Executive Summary
First reporting period (1st January 2019 – 30th April 2020)

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 drug repurposing for rapid clinical translation. We do so based on systems medicine and mechanistically related disease phenotypes as a virtual patient cohort. Patients will be stratified using a mechanistic biomarker panel thereby innovating two biomedical product classes, drugs and diagnostics. We establish generally applicable in silico trials for other mechanistically defined disease phenotypes. Scientifically, we reduce the uncertainty and vagueness of many current disease definitions describing symptoms in one organ rather than a precise molecular mechanism. We also reduce animal experimentation and animal numbers by preclinical systematic reviews and meta-analyses as a prerequisite for high quality preclinical randomised confirmatory trial (pRCTs) within our open access platform pre-clinicaltrials.org. 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 leveraging innovative crowd-sourcing strategies. Additionally, we have been developing a dedicated Cytoscape App and novel machine learning algorithms harnessing the integrated data. Together, this allows for custom projections and analyses of a wealth of diverse multi-scale data including but not limited to multi-omics data, pharmacological data, and comorbidity data. We started with two sets of three and 11 seed genes, respectively, and used our RepotrialDB with its interface CyPoTrial in WP1 to extract candidate genes as targets for discussion and validation with and by WP2. Importantly, the ROCG disease phenotype cluster was confirmed using multiscale approaches. Based on the *de-novo* constructed first neighbour ROCG signalling network, several targets including MPO and Cl-Tyrosin as a biomarker were deprioritised. For the pre-clinical validation, the initial focus was put on the most likely to be performed clinical trials. Here, ethics were successfully submitted and a-priori systematic reviews for metanalyses performed to analyse the state of the art for our target-disease couples in an unbiased manner. A biomarker strategy was developed suitable for point-of-care facilities. In addition, biobank samples were obtained to pre-analyse the possible clinical screening effort. The planning of two drug repurposing pilot studies in human beings, regarding stroke on the one hand and heart failure with preserved ejection fraction on the other hand, has become more concrete. In consultations with the competent regulatory agency in Germany (BfArM), the project has gained valuable input and in principle, received positive feedback on the systems medicine approach. The trial protocols are in ongoing preparation and will be the centrepiece in the clinical trial applications. REPO-TRIAL has established online presence (website, Twitter, LinkedIn); communicated project outline to industry stakeholders (via press release carried by industry news agencies and mentions of REPO-TRIAL in life science media) and 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. 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. 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. Pre-clinicaltrials.org has been upgraded to a fully automated online database ready for public use. As a new application we consider including automated meta-analyses.

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 increasing 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. Cases where a drug is given to a non-responding patient, who will then maximally experience unwanted side-effects but no benefit, will be highly reduced by which the overall safety of the human clinical trial will increase. Safety will further be increased by network pharmacology combining synergistic drugs at an individually lower-than-usual dose, further reducing the chance of dose-dependent unwanted side-effects. 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 for both data and sample sharing and to facilitate pre-clinical systematic reviews and meta-analyses. Drug repositioning is improved 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 developed in-silico models can be re-used in chemical testing by novel statistical models and algorithmic approaches in the area of graph-processing, graph-based learning, and combinatorial optimization of complex statistical models having graph-restricted constraints. Standards will be set for in-silico trials workflow using standard kits. Libraries of virtual patients can be re-used in pre- and post-competitive drug testing through a database of virtual patient libraries reflecting the demographic distribution of local (national, global) populations, and genotypic/phenotypic variance (if known or statistically estimable). The virtual cohorts will be clustered by their molecular mechanistic profiles and further grouped by their predicted treatment outcome distribution; all accessible through standard interfaces. Cross-cutting priorities, such as sex and age, are respected and included in all statistical models either as separate parameters to optimize for, or by separating the virtual patient collection correspondingly, and running cross-comparative analyses separately.

REPO-TRIAL Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777111. This reflects only the authors' view and the European Commission is not responsible for any use that may be made of the information it contains.