

Network pharmacology for mechanistically redefined comorbidities

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VALORISATION

The prevalence of comorbidities is increasing due to aging populations. This will lead to massive medical and socio-economic challenges. Comorbidity is not only associated with worse health outcomes, but also with more complex clinical management, and increased health care costs for public and private insurance payers, individuals, and families. Drug discovery and development does not have only long development times, but for many years its expenses have increased exponentially with a decreasing success rate. This is neither sustainable for the pharmaceutical industry but also the health care providers and tax payers who indirectly need to refinance these costs. One key knowledge gap in all of this is our current way of defining and treated diseases, i.e. by symptom without knowing the underlying causal molecular mechanisms. Obviously this is an imprecise and error-prone approach in medical valorisation that has to be overcome.

This thesis therefore suggests to redefine comorbidities based on their underlying causal molecular mechanisms as a first key step towards filling this key knowledge gap. Once these diseases are fully endo-phenotyped and mechanistically understood, they will segregate into several distinct mechanotypes that can be treated with different drugs. Both diagnostic and therapeutic approaches herein provide IP and socioeconomic benefit options. To achieve rapid market entry, a drug repurposing approach of registered compounds was chosen.

In hypertension, one molecular causal mechanism i.e. NADPH oxidase 5 (NOX5)-induced uncoupling of nitric oxide (NO) synthase (NOS), was identified. This mechanism was found only in some hypertensive patients (around 25%) i.e. as endotype and thus this would suggest that only those patients need to be treated with NOX5 inhibitors and NOS recoupling agents and not all hypertensive patients. These findings open up several lab-to-market opportunities, both in diagnostics and in therapies and deliver at least two products; i) biomarkers for precision diagnosis and ii) a first-in-class mechanism-based therapy. Biomarkers will help stratify the patients based on the underlying pathomechanism and therapeutics will target a causal disease mechanism and therefore are more precise than the current symptomatic treatments. Applying this mechanism-based theragnostic approach (Fig. 1) will decrease the number needed to treat and thus have a great socio-economic relevance.

In stroke only one approved drug is available which is a thrombolytic treatment, rt-PA, and there is no neuroprotective therapy. Here three targets within the ROCG network i.e NOX, NOS and soluble guanylate cyclase (sGC) were identified. This thesis suggests that a combination of NOX and NOS inhibitors and sGC activator as the first broadly applicable, safe and effective neuroprotective therapy. Using drugs that are already approved or in late clinical development i.e. drug repurposing allows fast testing of this network pharmacology approach in clinical trials. This neuroprotective treatment is a patentable finding that still requires further clinical development, therefore the right strategy for this specific finding is considered to be to further develop the patent into a spin-off company with matching scientific and commercial experience to develop and exploit the findings up to phase IIb/III clinical.

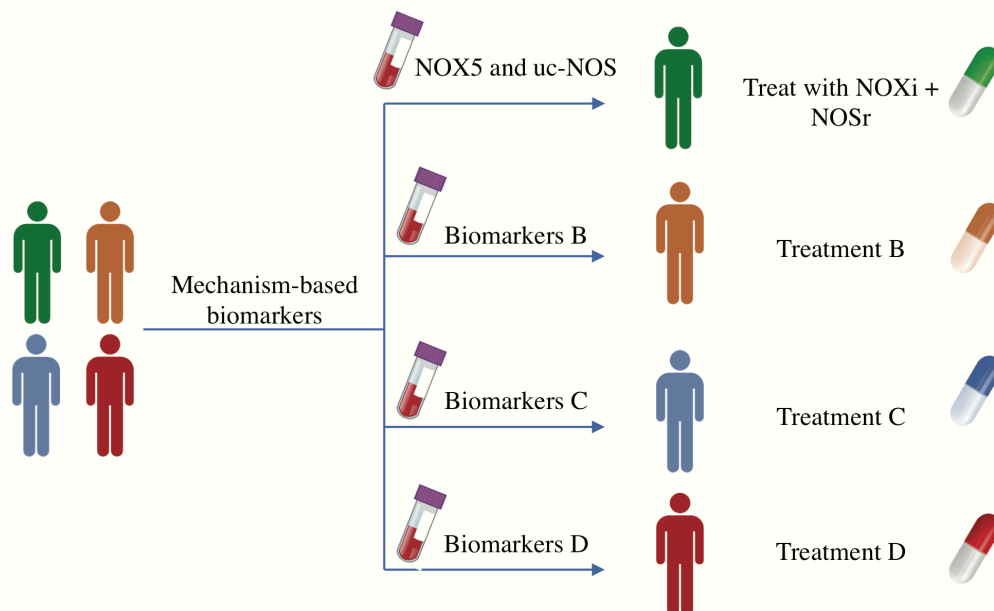


Fig.1| Mechanism-based theragnostic approach in hypertension. NOS_r, Nitric oxide synthase recoupling agent; NOX₅, NADPH oxidase 5; NOXi, NADPH oxidase inhibitor, uc-NOS, uncoupled NOS.

In conclusion, network pharmacology has several advantages that overcome the current knowledge gaps and unmet medical needs: (i) gathering investigators from different disciplines such as basic biology, clinicians, systems biology, network and data science to work together in addition to collaboration with pharma companies, (ii) drug repurposing within the same disease cluster which decreases time and costs of drug development and omits the need for further preclinical testing and (iii) combination of low-dose drugs for multiple targets within the same network to ensure

high efficacy and less side effects. This approach is of course not limited to the above-mentioned diseases and the ROCC mechanism, but can be applied within any complex, i.e. polygenic disease phenotype and delivers a remarkable and safe innovation for treatments of common comorbidities, which could rapidly save millions of lives of patients, improve the quality of life and decrease research and health care costs.