor Claudia Christina Hilt Pfleger
Moderator: Associate Professor Jacek Lichota

13.00 Opening by the Moderator
13.05 PhD lecture by Anne Skøttrup Mørkholt
13.50 Break
14.00 Questions and comments from the Committee
   Questions and comments from the audience at the Moderator’s discretion
16.00 Conclusion of the session by the Moderator

After the session a reception will be arranged