
Supplementary information

**Clinical trial strategies for rare
neurodevelopmental disorders:
challenges and opportunities**

In the format provided by the authors

About the workshop

A panel of leading experts was convened by F. Hoffmann La-Roche on 12–13 November 2018 to discuss current insights and future avenues for clinical development of novel therapies for rare neurodevelopmental disorders (RNDDs). The experts ranged from clinical researchers to preclinical scientists to industry partners who are all active leaders in the field. The organizing committee put together a broad range of current topics and questions around clinical trial development in RNDDs, and the goal was to discuss current hurdles and opportunities in clinical development of future trials for these RNDD populations, such as trial design, outcome assessments and biomarkers. The experts had as their mandate to envision the future of clinical trials in RNDDs, by critically examining the past and sharing examples of current efforts to move the field forward. The workshop consisted of structured facilitated discussions around key topics summarized below, and the discussion was recorded and incorporated into a summary that was circulated back to the expert panel for clarifying comments and alignment. The final summary of this discussion is presented in this manuscript, including subsequent updates to ongoing work.

Key topics:

- Angelman syndrome, preclinical developments
- Angelman syndrome, clinical developments
- Dup15q syndrome and syndromic ASD perspective
- Non-syndromic ASD perspective
- Rett syndrome
- Dravet syndrome
- Fragile X syndrome
- Tuberous sclerosis complex
- Electrophysiology as a biomarker
- Paediatric sleep in neurodisability
- Gene therapy in neurodisability
- What biomarkers can we use to detect early change in neurodevelopmental processes?
- Genetic epilepsy: quantifying impact of seizures/ how to disambiguate effects on seizures from cognition

Content included in each topic

- Current challenges for the field
- Recent insights with greatest potential for clinical development: e.g. animal models, cell-based approaches, enabling technologies, novel endpoints, regulatory perspectives
- Work in progress

Further reading by section

When to intervene?

Biological mechanisms potentially related to critical windows of neurodevelopment, and a specific example of the effects of intervention at different developmental stages in mouse model of Angelman syndrome.

- 1 Ismail, F. Y., Fatemi, A. & Johnston, M. V. Cerebral plasticity: Windows of opportunity in the developing brain. *Eur J Paediatr Neurol* 21, 23-48, doi:10.1016/j.ejpn.2016.07.007 (2017).
- 2 Sonzogni, M. et al. Delayed loss of UBE3A reduces the expression of Angelman syndrome-associated phenotypes. *Mol Autism* 10, 23, doi:10.1186/s13229-019-0277-1 (2019).

Clinical outcome assessments

Examples of application of growth scale scores.

- 3 Farmer, C. A. et al. Person Ability Scores as an Alternative to Norm-Referenced Scores as Outcome Measures in Studies of Neurodevelopmental Disorders. *Am J Intellect Dev Disabil* 125, 475-480, doi:10.1352/1944-7558-125.6.475 (2020).
- 4 Keute, M. et al. Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment. *Mol Psychiatry*, doi:10.1038/s41380-020-0858-6 (2020).

Interaction of seizures with cognition and neurodevelopment, and challenges in seizure quantification in clinic.

- 5 Capal, J. K. et al. Influence of seizures on early development in tuberous sclerosis complex. *Epilepsy Behav* 70, 245-252, doi:10.1016/j.yebeh.2017.02.007 (2017).
- 6 Elger, C. E. & Hoppe, C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. *Lancet Neurol* 17, 279-288, doi:10.1016/S1474-4422(18)30038-3 (2018).

Application of novel digital approaches to quantifying the effects of sleep on cognitive performance of children.

- 7 Colonna, A. et al. The Effects of Sleep on Emotional Target Detection Performance: A Novel iPad-Based Pediatric Game. *Front Psychol* 9, 241, doi:10.3389/fpsyg.2018.00241 (2018).

Biomarkers

Links between electrophysiological biomarkers and clinical outcomes including seizures and autism spectrum disorder.

- 8 Wu, J. Y. et al. Scalp EEG spikes predict impending epilepsy in TSC infants: A longitudinal observational study. *Epilepsia* 60, 2428-2436, doi:10.1111/epi.16379 (2019).
- 9 Dickinson, A., Varcin, K. J., Sahin, M., Nelson, C. A., 3rd & Jeste, S. S. Early patterns of functional brain development associated with autism spectrum disorder in tuberous sclerosis complex. *Autism Res* 12, 1758-1773, doi:10.1002/aur.2193 (2019).

Disease-specific electrophysiology signatures, with an example of modulation by genotype and translation from mouse models to human in Angelman syndrome.

- 10 Frohlich, J. et al. A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome. *PLoS One* 11, e0167179, doi:10.1371/journal.pone.0167179 (2016).
- 11 Frohlich, J. et al. Mechanisms underlying the EEG biomarker in Dup15q syndrome. *Mol Autism* 10, 29, doi:10.1186/s13229-019-0280-6 (2019).
- 12 Frohlich, J. et al. Electrophysiological Phenotype in Angelman Syndrome Differs Between Genotypes. *Biol Psychiatry* 85, 752-759, doi:10.1016/j.biopsych.2019.01.008 (2019).
- 13 Sidorov, M. S. et al. Delta rhythmicity is a reliable EEG biomarker in Angelman syndrome: a parallel mouse and human analysis. *J Neurodev Disord* 9, 17, doi:10.1186/s11689-017-9195-8 (2017).

Examples of quantitative electrophysiology biomarkers across RNDDs

- 14 Saby, J. N., Peters, S. U., Roberts, T. P. L., Nelson, C. A. & Marsh, E. D. Evoked Potentials and EEG Analysis in Rett Syndrome and Related Developmental Encephalopathies: Towards a Biomarker for Translational Research. *Front Integr Neurosci* 14, 30, doi:10.3389/fnint.2020.00030 (2020).
- 15 Ethridge, L., Thaliath, A., Kraff, J., Nijhawan, K. & Berry-Kravis, E. Development of Neural Response to Novel Sounds in Fragile X Syndrome: Potential Biomarkers. *Am J Intellect Dev Disabil* 125, 449-464, doi:10.1352/1944-7558-125.6.449 (2020).
- 16 Jannati, A. et al. Continuous Theta-Burst Stimulation in Children With High-Functioning Autism Spectrum Disorder and Typically Developing Children. *Front Integr Neurosci* 14, 13, doi:10.3389/fnint.2020.00013 (2020).

Applications of Transcranial Magnetic Stimulation as a biomarker of value in RNDDs

- 17 Tsuboyama, M., Lee Kaye, H. & Rotenberg, A. Biomarkers Obtained by Transcranial Magnetic Stimulation of the Motor Cortex in Epilepsy. *Front Integr Neurosci*. 13:57., doi:10.3389/fnint.2019.00057. eCollection 02019. (2019).
- 18 Premoli, I. et al. TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. *Ann Clin Transl Neurol* 6, 2164-2174, doi:10.1002/acn3.50896 (2019).