Executive Summary

Second reporting period (1st August 2019 – 31st January 2021)

Summary of the context and overall objectives of the project

Our programme develops an innovative in-silico based approach to improve the efficacy and precision of disease definition, diagnosis and therapy. For the most rapid clinical validation and translation, we apply in-silico predicted drug repurposing, i.e., finding new indications for already registered drugs with a known safety profile, which, so far, has been rather serendipitous. We also reduce animal experimentation by preclinical systematic reviews and meta-analyses and high quality preclinical randomised confirmatory trial (pRCTs). Following our in-silico predictions we conduct at least two clinical trials where patients are stratified using mechanistic biomarkers thereby innovating not only drug repurposing but also clinical diagnostics. Collectively, we reduce the uncertainty and vagueness of many current disease definitions. Successful drug repurposing generates rapid patient benefit, reduces drug development costs as well as its risks and enhances industrial competitiveness.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

We designed a large-scale data integration platform and a dedicated Cytoscape App (NeDRex), a corresponding web tool, and novel machine learning algorithms (like the Multi-Steiner Tree detector) harnessing the integrated data. Together, this allows for custom projections and analyses of multi-scale data including multi-omics, pharmacological, and comorbidity. We started with two sets of three and 11 seed genes, respectively, and used our NeDRexDB with its NeDRex app in WP1 to extract candidate genes as targets for discussion and validation with and by WP2. The NeDRexDB integrates the disease-gene-based and the comorbidity-based disease-disease networks into a combined disease-disease network covering both information sources. WP1 and WP2 are jointly working on de novo pathway generation and protein interaction networks based on first neighbours and clinically highly validated seed genes. The ROCG disease phenotype cluster was confirmed using multiscale approaches. Several targets including MPO and Cl-Tyrosin as a biomarker were deprioritised and instead NOX5 as key source of ROS predicted and validated. Systematic reviews for metanalyses were performed to analyse the state of the art for our target-disease couples. Pre-clinicaltrials.org has been upgraded to a fully automated online database ready for public use. Our biomarker strategy was developed suitable for point-of-care facilities and biobank samples obtained to pre-analyse the clinical screening effort. Two clinical drug repurposing pilot studies in stroke (REPO-STROKE) and heart failure with preserved ejection fraction (REPO-HFpEF have been presented to competent regulatory agency in Germany (BfArM). REPO-STROKE I has started. REPO-HFpEF will exploit technology and use data from UM's related CIPER trial. Patent applications have been filed. Dissemination efforts to the scientific public have been made concerning REPO-TRIAL's approach to ischemic stroke and hypertension, and preparations have been made for a wider campaign concerning REPO-STROKE. REPO-TRIAL has established an online presence (website, Twitter, LinkedIn); has communicated the project outline to industry stakeholders and to the scientific community (by several high-level conference presentations, including the World Government Summit and a Nobel Forum session). The Steering Committee has monthly TCs to enable timely progression of the consortium towards achieving deliverables and milestones. Any critical issues are identified rapidly, and discussions are held to develop solutions and implement them effectively. The public as well as the private part of the project website are kept up to date. The Project Management Office prepared a quality plan and a formal risk review. Members of the Scientific and Ethical Advisory Board (SEAB) were invited to the General Assembly Meetings. The SEAB members have given valuable feedback during and directly following the meeting and were also consulted by individual WPs for feedback on deliverables and other tasks before completion, if needed.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the action so far)

Expected impacts

REPO-TRIAL will reduce the size and the duration and increase the efficacy and safety of human clinical trials by mechanistic biomarker-guided stratification of drug treatment to those patients with a high likelihood to suffer from the targeted pathomechanism and thus respond. By targeting a mechanism that

is disease relevant, surrogate markers will predict late patient relevant outcomes and trials can be terminated earlier. Safety will be increased by network pharmacology combining synergistic drugs at an individually lower-than-usual dose. The evident major reproducibility crisis in pre-clinical research and relevance of animal testing is significantly improved through the introduction of REPO-TRIAL's pre-clinical randomised controlled trials (RCTs) approach and the pre- clinicaltrials.org platform to facilitate pre-clinical systematic reviews and meta-analyses. However, drug repositioning is improved by in-silico prediction, obviating in many cases the need for animal experiments, in a mechanism-based and more predictable manner to lower development costs and shorten time-to-market for new drugs by reducing the #1 cause of failure, lack of efficacy. The virtual in-silico cohorts are be clustered by their molecular mechanistic profiles and grouped by their predicted treatment outcome distribution.

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