Executive Summary

Third reporting period (1st February 2021 – 31st January 2022)

Summary of the context and overall objectives of the project

Medicine and biomedical research are in a deep crisis. We hardly understand the causes of any disease. Not knowing the cause makes disease not curable; thus, they become chronic with increasing costs for society. Not knowing the causes of disease leaves the pharmaceutical industry with the only option to treat or modulate the symptoms of disease, an approach which since the 1950s is getting constantly more and more inefficient, risky and costly. Even when a drug is registered, most patients have no benefit from it and two thirds of all new drugs have no benefit at all. Our knowledge gaps in disease also affect biomedical research. The dogma "from cells to animals to human to patient benefit" is broken at several points. How can we know whether an animal model of disease is relevant to study a human disease when it maximally mimics the symptom of that disease, but we do not know when the causes for these similar symptoms are the same? On top of that there are quality issues. More than 50% of published peer-reviewed biomedical research results are not reproducible. Almost no research is ever attempted to be applied for patient benefit and the success rate is 1 in 23,000 publications or less. The key cause for this dead-end road we are in is our definition of 'disease,' namely by organ. This is how Medicine and biomedical research has been structured for more than a hundred years. For every organ we have a clinic, a specialist and a research discipline. This assumes that a symptom in one organ of a patient can have nothing to do with symptoms in another organ of the same patient. So, we make two diseases out of them, which we both do not understand and cannot cure. There is, however, a group of diseases where we know the cause, i.e., rare diseases. They are typically not named after an organ or symptom but a specific gene or protein (the product of a gene), which is a very precise disease definition allowing for a precise and even potentially curative intervention, e.g., gene therapy. Also, these often single-gene diseases cause symptoms in more than one organ; our current approach to chronic diseases would easily make several "independent" diseases out of each symptom. All of this we want to change, exemplified in a focus area of a set of diseases causing symptoms in the heart, blood vessels, brain and lung. We want to reduce the use of animals for this as much as possible and thus begin with existing human data. In the end we want to cure humans and not mice or rats. We do this by advanced bioinformatic "big data" methods revealing the underlying common causal mechanism of these co-occurring symptoms. Next, we develop diagnostics to pick out those patients that share both one or more symptoms and we can also detect in a simple blood sample that this underlying causal disease mechanism is affected. In parallel we look at whether drugs are available to treat this mechanism. Here we prioritise the already registered drugs because this provides the safest and fastest way to clinical application as lengthy and risky drug discovery is not necessary. We then validate these new precision diagnoses and precision therapeutic intervention first in healthy volunteers, then in patients. Thus, we reduce the uncertainty and vagueness of many current disease definitions to change medicine from imprecision to precision, from chronic to cure - and ideally to prevention.

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 formed five work packages (WPs): WP1, on big data and in-silico clinical trial and virtual patients; WP2, on deriving precision diagnostics and select drugs based on WP1; WP3, on clinical application of the diagnostics developed and drugs selected in WP2; WP4, on disseminating these results broadly but also valorising and licencing them to companies so that they are commercially developed, a final but essential prerequisite to make our findings enter the market and cause patent benefit; and, of course, WP5 which manages REPO-TRIAL. WP1 allows for custom projections and analyses of multi-scale big data. With this, WP2 was able to construct one underlying causal disease mechanism relevant for a group of diseases that very often co-occur in different organs of the same patient. This mechanism contains several genes and named it the ROCG mechanism. For this we developed a blood-based diagnostic test. For intervention we identified drugs that can be repurposed to likely cure for the first-time hypertension, heart failure and stroke in those patients where we can identify the mechanism. We validated these therapies in relevant humanised mouse models and in WP3 completed the first two clinical trials in stroke and heart failure in healthy individuals. With these safety data, we now apply for approval of the same approach in patients. WP4 succeeded in finalising a licensing contract for the REPO-TRIAL technology with a drug repurposing company ensuring full commercial development.

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). In WP5, the project is managed through a coordinator, his Project Management Office (PMO), and monthly Steering committee conferences to enable timely progression of the consortium towards achieving their deliverables and milestones. The PMO prepared a quality plan and an ongoing risk review and implemented mitigation strategies. Members of the Scientific and Ethical Advisory Board (SEAB) were invited to REPO-TRIAL's General Assembly Meetings and gave valuable feedback on the quality of project deliverables.

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 pathomechanisms and thus respond. By targeting a mechanism that is disease relevant, precision diagnostics will predict late patient relevant outcomes and trials can be terminated earlier. Safety will be increased by combining safe drugs that synergise by acting on the same mechanism and can thus be individually lower-than-usual dosed. Animal research is reduced to only essential, predictive and relevant models. Clinical intervention by drug repurposing is improved by in-silico prediction in a more predictable manner to lower development costs and shorten time-to-market for new drugs by improving precision and lowering risk of failure, eventually for one overarching goal a new level of patient benefit.

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