

3Rs Management and Consulting ApS

Making novel approach methodologies (NAMs) the new standards in research, product development and new generation risk assessment

SenzaGen AB – **ToxGenSolutions BV**

Walking on the edge between physiology, pathology and toxicology

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A diagnostic/predictive miR profile for late-onset Alzheimer's disease (AD) and neurotoxicity (NT)

- 1) From systemic review (human data) and machine learning to a tau-driven AOP toward memory loss (AOP429). (<https://doi.org/10.3233/JAD-201418>)
- 2) Related AOPs in the AOPwiki were connected with key events (KEs) of AOP429 to build an AOP network . (Tsamou et al (2022) (accepted for publication))
- 3) Using miR's related to KEs of AD pathology and NT, genetic networks were constructed to identify gene and miR hubs. (<https://doi.org/10.3233/JAD-215434>)
- 4) In a pilot study, 8 miR's (out of 37) identified individuals at risk >5 years before current diagnostic approaches did. (Sens.:100%; Spec.:92%; Acc.:98% (**small study!!!**))
- 5) Next steps:
 - EuroStars – proAD (2021-2024)
 - Validation on 1,200 serum/plasma samples (including patients with non-AD dementia)
 - **Planned:** Incorporation into a microsensor device for quick (< 3hrs) and cheap diagnosis
 - **Considered:** high-throughput tool for assessing drug efficacy during large clinical studies
 - Assessing the potential of the identified miR's to identify neurotoxicants in an iPSC-based test system.
 - iPSC-based test system was developed by the Interreg. Project 'Memories'.

Probabilistic Risk Assessment

1) ONTOX (Horizon2020):

- Probabilistic Risk Assessment based on cutting-edge AI, fed by available biological, mechanistic, toxicological, epidemiological, physico-chemical and kinetic data
 - Integration of both external and internal exposure data
- Data gaps identified by AI will be filled by targeted state-of-the-art *in vitro* and *in silico* testing.
- 3RS MC is involved in WP6 on Risk Assessment and application, and is in close contact with regulatory and industrial stakeholders, and relevant NGO's.

2) ASPIS

- ONTOX is also part of the ASPIS cluster, which represents Europe's effort towards the sustainable, animal-free and reliable chemical risk assessment of the future
 - 3RS MC is involved in the working groups for chemical selection and risk assessment

New Generation Health Care

- 1) Based on the approaches used for developing the miR profile for late-onset AD and NT.
 - Still walking on the edge between physiology, pathology and toxicology
 - Targeted pathologies (with extreme focus on gender differences):
 - Neurodegenerative diseases, Cancer, Immunosuppression, Long-covid, Fibromyalgia, Chronic fatigue syndrome
 - Some of these diseases are overrepresented in the female population (why???, and what can we do about it???)
- 2) Status
 - Project being formulated
 - Budget being established
 - Relevant 'need-to-have' expertise being identified
- 3) Objectives and perspectives:
 - Finding and applying the tools for improving health and optimally manage disease
 - Contributing to sustainable health at affordable costs
 - Offering state of the art quality health care

Thank you for your attention