Report from ReCognitION: a milestone in an alternate pathway towards personalized medicine for myotonic dystrophy (DM1)

The EU-funded ReCognitION research project came to an end. This report summarizes its main findings.

ReCognitION is a follow-up program of the OPTIMISTIC clinical trial. OPTIMISTIC demonstrated the potential benefit of Cognitive Behavioral Therapy (CBT), a lifestyle intervention, on the activity and social participation of DM1 patients[1].

The central hypothesis of the program is that molecular processes associated with the positive response to Cognitive Behavioural Therapy (CBT) can be consolidated or reinforced by conventional drug therapies targeting the same processes.

ReCognitION is a pre-clinical study, taking advantage of all information and material collected from OPTIMISTIC, without additional clinical investigations.

The study was conducted in 3 steps:

- Screen molecules in the blood that reflect the disease severity and the response to CBT,
- Identify drugs that target molecular processes affected by CBT, prioritizing drugs which are already approved for clinical use (drug repurposing),
- Measure the effect of these drugs in DM1 patient cells and mouse models.

Molecular profiling, biomarker and biological pathways identification

We identified a large set of molecules in the blood that reflected the severity of the disease. Some of the biomarker molecules returned to more normal levels in patients who benefited most from CBT, singling these genes out as candidate biomarkers for therapy response.

These results highlight the ability to find disease relevant information in the blood of DM1 patients and pave the way for low-invasive blood tests that could be used to monitor the efficacy of new interventions in future clinical trials.

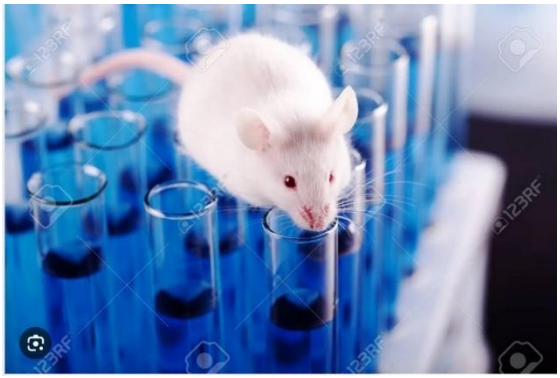
Some of the biomarker molecules pointed at possible targets for existing drugs and were subsequently tested in DM1 patients cells and mouse models.

Evaluation of drugs and drug targets in animal models

Bexarotene was the most promising compound coming out of the molecular screen. Bexarotene, already approved for use in humans, was tested in DM1 patients cells and DMSXL mouse models.

[1] Lancet Neurol. 2018 Aug;17(8):671-680. https://doi.org/10.1016/S1474-4422(18)30203-5

Unfortunately, the experiments did not provide evidence for a positive effect of Bexarotene on the disease mechanisms nor the muscle strength and behavior of mice.



The ReCognitION consortium also evaluated two previously identified drug candidates for DM1: metformin[2] and vorinostat[3]. Within ReCognitION, it was tested whether the combination of these two drugs was more effective than either drug alone.

This proved to be the case in cultured neurons from DM1 patients, where the combined treatment allowed for lower dosing of the individual drugs. In DM1 mouse models, vorinostat showed a positive effect, but metformin did not, making it impossible to evaluate the combination.

[2] *Metformin is an antidiabetic medicine*
[3] *Vorinostat is a drug approved to fight some cancers*

Conclusion

The ReCognitION project significantly improved collaborations in the DM1 field on biomarker and drug evaluation and produced a wealth of new data. It has been shown that DM1 leaves a strong RNA and protein fingerprint in the blood.

Candidate biomarkers for monitoring disease severity and response to therapy have been identified. These may serve as surrogate endpoints in future clinical trials.

ReCognitION mapped molecular processes associated with the positive response to Cognitive Behavioral Therapy (CBT) in patients with myotonic dystrophy and revealed new drug targets.

Existing drugs binding to these targets may improve the symptoms that DM1 patients are suffering from, but a promising new drug candidate is yet to be identified.

Want to learn more…

- Neault, N., Ravel-Chapuis, A., Baird, S. D., Lunde, J. A., Poirier, M., Staykov, E., ... & MacKenzie, A. E. (2023). Vorinostat Improves Myotonic Dystrophy Type 1 Splicing Abnormalities in DM1 Muscle Cell Lines and Skeletal Muscle from a DM1 Mouse Model. *International Journal of Molecular Sciences*, 24(4): 3794. https://doi.org/10.3390/ijms24043794

- Van Cruchten RTP, van As D, Glennon JC, Van Engelen BGM, 't Hoen PAC, OPTIMISTIC consortium, ReCognitION consortium (2022) Clinical improvement of DM1 patients reflected by reversal of disease-induced gene expression in blood. *BMC Med*. 20:1–17. https://doi.org/10.1186/s12916-022-02591-y

- Berenger-Currias, N., C. Martinat, and S. Baghdoyan (2023) Pluripotent Stem Cells in Disease Modeling and Drug Discovery for Myotonic Dystrophy Type 1. *Cells* **12**(4). https://doi.org/10.3390/cells12040571

- Website: www.optimistic-dm.eu/recognition