Mechanism-based diagnosis of cyclic GMPopathies and pharmacological interventions

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Impact

The efficiency of drug research and development as measured by the number of annually approved new drugs has been in constant decline since the 1950's. In parallel, the number of patients suffering from chronic diseases has majorly increased, and current pharmacological interventions only treat symptoms and do not cure diseases. Moreover, current treatments are also imprecise, characterised by high numbers needed to treat (NNT), i.e. the number of people that need to take a drug to prevent a single adverse outcome. Indeed, the ten highest-grossing drugs in the US benefit between 1 in 25 and 1 in 4 of the patients that get them. In some cases, such as with statins, they may help only 1 in 50 patients. Consequently, the economic impact and burden on the healthcare system is significant and the only way to be lowered is through precision medicine approaches.

The first step towards closing this gap is to redefine diseases based on molecular mechanisms. Most disease definitions are just diagnostic algorithms of clinical values and symptoms with no evidence for the underlying disease cause, grouping together heterogeneous patient populations under common umbrella-terms. Here, we propose a mechanism-based approach to disease definition and patient selection within the ROCG disease module of NADPH oxidase 5 (NOX5)-derived reactive oxygen species and impaired nitric oxide (NO)-cyclic cGMP (cGMP) signalling. NOX-5, through reactive oxygen species production, can affect different key enzymes of the NO-cGMP signalling such as NO synthase (NOS) and sGC. In such conditions, NOS uncoupling and sGC oxidation/heme-loss takes place and the cGMP signalling is disrupted.

A simple and precise protocol to analyse the ROCG signalling in peripheral blood cell samples was developed; feasible to be applied in a clinical setting since minimal efforts are required for sample handling. Impaired ROCG signalling is thought to be implicated in a subset of patients with heart failure (HF), i.e. those with preserved ejection fraction (HFpEF). HFpEF is a disease with unmet medical need and represents 40% of all HF patients. Impaired ROCG signalling is identified in approximately 30% of HFpEF patients. More specifically, elevated NOX5 levels are present in 25%-33% of HFpEF patients, while damaged sGC is present in 30%. Thus, a ROCG-biomarker patient stratification will be used in the REPO-HFpEF II trial, in which HFpEF patients will receive a ROCG - modulating pharmacological

intervention, i.e. an sGC stimulator and a NOS recoupling treatment. These mechanism-based selected patients are, thus, likely to respond and benefit from the treatment. The consequences of a successful trial are of utmost importance, since the current most prominent treatment in HFpEF has a NNT equal to 31. This mechanism-based diagnosis and treatment of HFpEF patients has been filed as a patent application (P6103072NL); at the moment on the national level (the Netherlands) but a PCT filling will follow. This patent has been licensed and a phase III trial is under preparation.

Moreover, to restore the ROCG signalling, compounds such as NOS-recouplers and apo-sGC activators have been suggested. However, currently only sGC stimulators are clinically approved. Here, we showed that sGC stimulators are able to act on apo-sGC as well, both in vitro and in vivo. This means that sGC stimulators can be repurposed for conditions where apo-sGC is highly prominent too, such as ischemic stroke. A patent application protecting the use of sGC stimulators in combination or not with sGC activators for indications where apo-sGC is present has been filled. The application (published internationally as WO/2021/167458) has now entered the regional and national phases in Europe, Canada and USA. Moreover, this finding led to the network pharmacology-based REPO-STROKE II trial. More specifically, an sGC stimulator in combination with a NOS inhibitor and a NOX inhibitor are being repurposed in patients with ischaemic stroke. Combinations of drugs acting on the same signalling module allow lower doses since synergistic effects are to be expected and thus, less side-effects. In an indication such as stroke - where only a single drug is available with 30 contraindications, leaving 85% of patients without treatment - the societal and economical impact will be of substantial importance, aiming towards less disabilities, better quality of life and less healthcare costs for rehabilitation.

Since most repurposing candidate compounds have regulatory approvals, and hence a broad range of safety and efficacy data, drug repurposing is a strategy that can accelerate early-stage development to a very significant degree and also entails economic advantages. Importantly, the chances of development success are vastly improved because safety data in humans already exist. In addition to that, with mechanistic biomarker-guided stratification patients with a high

likelihood to suffer from the targeted pathomechanism will be selected and thus respond to the drug treatment. It stands to reason that the closer the pharmacological strategy can be tailored to the underlying pathophysiologic mechanism, the more effective and safer it will be. Efficacy and safety can be further increased as network pharmacology approaches will be applied i.e. combining at least two synergistic drugs at an individually lower dose. Thus, network pharmacology approaches and mechanism-based diagnostics will pave the way towards precision medicine.