SIMPATHIC: Accelerating drug repurposing for rare diseases by exploiting SIMilarities in clinical and molecular PATHology

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ABSTRACT

Rare diseases affect over 400 million people worldwide, with approved treatment available for less than 6% of these diseases. Drug repurposing is a key strategy in the development of therapies for rare disease patients with large unmet medical needs. The process of repurposing drugs compared to novel drug development is a time-saving and cost-efficient method potentially resulting in higher success rates. To accelerate and ensure sustainability in therapy development for rare neurometabolic, neurological, and neuromuscular diseases, an international consortium *SIMilarities in clinical and molecular PATHology* (SIMPATHIC) has been established where we move away from the one drug one disease concept and move towards one drug targeting a pathomechanism shared between diseases, by applying parallel preclinical and clinical drug development. Here the consortium describes accelerators of drug repurposing pursued by the consortium, including 1) co-creation, 2) patient empowerment, 3) use of standardized induced pluripotent stem cell (iPSC)-derived disease models and cellular and molecular profiling, 4) high-throughput drug screening in neurons, 5) innovative clinical trial design, and 6) selection of appropriate exploitation and patient access models. In this way, a fast and effective drug repurposing pathway for several rare diseases will be established to reduce time from discovery to patient access.

Keywords: Drug repurposing, rare diseases, therapy development, induced pluripotent stem cells, drug screening, basket trial.

Abbreviations

AI: Artificial intelligence

CARE-SM: Clinical And Registry Entries Semantic Model

DRUP: Drug Rediscovery Protocol

EJP-RD: European Joint Program on Rare Disease

EMA: European Medicines Agency

ERN: European Reference Network

EUPATI: European Patients' Academy on Therapeutic Innovation

EURORDIS: European Organization for Rare Diseases

FAIR: Findability, accessibility, interoperability, reusability

FDA: Food and Drug Administration

GAS: Goal Attainment Scaling

HT: High-throughput

HTA: Health technology assessment

IP: Intellectual property

iPSC: Induced pluripotent stem cell

IRDiRC: International Rare Disease Research Consortium

MAB: Multistakeholder Advisory Board

Neuro-RDs: Rare neurological, neurometabolic, and neuromuscular disorders

NGN2 iN: Neurogenin-2 inducible neurons

PAO: Patient advocacy organization

PRO: Patient-reported outcome

PROM: Patient-reported outcome measure

RCT: Randomized controlled trial

REMEDI4ALL: Repurposing of medicines for all

REPO4EU: Precision drug REPurpOsing For Europe and the world

SIMPATHIC: SIMilarities in clinical and molecular PATHology international consortium

SOP: Standard operating procedure

TPP: Target Product Profile

TPVP: Target-patient value profile

1. Introduction

Millions of people worldwide are affected by one of the nearly 8,000 rare disorders, defined as a condition affecting less than one in 2,000 individuals according to European definitions (1). Rare diseases often pose an enormous burden on affected individuals, families, caregivers and the healthcare systems, implying clinical and economic burden as well (2). Less than 6% of rare diseases have an approved treatment option, emphasizing the unmet needs for therapies (3). Treatment targets are increasingly identified for many rare diseases, but there is a great need for evidence-based therapeutic interventions. However, implementation of therapeutic interventions via clinical trials for rare and heterogeneous patient populations faces specific challenges in methodology, outcome measures, and financial, organizational and regulatory barriers.

Drug repurposing is a key strategy in the development of therapies for individuals with rare disorders with large unmet care needs (4). Reductions in time and costs compared to traditional drug development are important

assets of drug repurposing strategies, contributing to sustainability (5). Especially in inherited metabolic disorders, where time is limited due to high morbidity and mortality, timely treatment is crucial to prevent possible irreversible damage (6). Drug repurposing strategies may result in higher success rates, which can therefore drastically reduce the investment risk of drug development inherent to rare disorders (7). Bottlenecks include the selection of target groups from heterogeneous patient populations, the availability of relevant drug screening models and outcome measures, the development of appropriate business models and intellectual property (IP) strategies, and the building of adequate regulatory dossiers (7,8). Diverse stakeholders are usually engaged in repurposing approaches. To help developers navigate the regulatory and development tools and resources for repurposing in new rare disease indications, the International Rare Disease Research Consortium (IRDiRC) developed the Drug Repurposing Guidebook (9).

To reach the IRDiRC's goal of developing 1,000 new therapies for rare disorders by 2027 (10), the development of new therapeutic interventions using drug repurposing should be accelerated for those with unmet medical needs. To accelerate the drug repurposing pathway for rare diseases, focusing on neurological, neurometabolic and neuromuscular disorders (neuro-RDs), the international consortium *SIMilarities in clinical and molecular PATHology* (SIMPATHIC) has been established in 2023. SIMPATHIC moves away from the one disease one-drug paradigm and proposes to let larger groups of patients across medical conditions benefit from existing medicines (11). This will be achieved through preclinical and clinical development of drug repurposing candidates targeting a group of rare neuro-RDs with different genetic diagnoses but overlapping clinical symptoms and shared molecular pathomechanisms. SIMPATHIC aims to develop an effective strategy to reduce time from discovery to patient access, which could serve as an example for other rare disorders that need evidence-based therapies. Here we describe accelerators of drug repurposing.

2. Accelerating therapy development

In SIMPATHIC, we aim to **accelerate** drug repurposing by 1) designing a co-creation process between all stakeholders, 2) empowering patients to become drivers of the drug repurposing process, 3) standardizing disease models and cellular and molecular profiling, 4) parallel in vitro drug screening, 5) innovative clinical trial designs, and 6) fit-for-purpose exploitation and patient access models (Figure 1).

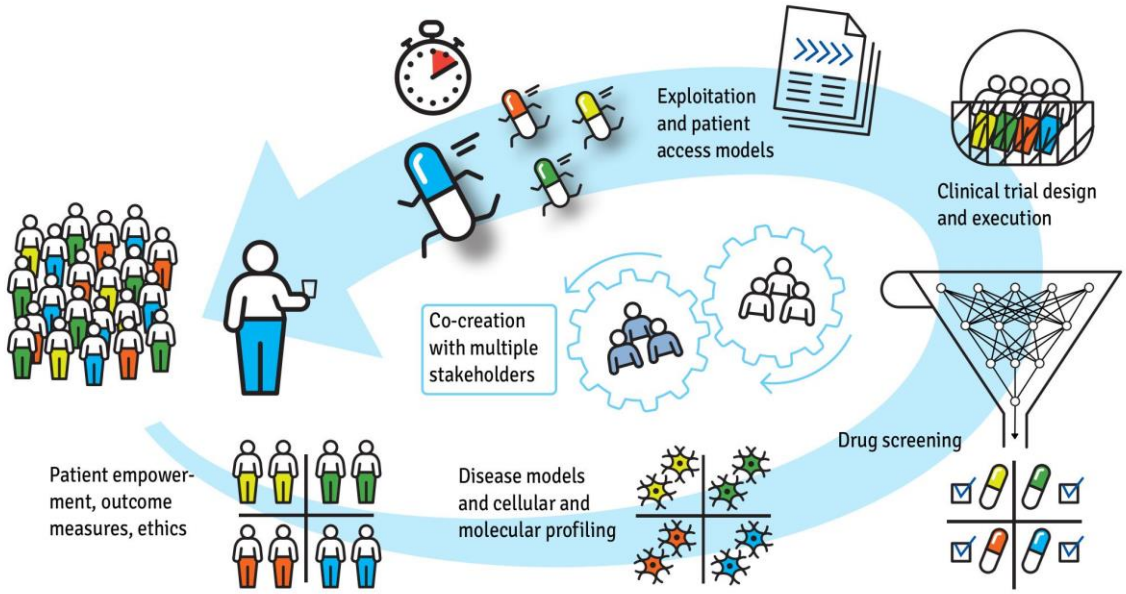

Figure 1. Accelerators of the drug repurposing pathway in SIMPATHIC. *SIMPATHIC's proposed activities are organized around key objectives that contribute to the acceleration of the drug repurposing pathway and the increase of efficiency.*

2.1 Drug repurposing in co-creation between all relevant stakeholders

The SIMPATHIC consortium intends to engage all relevant stakeholders from the beginning, following recommendations on sustainable approaches for drug repurposing in rare diseases from the IRDiRC Task Force (12). Stakeholders include clinicians, patient advocacy organizations (PAOs), regulatory experts, ethicists, and implementation experts in co-creation. Some of the researchers are engaged in related international projects, to generate synergy (e.g., REMEDI4ALL (13)). Stakeholders are either members of the consortium who lead work packages and perform the research needed, or are engaged in advisory roles, for instance in the Multistakeholder Advisory Board (MAB) that will function throughout the duration of the project, or attend one-time expert meetings.

A central element in attuning all stakeholders involved is the Target Product Profile (TPP) (14–16). This is a document specifying intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics, to address unmet clinical needs. The document would serve to discuss with all stakeholders what is needed to reach the common goal of medication becoming accessible for patients in due time.

Examples of elements to be specified include the minimal effect that would be useful for patients, the route of administration, aspects of safety and tolerability, and the costs.

Specific attention will go to needs and expectations of patients, such as governance related to induced pluripotent stem cells (iPSCs) used for drug screening in the SIMPATHIC project and within trial governance in general. By studying patients' preferences in interviews, surveys and focus groups, an ethical framework for drug repurposing will be developed.

To test efficacy of potential new drugs, appropriate and relevant outcome measures need to be defined. Patient organizations are involved from the beginning to identify specific versus common patient-reported outcomes (PRO), patient-reported outcome measures (PROMs) and real-world evidence. Focus group interviews and (online) questionnaires will be used, as well as a target-patient value profile (TPVP) (17) integrated in the TPP, in a co-creation process to create an inventory and prioritize the most relevant PRO for patients and caregivers (18). Prerequisites from the patients' perspective, such as governance issues, and the decision making on the use of PROs will be inventoried. Furthermore, Goal Attainment Scaling (GAS) will be used to allow personalized endpoints reflecting patient capacity in a shared decision-making process (19). Patients and their treating clinicians jointly define individual treatment goals and individual criteria for scoring the extent of success regarding those goals on a 5-point scale before start of the treatment. It enables individualized outcomes that can be evaluated at treatment group level as well (19,20).

If the holistic approach to generate evidence in a clinical (basket) trial does not fit the current system of market access and reimbursement, representatives from national and international regulatory bodies will advise on strategies to integrate current needs for receiving, for instance, orphan drug designation. Should a new regulatory approach need to be discussed in several member states, PAOs will develop training to empower their members to participate in discussions with their national regulatory agencies. Production of repurposed drugs is likely to be performed by pharmaceutical companies, which are also represented in the consortium.

2.2 Empower patients and patient representatives to become drivers of the drug repurposing pathway

SIMPATHIC envisions patients as shapers, active co-developers and important stimulators in mobilizing other stakeholders to jointly drive the drug repurposing pathway. SIMPATHIC positions PAOs as partners in drug development, by tailoring patient community engagement, involving them in all aspects of the project and applying shared decision-making approaches.

The objective is to build a patient-centered project, allowing patients to take a leading role in drug repurposing, by empowering them with essential training. SIMPATHIC's roadmap, to be used by multidisciplinary stakeholders, will allow for integration of patient's (as well as of caregivers) perspectives and preferences, in all relevant steps of the drug repurposing pathway. The active involvement of multiple patient organizations (one per disease) ensures that all efforts in the project are tailored towards the needs of patients with rare diseases (21).

Patient empowerment will increase the number of drug repurposing trials as well as the patient-centeredness of these trials (22). Patients as co-drivers of the drug repurposing process will facilitate the following processes: First, ensuring relevance of research activities regarding drug screening and prioritization of drug-diseases combinations; second, optimalisation of patient commitment to research activities, with attention to heterogeneity between disorders and patients; third, taking into account gender-specific aspects and specific needs of the pediatric population, of the relatives and of caregivers; fourth, the selection of outcomes that should be targeted, which is of importance to both preclinical and clinical studies for translational purposes; fifth, the selection of outcome measures for a clinical trial that are sensitive to pick up drug effects and best reflect the severity of symptoms without too much burden for the patient; sixth, the selection the appropriate patient populations and to optimize the recruitment process (23). Data collected from the inventories will support empowerment of patients, design of the clinical trial and regulatory decision-making. The necessity of those discussions has become clear in preparatory contacts with patient representatives and is documented in the literature (24–26). A discussion that surpasses single disorders, will also defragment the outcome measure field (27), which is currently characterized by many disorder-specific scales, and ensure cross-cultural applicability.

Patients with essential high-quality background will be equipped on the notions involved in SIMPATHIC, with a key focus on the drug repurposing process (28). First, patients' educational needs will be characterized and confirmed in collaboration with PAO partners. Missing educational resources will be created, based on an inventory of already existing resources and on internal expertise. Based on trainees' feedback, and lessons learned in the other work packages, improvements of the course will be implemented. Sustainability of the resources will be ensured by publication on PAOs partners websites, Foundation For Rare Diseases 'Research guide for PAOs' (29) and by offering them as part of the European Patients' Academy on Therapeutic Innovation (EUPATI) (30) and European Organization for Rare Diseases (EURORDIS) (31) training programs, which are already actively taking place.

2.3 Standardization of disease models and cellular and molecular profiling across neuro-RDs

In recent years, the downsides of target-centered drug discovery have led to the revival of phenotypic screenings, where common clinical phenotypes for multiple diseases are studied in, e.g., cellular models. Phenotypic drug discovery requires the identification of disease-specific traits (phenotypes) that can be identified and modulated within the physiological environment of a specific disease model (32). This approach is now particularly flourishing thanks to the use of patient-derived iPSCs (33–35). Since iPSCs can be coaxed to generate a variety of disease-relevant cell types, that are not commonly available from patients, such as neuronal cells, they allow identification of potentially highly significant cellular phenotypes that become apparent within patient-specific disease-relevant cellular contexts. The other advantage is that any compounds identified in phenotypic screening would have not only to exert a positive effect within complex biological environments but also to do that in the absence of overt toxicity (as far as possible), excluding specific safety risks.

One critical and bottleneck aspect of this iPSC-driven phenotypic-based drug discovery and selection approach is the necessity to identify robust disease-relevant phenotypes that can be efficiently modulated via detection methods that should be reliable, quantitative, and amenable to high-throughput (HT) automation. For this reason, there is a high need to develop and standardize the specific models and related phenotypes that would be needed for the screening. In the context of neurological diseases, this could be particularly challenging, as different diseases may affect different types of neuronal or glial cells. In addition, there is the possibility to generate three dimensional systems called organoids that could recapitulate even more patient-specific features, but their complexity may hinder their use in large-scale HT screening. For this reason, scientists embarking on this approach need to decide whether to invest in employing highly complex models (e.g., brain organoids) that could be more disease-relevant but also more challenging for HT approaches, or instead to employ more homogeneous and simple model systems (e.g., pure neuronal cultures) that are less disease relevant but more amenable to phenotypic screenings.

The community would benefit from collaborative efforts aiming to: 1) establish a set of standardized iPSC-derived neuronal cell models with relevance to neurological symptoms, including standard operating procedures (SOPs) for their generation and use; 2) develop and validate robust phenotypes for drug screening systems with relevance for common neurological manifestations across different diseases; and 3) assess whether multi-omics profiling of patient-derived tissues and analysis of clinical manifestations may help to better inform which neuronal cell types and which phenotypic assays should be more relevant and possibly shared among diverse neuronal disorders. This last effort could be of particular importance, as it could lead to accelerating the drug

discovery and repurposing pipeline by possibly leading to the identification of drugs that could benefit more patient populations.

Lastly, following the phenotypic screenings, a large set of validation experiments are required to better dissect the effect of hit compounds on specific neural cell types in 2D or 3D settings. Although these complex models could be demanding, their use could be beneficial for several reasons. In fact, by validating the effectiveness of compounds in multicellular organoids, it could be possible to understand the impact of the hit drugs on various cell types and their micro-environment and to exclude signs of toxicity or specific safety risks. Accordingly, new regulation from the American Food and Drug Administration (FDA) has recently determined that *in vitro* tests conducted in organoids or organoid-on-a-chip platforms may be sufficient for determining the effectiveness and indication for safety of new compounds, without the need for additional animal experiments (36).

2.4 Parallel drug screening

SIMPATHIC aims to select and pre-clinically identify and validate at least three drug repurposing candidates by selecting, screening and validating 2000 drugs that are either approved by the European Medicines Agency (EMA) or have at least successfully completed Phase I clinical trials in *in silico* and *in vitro* models relevant to neuronal phenotypes of the neuro-RDs. The library selection is based on an artificial intelligence (AI-)driven prioritization of druggable targets/pathways that exploits the knowledge about overlapping molecular mechanisms between the neuro-RDs. The target cell type for the screening are neurogenin-2 (NGN2)-inducible neurons (NGN2 iN) differentiated via an established SOP in 2D cultures. The differentiation of NGN-2 iN is compatible with automated systems (37,38), produces high purity neuronal cultures, and can be scaled up to meet the requirements of an HT screening campaign (39,40). Two acceleration strategies will be applied to identify repurposing candidates with efficacy in several if not all neuro-RDs. First, the same library will be used in parallel in two different screening approaches. On the one hand, an image-based phenotypic high content screening in which the efficacy of the drugs will be determined by using common phenotypes of the diseases as readouts. On the other hand, a biomarker-based mass spectrometric screening will use metabolite signatures that have been prior validated as disease relevant as readout. Using two independent screening approaches with the same library will reduce the number of false positive or irrelevant hits and increase confidence in the common hits. To accelerate the screening procedure, we have devised a cascade screening strategy that focuses on the identification of drugs with efficacy in more than one of the neuro-RD (Figure 2). In the first stage of the cascade the entire library will be screened on three different disease models. These diseases will be selected based on the observed cellular and molecular phenotypes and will

serve as phenotypic archetypes. At the end of this stage, drugs that showed hit activity in at least two of the three diseases will be selected for the next stage. Results from the two independent screenings will be compared to select common hits on both screenings. Additionally, the results of these screenings will be used for a new round of AI-assisted drug selection. At the end of stage one, a maximum of 100 drugs will be nominated for the second stage of the cascade in which the drugs will be screened on the next three disease models. After another iteration of this process, 10 drugs will be selected for the third and last stage of the cascade in which the remaining three disease models will be used in the screening. Drugs that have shown efficacy in most of the disease models will be nominated as repurposing candidates and further validated by experts in more sophisticated disease models. Drugs that showed promising activity in a single disease will be directly transferred for further validation.

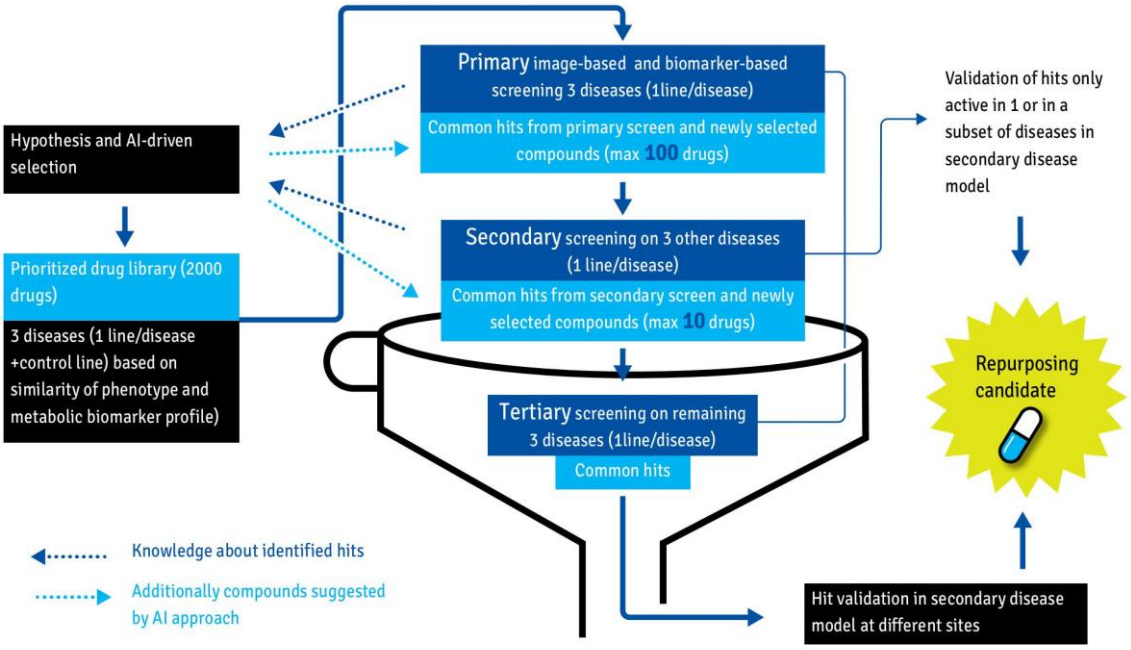

Figure 2. Cascade screening strategy focusing on the identification of drugs with efficacy in multiple diseases. *Yellow dotted arrows indicate knowledge about identified hits. Blue dotted arrows indicate additional compounds suggested by artificial intelligence approach. AI, artificial intelligence.*

2.5 Innovative clinical trial designs

To confirm the results of the *in vitro* iPSC screening in patients, a clinical trial will be conducted, comparing the resulting repurposing drugs against placebo. The objectives of the clinical trial will be exploratory in nature, including obtaining a first read out of efficacy on clinically relevant and patient-reported outcomes and on

biomarkers, and exploring safety and pharmacokinetics in the targeted patient group. Interventional research in rare diseases is challenging due to the rarity of the conditions and heterogeneity of manifestations, which typically show great inter- and intraindividual variability. Parallel group randomized controlled trials (RCTs), considered the gold standard for (confirmatory) interventional studies, are often not feasible to the usual standards of power and sample size in small and heterogeneous populations (41). To accelerate the evaluation of a candidate repurposing drug resulting from the drug screening, a basket trial design will be applied. The basket trial concept is specifically designed to evaluate a drug simultaneously for more than one rare disease (42), assuming a common pathway across the different diseases. It allows to treat groups of rare disease patients with common clinical manifestations and shared common molecular pathways (even though they suffer from heterogeneous genetic defects) with one (repurposed) drug, and allows borrowing of information across the cohorts of different genetic diseases, i.e. the baskets, to substantially increase the power of the analyses. The basket trial design is analogous to successful trial designs in oncology (e.g., vemurafenib in multiple nonmelanoma cancers (43)) where patients are included based on actionable molecular genetic variants, in neurodegenerative disorders (44), or in aminoacyl-tRNA synthetase deficiencies including multiple diseases with common molecular pathways (45). In SIMPATHIC, patient groups are included based on common clinical manifestations that can be linked to shared pathomechanisms (even though the genetic basis may differ across defects) and iPSC-driven phenotypic-based drug screening. These are the same pathomechanisms as first to be used in the iPSC screening to identify possible drug repurposing candidates for treating more than one disease in a basket trial design. To benefit maximally from the power gain of a basket trial design, it is fundamental that results of the various substudies as conducted per disorder can be combined in a second stage of the analysis, assuming the same underlying mechanism of action across the various disorders.

To maximize the power in SIMPATHIC even more, per basket a randomized, placebo-controlled cross-over design will be used with repeated outcome measurements, in which patients receive both placebo and active intervention with a washout period in between. Cross-over designs provide a powerful alternative to parallel group trials to test effectiveness of an intervention for individual participants who act as their own control (46), under certain conditions regarding the disease, outcome and anticipated treatment effects. Another advantage is that all patients will receive the intervention, which may facilitate patient recruitment. Analysis methods will be applied that leverage the natural history data recorded in the patient registries and model within-subject data through time series analysis or mixed models.

If more than one drug is identified in the screening, the basket trial design might be converted into a platform trial, with several diseases and several drugs to be evaluated over time, comparable to the Drug Rediscovery Protocol (DRUP) trial (47) which is a fairly complex combination of basket and umbrella designs. Related innovations to accelerate drug repurposing include 1) development of a master protocol that allows benefiting from logistical efficiency upon adding new cohorts and/or drug candidates, and 2) quick start-up of promising drugs within the same master protocol as well as early stopping of non-effective drugs. The concept of basket trials and master protocols is rather new to the rare disease field with some initial designs described (48,49), but a promising future for patients with (ultra-)rare diseases and/or genetic diagnoses for which costs for individual drug development are prohibitive. The availability of a platform trial combined with a master protocol for clinical evaluation of new drug repurposing candidates for neuro-RDs is expected to shorten the clinical development time by up to two years (44).

To prove the concept of parallel drug development clinically for multiple disorders for drugs identified by the iPSC screening, it will be explored whether compounds have similar effects in iPSCs-derived neuronal cultures for patients. Other strategic decisions come with the choice of the outcome measure and the pooling of the results. To combine the results of the various substudies the selection of appropriate outcome measures that are applicable across subjects suffering from different disorders is desirable, but not straightforward considering the heterogeneity across patients and disorders. Regarding pooling of safety results, different disorders may have different safety and tolerability profiles (44). Regarding efficacy, some substudies may end up being smaller than initially planned due to recruitment problems, given rarity of the disorders, or may show less positive results than others. Therefore, as part of SIMPATHIC different methods to combine the results across baskets (both frequentist and Bayesian) will be prospectively evaluated to assess the best approach for SIMPATHIC. This will include combining over the same outcomes across diseases as well as combining across different outcomes for different diseases, to appropriately address the heterogeneity, for various scenarios (50).

2.5.1 Importance of registries for symptoms, disease course, clinical trials

Patient registries play the role of capturing groups of patients who share a common diagnosis or a similar constellation of symptoms. These shared features make it feasible to capture more detailed and nuanced data facets, compared to a more generic clinical record, and to directly engage the patients with specific questionnaires to measure PROs and/or generate quantitative measurements based on these using PROMs. Nevertheless, the commonality of observations between disparate patient registries for the same rare disease often does not lead to

more interoperability, due to (for example) differences in data structure, data granularity, local languages, and the metrics used among others. SIMPATHIC is following the approach taken by the European Joint Program on Rare Disease (EJP-RD) (51) and the European Reference Network EURO-NMD (52) projects by implementing a harmonization layer over all participating registries, based on the FAIR Data Principles, i.e. findability, accessibility, interoperability, and reusability (53). This has three primary components: a public layer of metadata describing the "nature" of the underlying registry (e.g. it's provenance and scope), data access conditions, and contact information; a non-public layer of data that has been transformed using the Clinical And Registry Entries Semantic Model (CARE-SM) (54) designed by the EJP-RD; a set of privacy-preserving queries that allow pre-approved questions to be asked over the participating sites, using "shallot" Web services, a revision of a prior technology used by EJP-RD (55). This combination of technologies will allow SIMPATHIC members to quickly identify which registries include patients with a specific subset of phenotypes, alleles, or outcome measures that are of specific interest for a particular research question, while at the same time 1) preserving the privacy of the patients by allowing mechanized, anonymous data exploration without human intervention, 2) minimizing the effort of the registry curator in answering researcher questions and generating query responses, and 3) ensuring that the response from all participating registries is uniform and accurate, due to the shared common representation of the underlying data following the FAIR principles.

2.6 Exploitation and patient access models

Accelerating therapy development through drug repurposing requires early involvement of regulatory and health technology assessment (HTA) bodies, the development of exploitation and innovative patient access models, and establishing relationships with authorities regarding registration, reimbursement, and accessibility (56).

The early involvement of regulatory and HTA bodies is also crucial in advancing the repurposing process itself, as they play key roles in evaluating the safety, efficacy, and cost-effectiveness of repurposed drugs for their new indication (e.g., through label extension of generic drugs) before market authorization and reimbursement decisions, in order to realize patient access. Engaging with regulators and HTA agencies at early stages of the drug development process can bring valuable insights regarding the regulatory requirements, innovative clinical trial design, and HTA expectations. This early collaboration helps streamline the development pathway, identify potential hurdles, and ensure that repurposed drugs meet regulatory and reimbursement criteria towards market authorisation of new formulations, dose strength or label extensions of existing drug products.

Developing exploitation and innovative patient access models is also essential for maximizing the impact of repurposed drugs. Traditional commercialization models may not be suitable for repurposed drugs as they often lack patent protection and face the challenge of securing market exclusivity. However, other models such as licensing agreements, partnerships with healthcare providers, or participation in government-funded initiatives, can help ensure affordable access to repurposed drugs while incentivizing further research and development.

Establishing relationships with authorities regarding registration, reimbursement, and accessibility is critical for facilitating drug repurposing. Regulatory approval and reimbursement are essential for ensuring that repurposed drugs will in the end be accessible to patients who need them. In this respect, the draft new pharma legislation (57), with its position adopted by the EU parliament (58) and to be adopted by the EU council, provides opportunities for drug repurposing with a more prominent role for public organizations, incentives and obligations for developers (in particular Art. 48 of the Regulation and Art. 84 of the Directive) that will promote the registered (new) use(s) of existing drugs to address unmet medical needs. Regulatory and reimbursement challenges, such as demonstrating the clinical value of repurposed drugs and negotiating favorable pricing and reimbursement, can be addressed much early on by engaging with regulatory agencies and payers early. This dialogue (e.g., through the EMA innovation task force and through scientific advice with (international) agencies) is intended to explore the current possibilities and limitations to move from the one disease one drug approval pathways to mechanism- or molecular signature-based approval for groups of similar rare diseases at the same time (11). In addition, collaborations with patient advocacy groups and healthcare providers are key in helping raise awareness about the potential benefits of repurposed drugs and advocate for their approval and reimbursement. The current environment often presents unsurmountable challenges due the ‘failing market model’ for drug repurposing, with on the one hand to ensure affordable prices for newly registered uses for repurposed medicines and on the other hand providing a fair price for the market authorization holder to recoup investments for (clinical) development (59,60). By working together with stakeholders across the healthcare ecosystem, developers can build support for drug repurposing initiatives and overcome barriers to access.

Hence, accelerating drug repurposing requires a multifaceted approach that involves early engagement with regulatory and HTA bodies, the development of exploitation and innovative patient access models, and collaboration with authorities, patient advocacy groups, and healthcare providers. By adopting these strategies, developers can foster the development and commercialization of repurposed drugs, ultimately improving patient outcomes and addressing unmet medical needs.

3. Conclusions

The initial successes of curative gene and genetic therapies for rare disorders are emerging (61–64). These therapies typically target a specific gene or even a specific pathogenic variant, and potentially help increasingly small patient populations at high costs. To meet the large unmet medical needs of the 400 million rare disorder patients around the world, the SIMPATHIC consortium proposes complementary approaches to make (small molecule) drugs available to large(r) groups of rare disease patients: Moving away from the one disease one drug paradigm will make that larger groups of rare disease patients benefit and that it becomes more attractive for commercial parties to develop and register drug repurposing candidates due to the larger potential market and revenues. Admittedly, these drugs are likely to treat (subsets of) symptoms. Yet, they may have significant impact on the quality of life of individuals affected by rare diseases. We also foresee simultaneous application of gene and drug repurposing therapies, because some of the phenotypes may not be fully reversible by gene therapies and/or because the gene therapy vectors may not reach all the tissues affected.

To allow larger groups of patients to benefit from the resources developed by SIMPATHIC, we need to scale the approaches and extend the outreach to rare disease patients with similar clinical phenotypes. To this end, we started to build a comprehensive list of rare neurological, neurometabolic and neuromuscular disorders and proposed to start, with additional funding and partners, projects that test for feasibility using the screening systems for common molecular and cellular phenotypes. Subsequently, these additional disorders may benefit from the master trial protocols developed in SIMPATHIC. This will increase the efficiency of clinical trials as it obviates the need to design trials from scratch and might expedite trial approval by regulatory authorities and ethical review boards. Through a visible catalog of services such as the ones built by REMEDI4ALL (13) and REPO4EU (65), SIMPATHIC resources will be incorporated and made accessible to the research community to increase the impact.

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Author contributions (CRediT):

CvK: conceptualization; funding acquisition; methodology; resources; supervision; writing – original draft.

AM: investigation; methodology; writing – original draft.

LB: conceptualization; methodology; writing – original draft.

IB: conceptualization; methodology; software; visualization; writing – original draft.

MC: methodology; investigation; writing – original draft.

JIH: methodology; data curation; formal analysis; investigation; writing – original draft.

MdK: conceptualization; methodology; writing – original draft.

SdOM: investigation; writing – original draft.

AP: conceptualization; methodology; visualization; writing – original draft.

TR: investigation; writing – original draft.

KR: methodology; supervision; writing – review & editing.

AS: investigation; writing – original draft.

RS: project administration; resources; visualization; writing – review & editing.

MW: data curation; resources; software; writing – original draft.

PBtH: conceptualization; funding acquisition; methodology; resources; supervision; writing – original draft.

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