# Erasmus University Rotterdam CSC PhD 2013

## Project Description

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| ***School/Department:*** | Department of Neuroscience  Erasmus University Medical Center, Rotterdam, The Netherlands |
| ***Project Title:*** | **New Therapies For Cerebellar Autism** |
| ***Abstract:*** | Autism comprises a heterogeneous group of neurodevelopmental  disorders characterized by variations in social interactions, communication, and the manifestation of ritualistic behaviors. A large number of rare high-impact mutations have been identified in autistic patients often suffering from cerebellar pathology. However, most insights into the synaptic pathophysiology of autism are derived from models of monogenic syndromes, such as fragile X syndrome, where  about 25% of patients meet diagnostic criteria of autism. In fragile X, the key defect in synaptic transmission is elevated group I metabotropic glutamate receptor-dependent synaptic plasticity (mGluR-LTD) (for cerebellar deficits see e.g. Koekkoek et al., 2005, *Neuron*). However, most cases of autism are nonsyndromic, and until recently, it was unclear whether these share pathophysiology with fragile X. One class of nonsyndromic forms of autism is associated with mutations in the Neuroligin genes (*Nlgn1,2,3,4*), which encode postsynaptic adhesion molecules involved in synapse assembly (proteins NL1,2,3,4). We have now demonstrated that mGluR-dependent cerebellar plasticity is also affected in Neuroligin-3 knock-out mice and that large parts of the neuro-developmental signs of  autism can be rescued by specific re-expression of neuroligin-3 in Purkinje cells of the cerebellum in juvenile mice, highlighting the possibility for reverting neuronal circuit alterations in autism after completion of development (Baudouin et al., 2012, *Science*). Moreover, we have recently also demonstrated that the behavioral deficits resulting from altered mGluR-dependent plasticity in fragile X can be rescued by application of mGluR antagonists (Vinueza Veloz et al., 2012, *Genes Brain Behav.*). Since activation of mGluRs does not only affect Purkinje cell plasticity but also directly its firing rate (Coesmans et al., 2003, *Ann of Neurol*.; Gao et al., 2012, *Nature Reviews*) and since these firing patterns directly control behavior (De Zeeuw et al., 2011, *Nature Reviews*), it will be interesting to find out to what extent mGluR-modifying drugs can also rescue various autism aspects in Neuroligin-3 knock-out mice. This is the long-term  goal of the current CSC proposal. Thus, we will investigate the  neurodevelopment, cell physiological characteristics and behavior of Neuroligin-3 knock-out mice before and after treatment with mGluR-modifying drugs similar to what we did in fragile X mice. Moreover, these results will be compared to rescues of other mouse models of autism such as Shank2 and Tsc1 mutant mice (Tsai et al., 2012, *Nature*; Won et al., 2012, *Nature*). Together, our key objectives should elucidate to what extent the pathophysiology of syndromic and nonsyndromic forms of cerebellar autism share common underlying  mechanisms mouse models enable us to unravel the molecular mechanisms of plasticity and transmission and to study the effects of channelopathies on the cerebello-cerebral interaction. |
| ***Requirements of candidate:*** | Background: The student should have a background and  bachelor-master degrees in Biomedical Sciences, Molecular  Biology and/or Neuro-Psychology. He/she should be interested  in the mechanisms underlying cerebellar function and autism.  The level in English reading, writing and speaking should be at  the highest possible standard.  Bachelor & Master degree: Yes, both degrees are required, but  they don’t need to be in the same field.  IELTS Grade: 7.0 *(minimal 6.0 per subscore)*:The higher the better. or  TOEFL: *100 (minimal 20 per subscore):*The higher the better. |
| ***Supervisor information:*** | C.I. De Zeeuw, Erasmus MC, Department of Neuroscience  Dr. Molewaterplein 50, 010 – 7043299,  Email: [c.dezeeuw@erasmusmc.nl](mailto:c.dezeeuw@erasmusmc.nl)  General website: http://www.neuro.nl  Personal website: <http://beta.neuro.nl/research/dezeeuw/>  *References related to topic (complete list: C.I. De Zeeuw at PubMed)*  - Sillevis Smitt, P., A. Kinoshita, B. De Leeuw, W. Moll, D. Jaarsma, S.  Henzen-Logmans, C.I. Vecht, C.I. De Zeeuw, M.P.H. Coesmans, N.  Sekiyama, S. Nakanishi, and R. Shigemoto (2000) Passive transfer of  mGluR1-blocking autoantibodies in Hodgkin's disease causes cerebellar  ataxia. *The New* ***England Journal of Medicine*,** Volume 342(1):21-27.  - Coesmans M., P.A. Sillevis Smitt, D.J. Linden, R. Shigemoto, T. Hirano,  Y. Yamakawa, A.M. van Alphen, C. Luo, J.N. van der Geest, J.M. Kros,  C.A. Gaillard, M.A. Frens, and C.I. De Zeeuw (2003) Mechanisms  underlying deficits in cerebellar motor coordination due to auto-antibodies  against mGluR1. ***Ann. of Neurol.,*** 53:325-336.  - Feil, R., J. Hartmann, C. Luo, W. Wolfsgruber, K. Schilling, S. Feil, J.J.  Barski, M. Meyer, A. Konnerth, C.I. De Zeeuw, and F. Hofmann (2003)  Impairment of LTD and cerebellar learning by Purkinje cell-specific ablation  of cGMP-dependent protein kinase I. ***J. Cell Biol.,*** 163:295-302.  - Koekkoek, S.K.E., H.C. Hulscher, B.R. Dortland, R. Hensbroek, Y.  Elgersma, T.J.H. Ruigrok, and C.I. De Zeeuw (2003) Cerebellar LTD and  Learning-Dependent Timing of Conditioned Eyelid Responses. ***Science,***  301:1736-9.  - Coesmans, M., J.T. Weber, C.I. De Zeeuw, and C. Hansel (2004)  Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber  control. ***Neuron,*** 44:691-700.  - Koekkoek, S.K., K. Yamaguchi, B.A. Milojkovic, B.R. Dortland, T.J.H.  Ruigrok, R. Maex, M. Vellema, A.E. Smit, F. van der Werf, C.E. Bakker, R.  Willemsen, T. Ikeda, S. Kakizawa, K. Onodera, D.L. Nelson, E. Mientjes, M.  Joosten, E. De Schutter, B.A. Oostra, M. Ito and C.I. De Zeeuw (2005)  Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges  spines, and attenuates eyelid conditioning in a manner which phenocopies  human Fragile X syndrome. ***Neuron***, 47:339-352.  - Schonewille M, Khosrovani S, Winkelman B, Hoebeek FE, De Jeu MTG,  Larsen IM, Schmolesky MT, Frens MA, and De Zeeuw CI (2006). Purkinje  Cells in Awake Behaving Animals Operate in Stable Upstate Membrane  Potential. ***Nature Neuroscience***, 9:459-461*.*  - Christian Hansel, Marcel T. De Jeu, Amor Belmeguenai, Simone H.  Houtman, Gabriëlle Buitendijk, Dmitri Andreev, Chris I. De Zeeuw and Ype  Elgersma (2006) αCaMKII is essential for cerebellar LTD and motor learning.  ***Neuron****,* 51(6):835-43. |