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Abstract Title: Meta-analysis for Neurofilament Light Chain (NfL) as Biomarker in Mouse Experimental Autoimmune Encephalomyelitis (EAE) Studies

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Introduction:
NfL, a neuron-specific cytoskeletal protein released upon neuro-axonal damages, is considered a promising prognostic biomarker of disease activity in multiple sclerosis. In humans, the relationship between NfL measured in the CSF (cNfL) and plasma (pNfL) is highly correlated. Because pNfL can be easily measured, it can be a potential additional tool for evaluating MS disease prognosis in patients. Its value, in preclinical models such as mouse EAE, is however still debated.

Objectives/Aims:
Assess the correlation of NfL, a potential biomarker for MS disease activity, in CSF and plasma in an EAE mouse model.

Methods:
A total of 25 independent mouse EAE studies were conducted over 2 years, under similar protocols (C57BL/6J mice; induction via ratMOG$_{28\text{-}152}$ in complete Freund's adjuvant). They aimed at assessing the effects of pharmacological interventions, *vs* vehicle controls, on changes in clinical scores, cNfL and pNfL levels (ELISA kit #10-7001, Uman Diagnostics). All available data was pooled and subject to meta-analysis.

Results:
In healthy mice, the mean cNfL and pNfL levels were 10.4 ± 0.1 (n=45) and 0.42 ± 0.03 (n=50) ng/mL, respectively, indicating a CSF/plasma ratio of ~25.
In vehicle-treated EAE mice, cNfL and pNfL levels significantly increased post-disease induction (pDI), although with a high degree of inter-individual variability. At peak of disease, which occurred typically around day 19 pDI, cNfL and pNfL reached maximal mean values of 287 ± 27 (n=114) and 8.0 ± 0.8 (n=126) ng/mL, respectively, indicating a CSF/plasma ratio of ~35. These levels remained elevated up to one-month pDI (n=61 and 50, respectively) and showed a ~10-fold reduction at 2 months pDI (n= 10 and 9, respectively).
Overall, the meta-analysis demonstrated that correlations between cNfL or pNfL *vs* EAE clinical scores and between pNfL *vs* cNfL levels were highly significant ($p<0.0001$ for all), consolidating pNfL as a robust predictor of cNfL in the EAE model.

Conclusion:
In mice, pNfL was highly correlated with cNfL, consistent with the observation in humans. The present meta-analysis suggests that the translational value of mouse EAE studies for assessing the therapeutic potential of new DMT candidates could be markedly increased by introducing measurement of cNfL and/or pNfL. This also establishes an additional measure by which to assess disease evolution and tissue damage in EAE mice.

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Marc Bigaud, Sarah Tisserand, Pamela Ramseier, Tatjana Uffelmann, Catherine Huck, Giuseppe Locatelli, Bruno Cenni, Barbara Nuesslein-Hildesheim are employees of Novartis.

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