Advancing the European Multidisciplinary Initiative on Neuroacanthocytosis – EMINA-2: Dissecting the molecular pathophysiology of Chorea-Acanthocytosis

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Principal Investigators

Dr. ir. M.J.W. Adjobo-Hermans

Institution

Radboud Universiteit Nijmegen

Contact information of lead PI
Country

Netherlands

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Advancing the European Multidisciplinary Initiative on Neuroacanthocytosis - EMINA-2: Dissecting the molecular pathophysiology of Chorea-Acanthocytosis

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ZonMw

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3

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Research Abstract
Neuroacanthocytosis (NA) syndromes are a group of rare disorders displaying neurodegeneration and misshaped spiky red
blood cells (acanthocytes). NA syndromes include Chorea-acanthocytosis (ChAc), McLeod

syndrome (MLS), Huntington's
disease-like 2, and pantothenate kinase-associated neurodegeneration (PKAN) with ChAc as the prototype of this disease
family. The European Multidisciplinary Initiative on Neuroacanthocytosis (EMINA-1) funded by the E-Rare-program 2009
provided detailed clinical characterization of the different NA syndromes and collected valuable brain and muscle tissue
samples of ChAc patients. ChAc is caused by loss-of-function mutations within the gene VPS13A encoding for a protein of
unknown function named Chorein. Within the EMINA-1 initiative, we recently found two signalling kinases as involved in ChAc
pathogenesis, but its exact pathophysiology remains enigmatic.
Based on the successful EMINA-1 network, the EMINA-2 consortium brings together 5 Young Investigators from leading
European laboratories in the fields of human cell models (induced pluripotent stem [iPS] cells), neurodegeneration, erythrocyte
biology, as well as murine and Drosophila ChAc models with the aim to explore in depth the molecular pathophysiology of
ChAc and translate this knowledge into new curative therapeutic approaches. Together we will combine our complementary
expertise involving molecular genetics, cell biology and protein biochemistry, neurophysiology and behavioural studies to
address how loss-of-function of VPS13A/Chorein translates into neurodegeneration and erythrocyte pathology with focus on
alterations of intracellular signalling cascades and their cross-talk to cytoskeleton function. We will use human iPS cells,
VPS13A knockout mice and mutant Drosophilae as ChAc models as well as patient materials generated by EMINA-1. The new
knowledge that we will acquire will provide us with potential drug targets for compound library screening with our Drosophila
ChAc models seeking to identify efficacious treatments to be explored in mammalian and human models. Since ChAc can be
seen as paradigmatic disorders to study the reasons for selective vulnerability of specific cell types, the results of EMINA-2 will
help to understand other diseases affecting erythrocytes membrane physiology and basal ganglia circuitries.

Further information available at:

http://www.zonmw.nl/nl/projecten/project-detail/advancing-the-european-multidisciplinary-initiative-on-neuroacanthocytosis-emina-2-dissecting-the/samenvatting/

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