#iDR24

DIGITAL POSTER PACK

BRIDGING BOUNDARIES

INNOVATING, CONNECTING & RESHAPING DRUG REPURPOSING

6-7 MARCH 2024, BARCELONA

LifeArc

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LifeArc MRC Repurposing Toolkit

Navigating the complex translational and regulatory landscape can be a challenge in drug repurposing projects.

Together with the MRC, we created MRC LifeArc Repurposing Medicines Toolkit, where you can find information on:

- Research steps for demonstrating safety and efficacy
- The regulatory environment
- Patient engagement
- Accessing the medicine and existing data
- Intellectual property (IP)
- Funding sources.

Find out more

repurposingmedicines.org.uk

£5 million MND repurposing programme

LifeArc is launching new **£5m programme** to help find new treatments for motor neuron disease (MND).

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Strategy for repurposing drugs in monogenetic disorders: Application to Zellweger Spectrum Disorder

apteeus
HEALTH SCIENCE FOR ALL OF US, EACH OF US

#iDR24

A. Paquot, PharmD, PhD; L. Belloy, MSc; C. Moreau, MSc.; A. Grenon, MSc; N. Hammoudi, MSc; T. Beghyn, PharmD, PhD

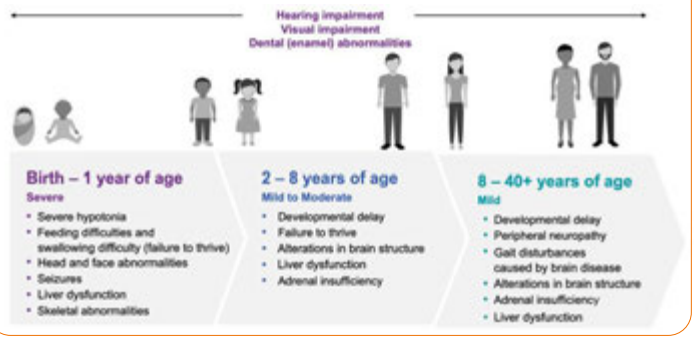
Monogenetic diseases and particularly Inherited Metabolic Disorders (IMD) are giving to phenotypic drug discovery an high predictive validity (=translatability to the clinic). They often involve a single gene encoding a transporter, enzyme, or protein essential to one cellular function. Sometimes leading to the accumulation or the deficit of a cellular metabolite, IMD can be studied through the analysis of those metabolites directly on cell cultures. As IMD are often cell autonomous, *ex vivo* cultures allow for the measurement of the effect of all drugs worldwide on the causal defect of symptoms. APTEEUS has been pursuing this original strategy for 10 years to identify new opportunities of drug repurposing by running individualized drug screening. The key points have always been the chains of translatability, that is to say the predictive validity of the newly discovered activities of a drug combined with its known properties for its new clinical use. We propose to illustrate APTEEUS approach with one of the about 30 different projects : The Zellweger spectrum disorders (ZSD) program.

Zellweger Spectrum Disorder:

Autosomal recessive mutation in one of the 14 *PEX* genes. *PEX* genes code for peroxins which are involved in peroxisome biogenesis:

- Peroxins manage the peroxisome membrane assembly.
- Peroxins are required for the matrix protein import.
- Peroxins are involved in the peroxisome proliferation process.

Clinical Manifestations:

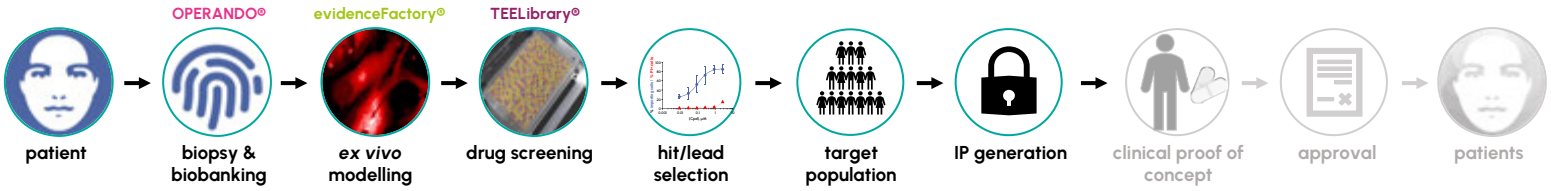


FROM THE CELLULAR PHENOTYPE TO THE CLINICAL MANIFESTATIONS

Genetic level	Protein level	Organelle level	Cellular level	Organ level
mutations in PEX genes	unfunctional peroxins	defect in peroxisomal enzyme import	defect in peroxisomal functions	neurological and liver symptoms

A phenotypic assay recapitulating the function of peroxins and peroxisomal functions would be a good model for discovering molecules with adequate primary pharmacodynamic properties.

ILLUSTRATION OF APTEEUS' DISCOVERY ENGINE PROCESS



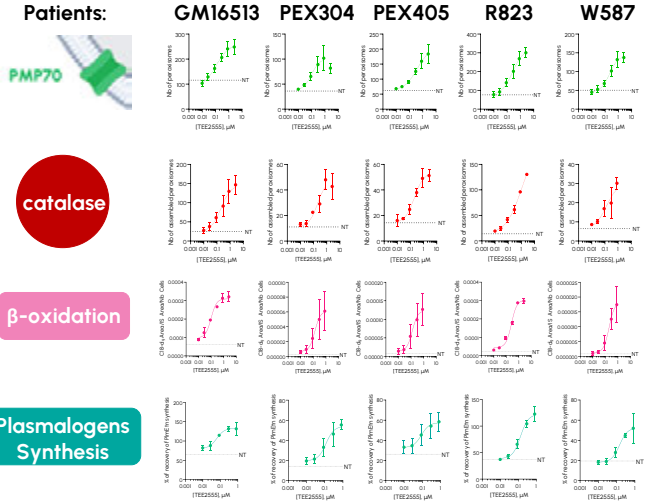
OPERANDO®
Clinical program allowing us to perform skin biopsies and build primary skin fibroblasts collections for modelling the patient diseases.

EvidenceFactory®
Our technological platform with expertise in:
- cellular modelling and microscopic characterization
- LC-MS based high throughput methods

TEELibrary®
Proprietary repurposable drug library containing +7600 drugs including +2600 drugs physically available in our collection, which we can use for drug repurposing.

TEE2555 AS CLINICAL CANDIATE FOR TREATING ZSD

- TEE2555 increases the quantity of peroxisomes in patient primary cells.
- TEE2555 restores the import of peroxisomal enzymes into the peroxisome of deficient patient primary cells.
- TEE2555 restores peroxisomal β-oxidation of VLCFA in patient primary cells.
- TEE2555 restores peroxisome plasmalogens synthesis in patient primary cells.



Thanks to:
McGill University · IPG · La Marche de Noé · Centre Hospitalier Régional Universitaire de Lille · CHU Angers · HCL · Les Hôpitaux Universitaires de Strasbourg

Program supported by: bpifrance

HARNESSING DRUG METABOLITES IN PRECISION MEDICINE

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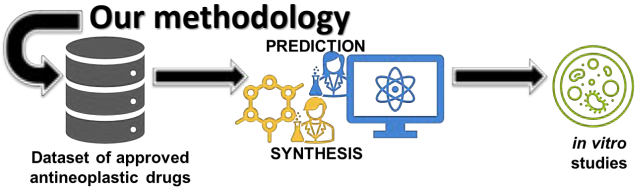
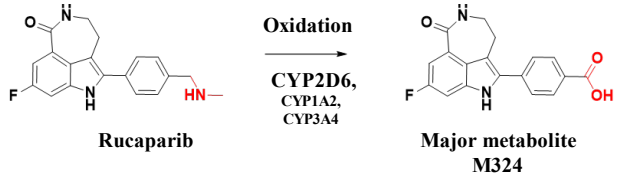
Introduction

Drug **metabolites can modulate different proteins than their parent drugs** that could be quickly translated into **meaningful clinical applications**. Approximately 20% of drug metabolites are believed to possess the necessary characteristics for exhibiting cellular activity[1]. Among these metabolites, certain ones have been proven to present the same biological activity than their parent drugs and some have even advanced into becoming **independent drugs**[2]. Furthermore, recent evidence highlights that metabolites once considered inactive due to their limited biological impact on the same target as the parent drug might actually exhibit notable activity against different targets[3]. This discovery underscores the need for deeper exploration.

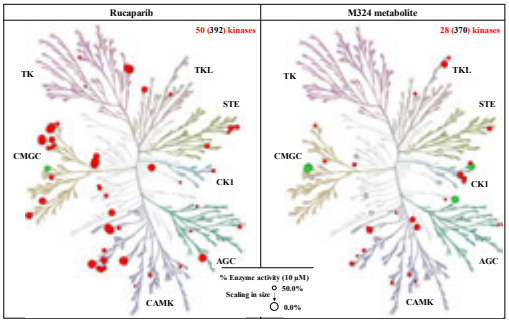
Our methodology



Rucaparib & M324 case of study

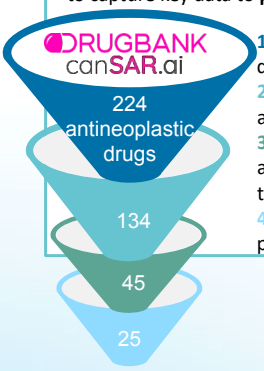


Rucaparib's primary metabolite, **M324**, and **Rucaparib** exhibit inhibition of distinct off-target kinases. Notably, M324 demonstrates a **distinct kinase polypharmacology profile**, notably marked by potent inhibition of GSK3A and PLK2 (IC_{50} < 600 nM), both of which are not strongly inhibited by rucaparib[4].



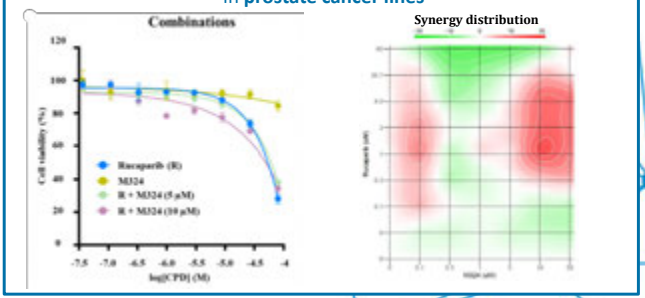
Major drug metabolite database

Aiming to discover **new applications** in precision medicine, a **curation** of a major **drug metabolite dataset** has been performed to capture key data to **prioritize** the most promising metabolites.



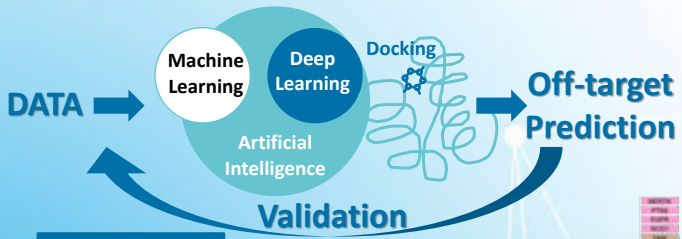
1st filter: Only FDA/EMA approved antineoplastic drugs that are small molecules were considered
2nd filter: Chemotherapy agents, photosensitizers and discontinued drugs were discarded.
3rd filter: Compounds presenting a metabolite accounting for >10% of in-plasma concentration of the parent drug were selected.
4th filter: Metabolites presenting off-target predictions different from its parent drug.

Intracellular kinase activity of M324 and drug-metabolite combinations in **prostate cancer lines**

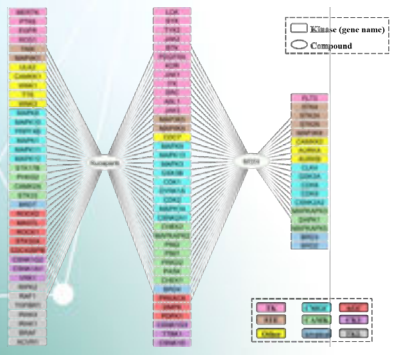


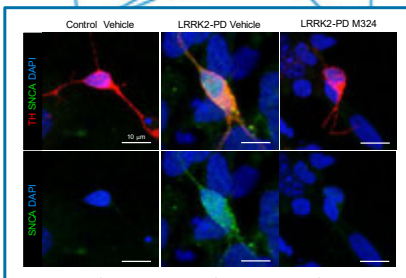
Computational approach

Through **polypharmacology prediction methods**, we can predict new activities against new **off-targets** of small molecules using public data connecting drugs, metabolites, targets, clinical outcomes, and even side effects. Plus, **crystallized protein structures** in the RSCB Protein Data Bank allows us to confirm our predictions through modelling studies such as **docking methodologies**. Finally, the **biological validation** gives us key information to better train the AI models in a looped process.



Commercial and web-based tools:
- Clarity
- Polypharmacology Browser 2 (PPB2)
- GalaxySagittarius
- SEA algorithm.





M324 reduces α-synuclein accumulation in hiPSC-derived neurons from a Parkinson's disease patient

Summary

M324 demonstrates that metabolites can be pharmacologically active and could potentially be used in precision medicine and repurposed for novel diseases like Parkinson's. Thus, the investigation of major metabolites opens a new promising approach for precision medicine, drug repurposing and side effect understanding.

References

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2. Hidalgo M. *et al. Clin Cancer Res* (**2006**). DOI: 10.1158/1078-0432.CCR-06-0118
3. Li, Z. et al. *Nature* (**2015**). DOI: 10.1038/nature14406
4. **Hu, H., ..., Antolin AA.** ***Cell Chemical Biology, in press***. BioRxiv DOI: 11.22.517505

MedChem D²
Medicinal Chemistry & Drug Design Lab
IDIBELL Institut d'Investigació Biomèdica de Bellvitge
IQAC CSIC Instituto de Química Avanzada de Cataluña
CSIC Consejo Superior de Investigaciones Científicas
ICR The Institute of Cancer Research

Identifying cohesion of barriers and viewpoints across different stakeholders in drug repurposing

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National Center for Advancing Translational Sciences

BACKGROUND

Drug Repurposing

- Drug repurposing can decrease the time frame and costs compared to the typical timeline for new drug development
  - Novel drug: 10+ years, $1.24 billion cost
  - Repurposed drug: 3+ years, $300 million cost

Figure 1. Stages of traditional drug development vs drug repurposing

- Drug repurposing is not a new practice but has gained awareness since the onset of the COVID-19 pandemic
- Drug repurposing addresses unmet needs in diseases with little to no incentive for novel drug development
- Technological advancements, such as AI are providing faster and accessible avenues to identify signals, sort large data sets, etc. Understanding these capabilities as well as the risks could push drug repurposing forward
- Many stakeholders are involved at different stages in the translational pathway of drug repurposing, and it is important to understand opportunities for collaboration to increase efficiency

PROJECT AIM: Develop and conduct a qualitative study to capture diverse stakeholder viewpoints on the challenges in the translation of preclinical to clinical research in drug repurposing with the potential to identify paths to improve the repurposing process.

METHODS

STUDY DESIGN

- ❑ 5-6 rounds of interviews with up to 6 interviewees per round
- ❑ Questions designed to be generalized and applicable to every interviewee despite variety of backgrounds
- ❑ Goal is to get participants' perspectives as well as understand the challenges different types of stakeholders may face
- ❑ Identify cohesion of viewpoints focusing on barriers as well as suggestions for improvements

Study Outline

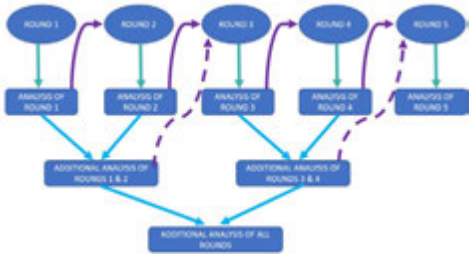

Figure 2 Study outline showing interview rounds and analysis framework.

INTERVIEWS

- ❑ Emphasize experts' knowledge/experience in the preclinical to clinical translation of drug repurposing

Breakdown of Interviewees

- ❑ Types of institutions

Academic institutions	Government Agencies	Hospitals/ Medical Institutions
Non-profit/ Disease Advocacy	Biotech / Pharma	Venture Capital/ Private Equity

- ❑ Types of positions

Researchers	Clinicians
Regulators	Advocates

- ❑ Experts that work in different stages of drug repurposing
- ❑ Diverse demographic representation
- ❑ Multiple disease specialties
- ❑ Varying stages of career

Four Interview Themes

- ❑ Background
- ❑ Personal experience
- ❑ Challenges
- ❑ Potential solutions

ANALYSIS

Analysis Coding and Comparisons

- ❑ Grounded Research Model: Perform analysis on each round of interviews and continually build on analyses after each round
- ❑ Thematic Coding Analysis: Analyze data using specific themes, words/codes, etc.
  - Utilize NVivo Software (Lumivero)

Analysis Coding and Comparisons

- ❑ Four interview themes
- ❑ Compare across stakeholder type
- ❑ Compare across job position type
- ❑ Compare across disease type
- ❑ Compare across stage of drug repurposing
- ❑ Compare answers for each question

PROTOCOL

Project Design

- IRB-exempt study
- Interviewees are not given any financial incentives for participation, all participation is voluntary
- Conduct 5-6 rounds of interviews that build on each other
- Perform qualitative analysis

Protocol Outline:

1) Identify and outreach to interviewees
2) Conduct recorded interviews
3) Deidentify recordings
4) Transcribe/edit interview transcripts
5) Analyze interview data

REPURPOSED DRUGS AND PATHWAYS

PRELIMINARY RESULTS

Comparisons across stakeholder types

- Interviewees identified similar challenges (even if they were from different institutions)
  - Examples: funding, accessibility to patients
- A few interviewees recognized the importance of involving multiple stakeholders early on rather than later stages
- Interviewees defined ultimate success of a repurposed drug differently though most agree that basic success is once it helps a patient

NEXT STEPS

- Complete all rounds of interviews
- Continue analyses of interview data
- Aim to draft manuscript with findings

➢ Potential to add improvements to the work done by CURE ID and CDRC

Visit us at https://cure.ncats.io

CDRC CURE DRUG REPURPOSING COLLABORATORY CRITICAL PATH INSTITUTE

CURE ID

DREAMS - *Drug REpurposing with Artificial intelligence for Muscular disorderS*

Dreams

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Lino FERREIRA (Coimbra Universidad, Portugal)
Teresinha EVANGELISTA, Karim WAHBI (APHP, France)
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Alexandre MEJAT (AFM-Téléthon, France)
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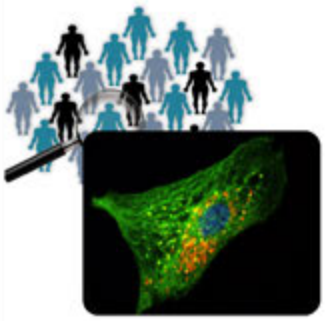
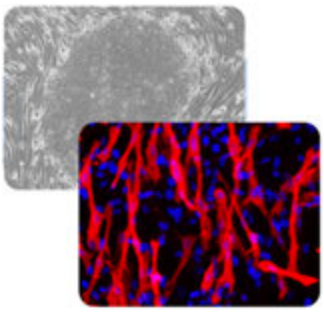
The World Health Organization highlights a critical need for treatments in rare diseases, with less than 6% currently having approved therapies. The EU-funded DREAMS project addresses this by discovering therapies for five rare neuromuscular disorders with similar pathophysiological traits. The project's innovative approach involves using skeletal muscle cells from induced pluripotent stem cells to discover common biomarkers across these disorders. Additionally, it employs Artificial Intelligence to identify shared therapeutic targets and potential drug candidates from phenotypic drug screenings and -omics data. The resulting platform will combine Artificial Intelligence and induced pluripotent stem cells to develop small molecule treatments applicable to multiple neuromuscular disorders, setting a new standard in rare disease therapy research.

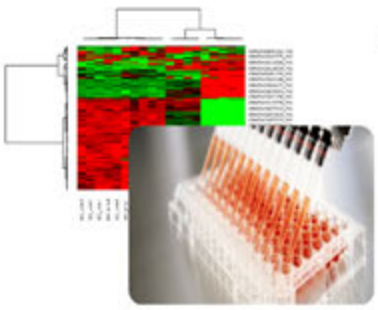
Objectives of the Horizon Europe DREAMS project:



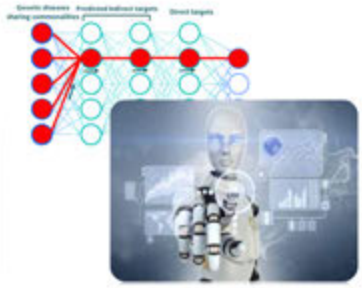
Identify shared clinical features (muscle weakness) and shared phenotypes (autophagy impairments)



Develop iPS based cellular models to decipher 5 neuromuscular disorders and identify common biomarkers

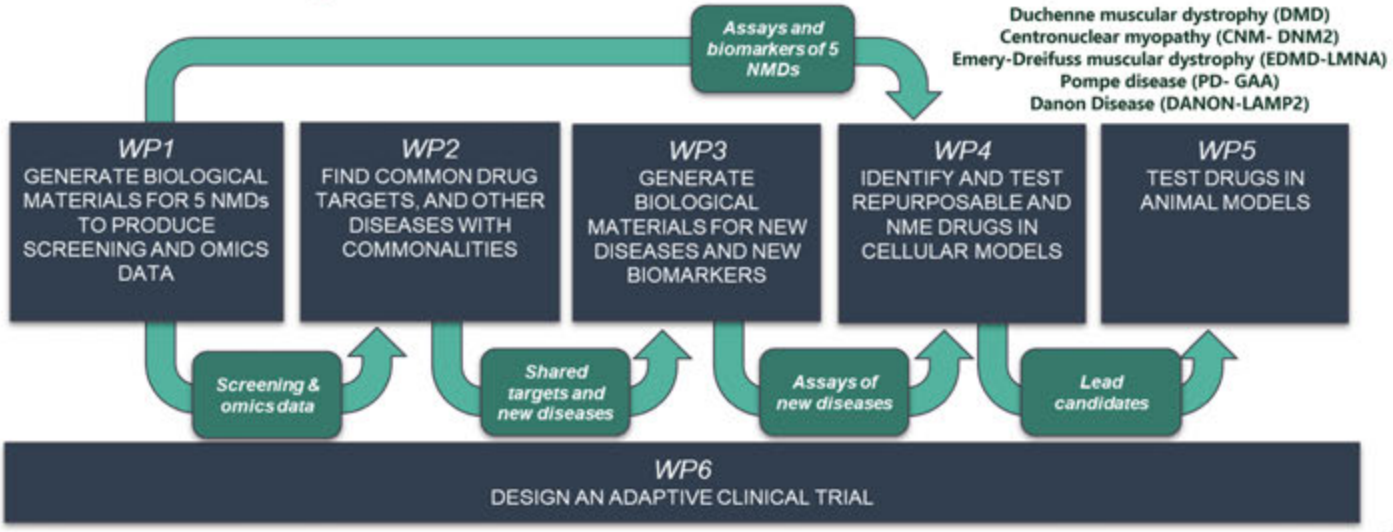


Phenotypical drug screening to identify drugs rescuing autophagy related targets and common biomarkers



AI based identification of hits' mechanism of action
AI based identification of new diseases

Organization of DREAMS (Nov 2023-Nov 2028):



DREAMS project. Funded by the European Union under 101080229-2. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union (EU) or European Research Executive Agency (REA). Neither the EU nor REA can be held responsible for them.

Funded by the European Union

ON-PATENT DRUG REPURPOSING – FUNDER'S PERSPECTIVE

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Executive summary

A whitepaper (QR code below) was developed from the perspective of research funders, investigating challenges in repurposing on-patent medicines, particularly in oncology. It highlights commercial, regulatory, and social factors relevant to funders and emphasizes the tension between market exclusivity and emerging competitors. The role of clinical trials and marketing authorization holders in label extension pathways is underscored, contrasting it with the suboptimal use of drugs 'off-label.' As a result of this landscape analysis, decision trees were developed to help advise on the key factors for philanthropic funders when selecting on-patent drug repurposing projects.

Why on patent drug-repurposing?

RATIONALE

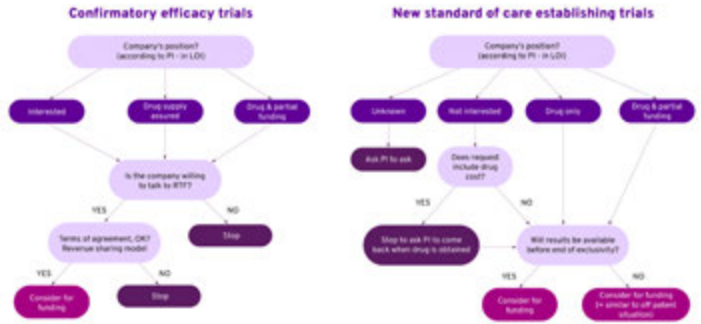
- Finding new therapeutic uses for existing medicines (including rare cancers where there is no commercial support from the marketing authorization holder)
- Leverage knowledge previously generated on safety and effectiveness of a known drug leading to label extensions.

POTENTIAL

- Less costly and quicker drug development process
- Bring (much needed) new therapeutic options to patients, faster
- Ideal collaborative model for academics, clinicians and patients for more efficient research with high social impact

Pathways for the development of repurposed drugs

Decision trees for on-patent drug repurposing applications' selection



This landscape analysis has highlighted the lack of funding in the on-patent drug repurposing field. Therefore, philanthropic funds are needed to help close the gap in this space. RTFCCR has decided to consider applications in this area for patient populations with high unmet need. Proposals will be assessed case-by-case, taking into consideration the likelihood of the trial to establish new standards of care.

Conclusions

Drug repurposing is a complex area for philanthropic funders. Here, we highlight the need for careful navigation of label extension opportunities and an unmet need for philanthropic funding in the space of on-patent drug repurposing. Decision trees were developed to guide funders on the key factors to consider when selecting on-patent drug repurposing projects. We will test the effectiveness of these tools by applying them to real-world grant applications and assessing their impact on the selection process.

Learn more at www.risingtide-foundation.org

Scan the QR code to download the full whitepaper

Anticancer Fund

RISING TIDE. Foundation for Clinical Cancer Research

Rare Diseases Clinical Trials Toolbox: public resources and main considerations to set up a clinical trial on medicinal products of human use in Europe

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Background

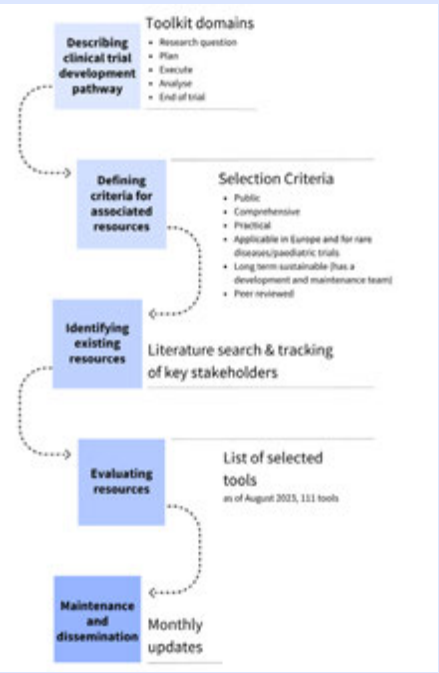
Drug development programs in rare diseases have many challenges[1], some of which differ from those facing researchers working on common diseases, like the scarcity of patients, incomplete understanding of the natural history to inform trial design and lack of validated outcome measures (1, 2).

Over the past years, research, regulatory initiatives and resources have been introduced to expedite drug development for rare diseases. Nevertheless, these tools have been developed with different aims and therefore they have not yet been framed as a whole for the conduct of clinical trials. To address this issue, the EJP RD (European Joint Program for Rare Diseases) has developed the **Rare Diseases Clinical Trial Toolbox.**

Objective

Collect the accumulated knowledge, experience and resources generated by previous projects into a practical and guided toolbox to help clinical trialists understanding of the regulations and requirements for conducting clinical trials, with a special focus on academic trials.

Methodology

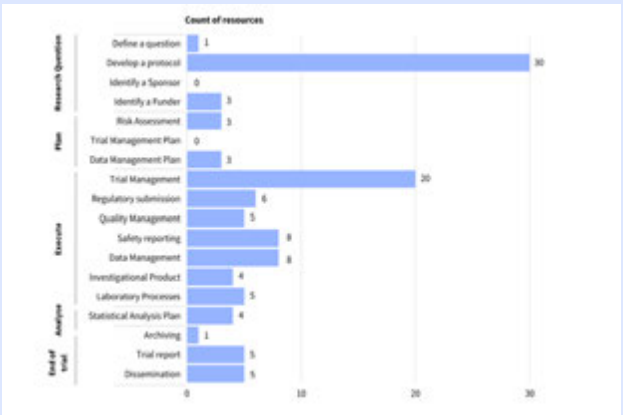


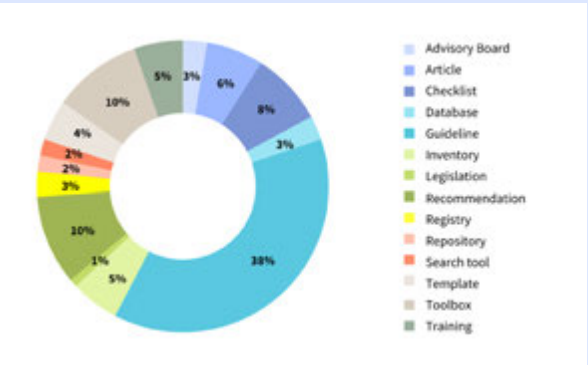
Clinical Trial Development Pathway

The Toolbox is organized into five domains: research question, plan, execute, analyse, and end of trial. Each domain describes one or several activities to be considered and indicates at what stage of the trial pathway these activities should take place. Each activity is further linked to specific resources that are relevant to those activities. The current version of the Toolbox includes 111 resources.

https://ecrin.org/rare-diseases-clinical-trials-toolbox
https://www.ejprarediseases.org/rare-diseases-clinical-trials-toolbox/
https://imt.ejprarediseases.org/collection/clinical-trials-toolkit/
https://irdirc.org/resources-2/irdirc-recognized-resources/

Results and Conclusions





Representation of the different type of resources

The current version of the Toolbox includes 111 resources. 75 % of all resources are relevant to any clinical trial while 25 % are tagged as "rare disease specific".

Although the current version of the Toolbox does not tag specific "drug repurposing resources" many of the current tools are relevant for repurposing projects.

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2. Rath *et al*. Trials. 2017; 18 (1): 556

Co-funded by the European Union

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How Can Health Technology Assessment Help in Addressing Challenges in Drug Repurposing? A Conceptual Framework

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1. Introduction

Drug repurposing is finding new indications for already existing drugs that can address unmet medical needs. However, it faces **many challenges** hindering its full potential[1,2], and the role of health technology assessment (HTA) in supporting drug repurposing remains **unexplored**.

2. Objective

To develop a **comprehensive framework** of key challenges in drug repurposing and explore **how and when HTA** can help in addressing them.

3. Methods

- 1,478 articles were reviewed for identifying challenges in drug repurposing
- Thematic analysis used for developing the framework by creating categories and sub-categories among the challenges
- A focus group and semi-structure interviews with experts from the **REPO4EU consortium**; an EU platform for supporting drug repurposing research, were conducted for assessing the completeness of the framework
- Challenges were matched with HTA methods that can help in addressing them, using two reviews[3,4] that categorized HTA methods according to their objectives.

4. Results

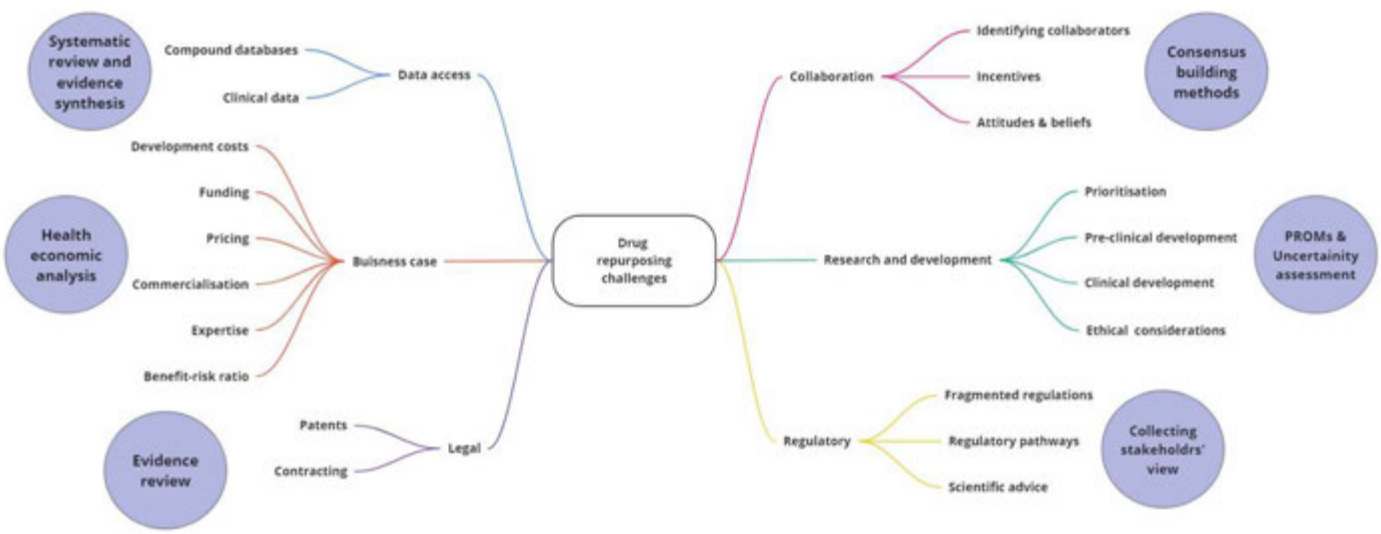

Figure (1): Framework of challenges in drug repurposing and HTA methods that can help in addressing them

5. Conclusion

- **Our framework of challenges in drug repurposing highlights the need of collective solutions, including HTA methods, to help address these interconnected challenges**
- **Incorporating HTA methods on iterative and flexible basis in drug repurposing research can provide evidence for decision-making, assess the value proposition of the repurposed drug and inform further research.**
- **The REPO4U platform will include an HTA toolbox that includes economic evaluation templates, guidance on patient-reported outcome measurement, prioritizing drug repurposing candidates, pricing arrangements and regulatory recommendations that can support bringing the value in drug repurposing research.**

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UNLOCKING AND OPTIMAL UTILIZATION OF DRUG REPURPOSING PATENTING POTENTIAL:

BUILDING A WALL OF PROTECTION AND IMPROVING THE ODDS OF SUCCESSFULLY PROVIDING PATIENTS WITH NEW THERAPIES

NLO
EUROPEAN PATENT AND TRADEMARK ATTORNEYS

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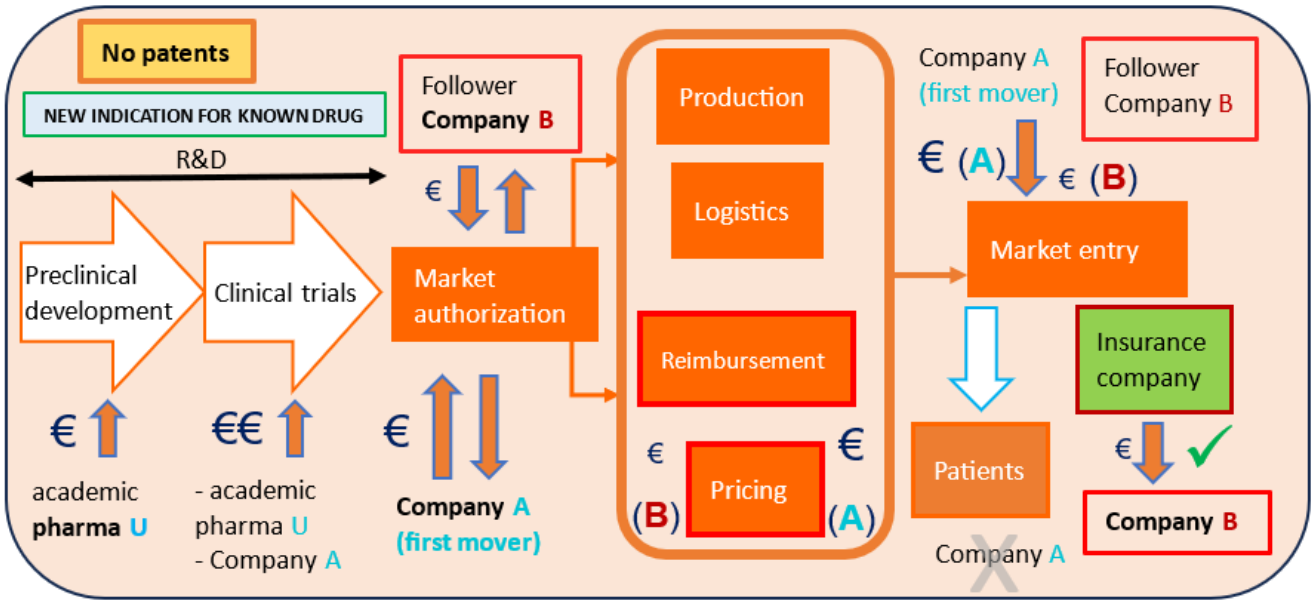
CASE: Generic drug suitable for developing a new therapy for an unmet medical need (*drug repurposing program*) [I]

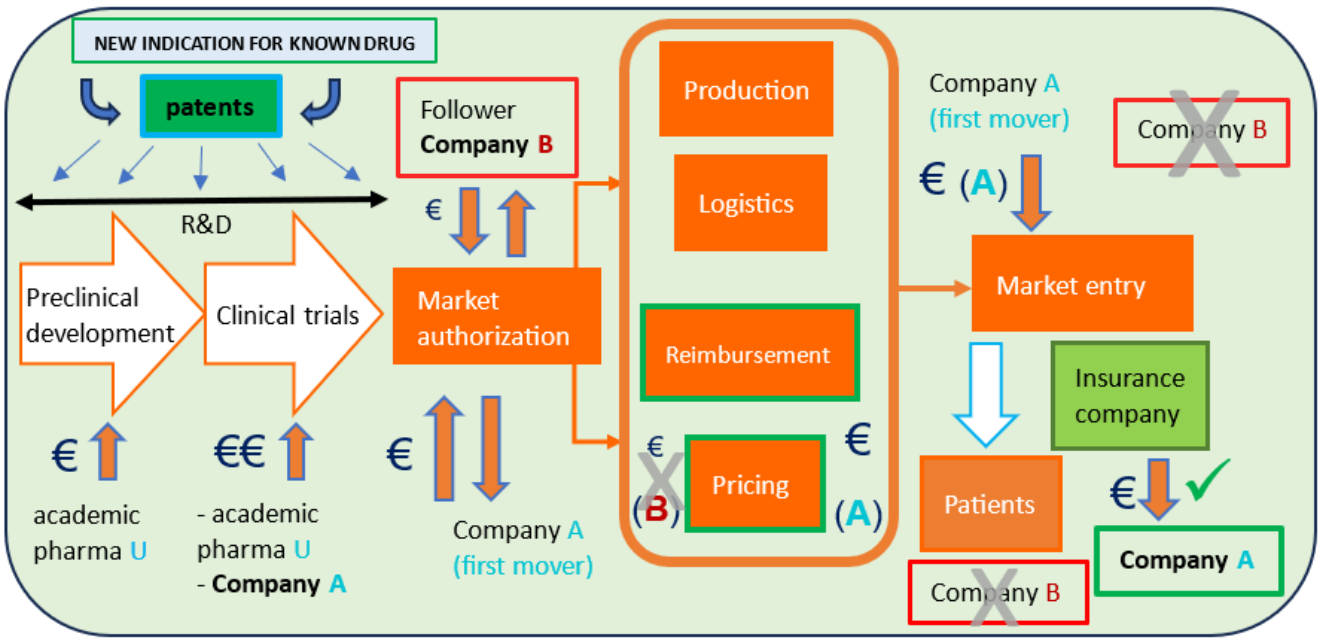
CATCH 22: Without any patent protection for the drug repurposing program, Company **A** will have little to no incentive to invest in market authorization (registration) for the new indication due to the lack of market protection against generics Company **B**, which (patent) protection is a prerequisite to warrant the investment in necessary clinical clinical trials for the new indication. Company **A** does not develop and invest at all in the registration of the use for the new indication since soon Company **B** can have a cheaper case without the expenditure on clinical trials, resulting in the possibility to sell at lower price. Uncontrolled off-label use without proper surveillance might occur.

[I]



IMPROVED SITUATION: With patent protection on the NEW INDICATION for Company **A** for the drug repurposing program, a reasonable pricing and reimbursement still needs to be negotiated but Company **B** cannot do the same and cannot produce and offer the new therapy for the unmet medical need (new indication) at lower price. Only the patent-protected therapy of Company **A** can be prescribed and reimbursed. The NEW INDICATION for the KNOWN DRUG can be patented. In addition, also for example, a new formulation; dosing; route of administration; combination therapy, etc., can be patented by Company **A** for this purpose. Such '**second medical use**' patent protection is possible in a.o. Europe, USA, Japan, Australia, China, etc. See [II]. A new package with a new label (new indication) is helpful.

[II]



Analysis of Rare Infectious Diseases and Potential Use of Drug Repurposing

Authors: Tahsin Farid[1], Keyla Tumas[2], Reema Charles[3], Heather Stone[3], Raghav Tirupathi[4]

Affiliations: 1. United States Food and Drug Administration (FDA), 2. National Center for Advancing Translational Sciences (NCATS), 3. FDA, 4. Keystone Health

❖ This project was supported in part by an appointment to the ORISE Research Participation Program at the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA/CDER.

❖ The views and opinions presented here represent those of the authors and should not be considered to represent advice or guidance on behalf of FDA or NCATS.

Summary

Here the landscape of rare bacterial infections (RBIs) is reviewed. 22 established RBIs were identified and information regarding their transmission, incidence, and therapy were recorded to identify areas of greatest need and use of repurposed drugs. Very few RBIs had approved therapy (7). Zoonosis was the most common mode of transmission (10), with a worldwide pattern of incidence (8). The observed transmission and incidence patterns are likely influenced by low endemicity, outbreaks in different regions, and socioeconomic, demographic, and/or climate change. The intention of this group is to expand this research to all rare infectious diseases and propose a systematic approach to aggregating real-world data of drug repurposing to better inform therapy.

Background

Rare infectious diseases (RIDs) are a significant source of morbidity and mortality[1]. Most lack approved treatments as it is difficult to perform comprehensive trials on therapeutic efficacy due to their sporadic nature and distribution in resource limited settings[2]. Lack of monetary incentives has also discouraged drug development[3]. RIDs therefore represent an area of high unmet medical need. Here the landscape of rare bacterial infections (RBIs) is reviewed, as a pilot, to explore areas of current and potential drug repurposing. The aim of this group is to propose a systematic approach to aggregating real-world data of drug repurposing o better inform therapy.

Materials and Methods

A list of bacterial infections was curated by combining reportable infections from health agencies[4-7] with the CURE ID[8] database of diseases. This list was independently reviewed by two experts in infectious diseases to identify potential RBIs. A literature review identified which of these bacteria met the inclusion criteria: a global incidence of less than or equal to 10,000 cases per year (Figure 1). Data on each RBI that met the inclusion criteria was collected (Table 1) and analyzed.

Conclusion

It was expected that a majority of RIDs would occur through zoonoses while environmental and commensal organisms cause opportunistic infections in the immunocompromised. The majority of zoonoses had worldwide distributions. This does not imply higher incidence, but rather may indicate a lack of sustained endemicity with outbreaks in varied geographic areas when animal to human spillover occurs. Transmission patterns may also relate to socioeconomic conditions, climate change, war/civil unrest, and population growth. The lack of FDA-approved therapies for RIDs stems from the paucity of cases and little financial interest; real-world data may help improve treatment efficacy. This project aims to explore these possibilities and expand to all RIDs.

Results

From the comprehensive list of 163 bacterial infections, 22 met the inclusion criteria. Figure 2 displays the distribution of World Health Organization (WHO) Regions where each RBI has the highest incidence. The most frequent mode of transmission amongst analyzed RBIs was zoonotic (Figure 3). 13 RBIs did not have FDA-approved therapies, but only 2 lacked a standard of care therapy (Table 2). Figure 4 depicts the transmission mode of RBIs according to the WHO region where they are most frequent.

Figure 1. Data Flow Diagram

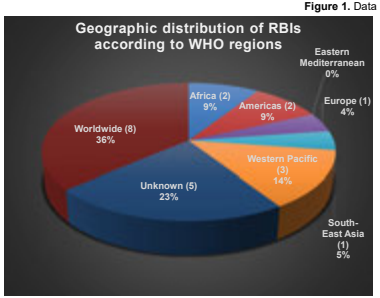


Figure 2: Percentage and number of diseases listed in table 1 by highest Incidence occurring per WHO Region

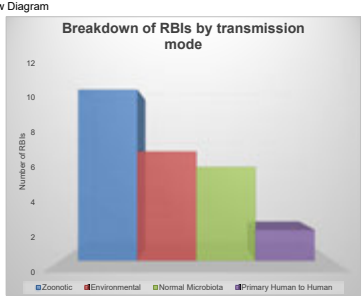


Figure 3: Breakdown of diseases in table 1 by mode of transmission

FDA Approved Therapy	Standard of Care	
	Yes	No
Yes	7	0
No	13	2

Table 2: Standard of care availability plotted against FDA approved therapy availability

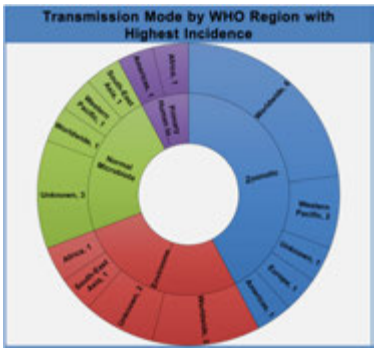


Figure 4: Plot of transmission mode by WHO region

Disease	WHO Region w Highest Incidence	Transmission	Standard of care data available	FDA-approved therapy?
Actinomycosis, Respiratory tract	South-East Asia	Normal microbiota, Environmental	Yes	None
Aerococcus Infective Endocarditis	Unknown	Environmental	Yes	None
HACEK Infective Endocarditis	Western Pacific	Normal microbiota	Yes	None
Bartonellosis	Americas	Zoonotic	Yes	Yes
Glanders	Worldwide	Zoonotic	Yes	None
Capnocytophaga infection	Unknown	Zoonotic	Yes	None
Clostridium butyricum infection	Unknown	Normal Microbiota, Environmental	No	None
Elizabethkingia infections	Worldwide	Environmental	Yes	None
Erysipeloid	Worldwide	Zoonotic, Environmental	Yes	Yes
Eubacterium infections	Unknown	Normal Microbiota	No	None
Epidemic Typhus	Worldwide	Zoonotic	Yes	Yes
Murine Typhus	Worldwide	Zoonotic	Yes	Yes
Buruli Ulcer	Africa	Environmental	Yes	None
Rhodococcus equi infection	Worldwide	Zoonotic, Normal Microbiota	Yes	None
Mediterranean spotted fever (MSF)	Europe	Zoonotic	Yes	Yes
Japanese spotted fever	Western Pacific	Zoonotic	Yes	None
North Asian Tick-Borne Rickettsiosis	Western Pacific	Zoonotic	Yes	Yes
Rothia mucilaginosa infection	Unknown	Normal Microbiota	Yes	None
Vancomycin-resistant Staphylococcus aureus (VRSA) infection	Worldwide	Environmental	Yes	None
Rat Bite Fever (RBF)	Worldwide	Zoonotic	Yes	None
Pinta	Americas	Primary Human to Human Transmission	Yes	Yes
Bejel	Africa	Primary Human to Human Transmission	Yes	None

Table 1: List of Included Rare Bacterial Infections

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Towards novel public–private partnerships in academia-driven drug repurposing for rare diseases and inborn errors of metabolism

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BACKGROUND

Traditionally, academic researchers have played in a key role in drug repurposing, i.e the identification of novel applications for existing medicinal products.[1] This holds particular relevance for rare diseases such as inborn errors of metabolism (IEMs). However, the translation of academic innovations into successful therapies that benefit patients often encounters obstacles, either stalling in the translational stage or facing challenges related to patient access influenced by pricing or uncertain effectiveness. This review explores both traditional and innovative collaborative approaches in the development of medicines for rare diseases that can be applied to drug repurposing, with a specific focus on IEMs.

METHODS

We performed a narrative review on the traditional role of academia in PPPs for medicine development for rare diseases including IEMs, with a specific focus on social responsibility. We retrieved purposively sampled scientific literature from the PubMed database using keywords "knowledge transfer offices," "university-industry collaborations," "public-private partnerships" in combination with "social responsibility" or "socially responsible" and "rare disease" or "orphan medicine." Only English articles were considered. Additionally, we included relevant policy documents and position papers.

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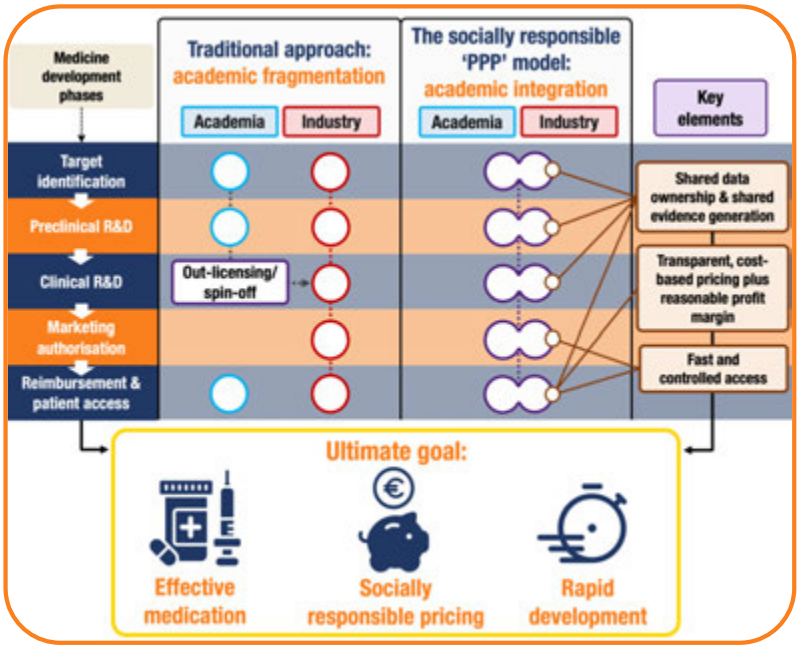

PPP FRAMEWORK

Data ownership and evidence generation

Available to stakeholders, FAIR/GDPR compliant.

Socially responsible pricing

Disclosure of investment/pricing breakdown, cost-based pricing (+reasonable profit margin) with adaptations after sufficient ROIs. Public revenues benefit revolving fund for new projects.[2] Cost-priced clinical trials at academic centers, minimal marketing activities, risk sharing.

Fast access

Parties commit to patient access, no pausing if benefit evidentiary + positive business case. No third-party sale of inventions without stakeholder consent and even then, selling/out-licensing only on socially responsible terms.

CONCLUSION

Academia-driven initiatives and PPPs are emerging in medicine development, including drug repurposing[3], with a small number realizing patient access.[4] Recent examples[5] that did not lead to sustainable and equal access for all highlight the need for socially responsible terms. A paradigm shift from traditional out-licensing and PPPs operating solely in a single development stage (e.g. the identification of novel applications for existing compounds) to a more integrative, socially responsible approach during development is needed. To help realize this, we propose a framework for academia-driven PPPs under socially responsible terms, including agreement on data sharing, pricing, and fast access. This framework aims to empower sustainable, academia-driven development of accessible (repurposed) drugs for rare diseases.

#iDR24

Repurposing of Valproic Acid and Simvastatin to potentiate first line chemotherapy regimen in metastatic pancreatic cancer patients: from preclinical evidence to clinical testing in VESPA trial.

RE-PURPOSING OF MEDICINES 4ALL

March 6-7, Barcelona

Alfredo Budillon[1], Maria Serena Roca[2], Federica Iannelli[2], Veronica Barile[2], Rossella Migliorino[3], Eugenia Passaro[3], Cristina Testa[2], Laura Addi[2], Laura Grumetti[2], Tania Moccia[2], Carlo Vitagliano[2], Lucrezia Silvestro[3], Francesca Foschini[2], Carmine Carbone[4,5], Lorenzo Prisco[6], Maddalena Fratelli[6], Laura Fiorenza[6], Maria Laura Garcia Bermejo[7], Bruno Sainz Jr[8], Francesca Bruzzese[9], Diana Giannarelli[10], Mercedes Rodriguez Garrote[11], Giampaolo Tortora[4,5], Michele Milella[12], Michele Reni[13], Elena Di Gennaro[2], Christine Kubisch[14], Eve Scott[15], Claudia Fuchs[16], Alessandra Leone[2], Antonio Avallone[3].

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BACKGROUND

- Patients with metastatic pancreatic ductal adenocarcinoma (PDAC) have a very poor prognosis, despite all the improvements in cancer therapy [Lambert et al. Semin Oncol, 2021], indicating the urgent need for new treatments. Repurposing already-approved non-oncology medications may be a desirable approach in terms of helping to provide efficacious therapeutic alternatives that are easily transferred to early clinical trials.
- In tumor models including PDAC, valproic acid (VPA), a generic low-cost anticonvulsant with histone deacetylase (HDAC) inhibitory activity, has been shown to have anticancer characteristics when used alone [Luo D et al. Carcinogenesis, 2020] or in combination with gemcitabine [Lin T et al. JECCR, 2019].
- As we recently shown [Roca MS et al. JECCR, 2022], HDAC inhibitors have the ability to sensitize PDAC cells to gemcitabine/abraxane doublet. VPA in combination with conventional chemotherapy is under investigation in different solid tumors, and the results generally support the viability and safety of this strategy [Avallone A et al. BMC cancer, 2016; Budillon A et al. Ann Onc, 2018].
- Originally designed to decrease cholesterol by blocking HMG-CoA reductase, statins have also shown a direct antitumor impact when used alone or in combination with chemotherapy and target treatment in a wide range of tumor models, including pancreatic cancer [Gupta V et al, Cancer Lett 2018].
- We have just demonstrated that VPA and the cholesterol-lowering drug simvastatin have a preclinical synergistic anticancer interaction in metastatic prostate cancer models. Additionally, the combination therapy has the potential to both sensitize prostate cancer cells to docetaxel and reverse docetaxel resistance. This impact has a mechanistic connection to the combined approach's ability to suppress the oncogene YAP and target the cancer stem cells compartment [Iannelli F et al. JECCR, 2020].

KEY FINDINGS

- **In a panel of human and murine pancreatic ductal adenocarcinoma cells, we demonstrated a strong synergistic antiproliferative and pro-apoptotic effect of valproic acid (VPA) and simvastatin (SIM) combination, either alone or plus chemotherapy. This effect was strengthened by a technical cross-validation carried out in the framework of the EU-funded REMEDI4ALL project.**
- **Synergistic antitumor interaction was further observed as impairment of clonogenic capability as well as growth inhibition in 3D models, such as fibroblast/tumor cell microtissues and patient derived-organoids.**
- **The antitumor efficacy has been confirmed in vivo in orthotopic and heterotopic xenograft pancreatic ductal adenocarcinoma models in nude mice.**
- **Mechanistically, we also provided evidences that VPA/SIM combination regulate several protumorigenic pathways through TGF-β and YAP signaling modulation, thus potentiating chemotherapy.**
- **These findings represent the rationale for the ongoing VESPA trial (EudraCT: 2022-004154-63-NCT: 05821556), a multicentric, patient-centric, open-label, proof-of-concept, "randomized phase 2 study of Valproic acid combinEd with Simvastatin and gemcitabine/nab-paclitaxel-based regimens in untreated metastatic Pancreatic Adenocarcinoma patients," that has already enrolled 27 patients.**
- **Overall, we proposed a novel and affordable combination therapy, based on two orally safe and generic drugs, to sensitize a widely employed first-line treatment in poor prognosis mPDAC patients.**

Preclinical evidences of synergistic antitumor effect of VPA/SIM alone or in combination with gemcitabine/taxol

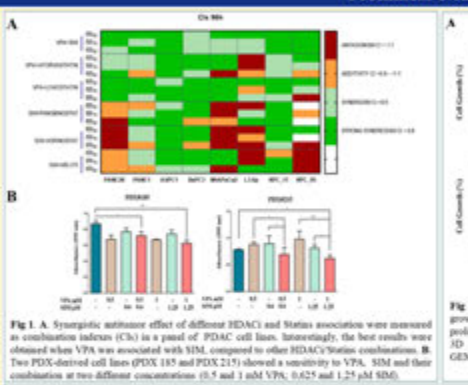


Fig 1. A. Synergistic antitumor effect of different HDACi and Statins association were measured as combination indexes (CIs) in a panel of PDAC cell lines. Interestingly, the best results were obtained when VPA was associated with SIM, compared to other HDACi/Statins combinations. **B.** Two PDX-derived cell lines (PDX 185 and PDX 215) showed a sensitivity to VPA, SIM and their combination at two different concentrations (0.5 and 1 mM VPA; 0.625 and 1.25 μM SIM).

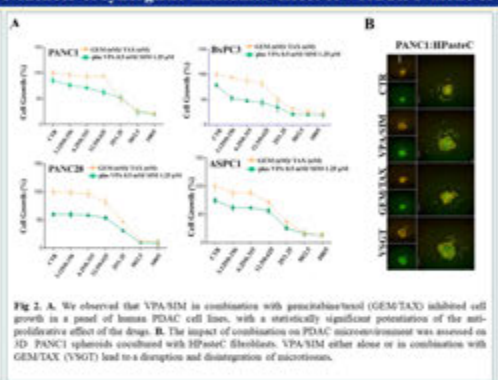


Fig 2. A. We observed that VPA/SIM in combination with gemcitabine/taxol (GEM/TAX) inhibited cell growth in a panel of human PDAC cell lines, with a statistically significant potentiation of the anti-proliferative effect of the drugs. **B.** The impact of combination on PDAC microenvironment was assessed on 3D PANC1 spheroids cocultured with HPasteC fibroblasts. VPA/SIM either alone or in combination with GEM/TAX (VSGT) lead to a disruption and disintegration of microtissues.

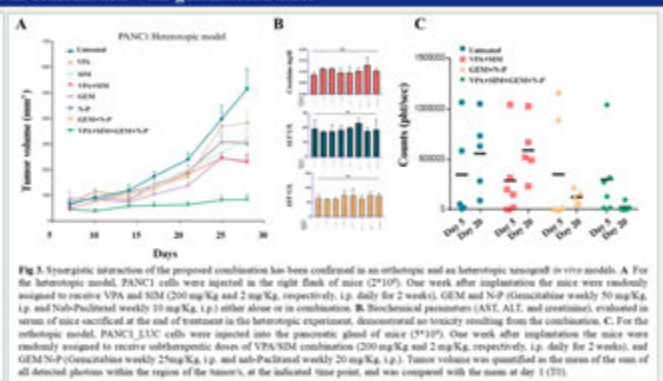
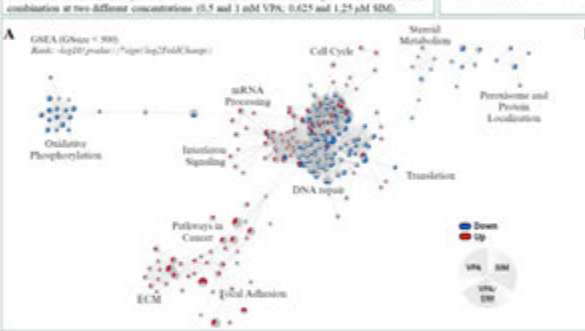
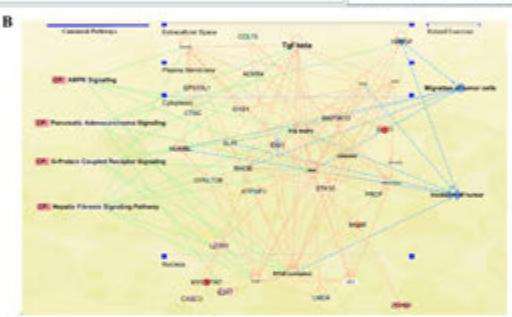


Fig 3. Synergistic interaction of the proposed combination has been confirmed in an orthotopic and an heterotopic xenograft *in vivo* models. **A.** For the heterotopic model, PANC1 cells were injected in the right flank of mice ($2*10^6$). One week after implantation the mice were randomly assigned to receive VPA and SIM (200 mg/Kg and 2 mg/Kg, respectively, i.p. daily for 2 weeks), GEM and N-P (Gemcitabine weekly 50 mg/Kg, i.p. and Nab-Paclitaxel weekly 10 mg/Kg, i.p.) either alone or in combination. **B.** Biochemical parameters (AST, ALT, and creatinine), evaluated in serum of mice sacrificed at the end of treatment in the heterotopic experiment, demonstrated no toxicity resulting from the combination. **C.** For the orthotopic model, PANC1_LUC cells were injected into the pancreatic gland of mice ($5*10^6$). One week after implantation the mice were randomly assigned to receive subtherapeutic doses of VPA/SIM combination (200 mg/Kg and 2 mg/Kg, respectively, i.p. daily for 2 weeks), and GEM/N-P (Gemcitabine weekly 25mg/Kg, i.p. and nab-Paclitaxel weekly 20 mg/Kg, i.p.). Tumor volume was quantified as the mean of the sum of all detected photons within the region of the tumor/s, at the indicated time point, and was compared with the mean at day 1 (T0).





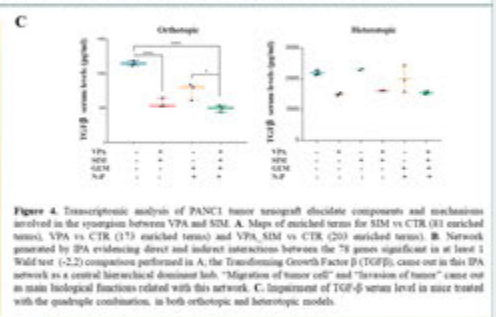
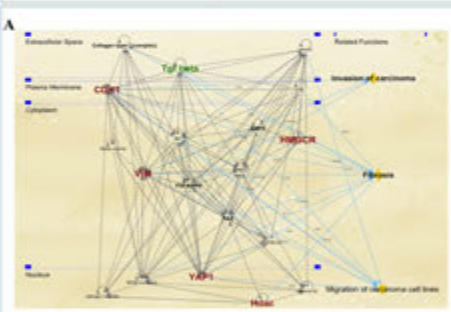
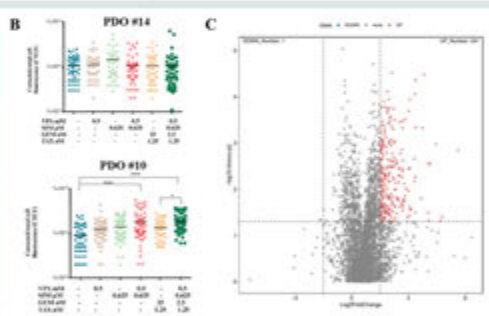


Figure 4. Transcriptomic analysis of PANC1 tumor xenograft elucidate components and mechanisms involved in the synergism between VPA and SIM. **A.** Maps of enriched terms for SIM vs CTR (81 enriched terms), VPA vs CTR (175 enriched terms) and VPA_SIM vs CTR (203 enriched terms). **B.** Network generated by IPA evidencing direct and indirect interactions between the 78 genes significant in at least 1 Wald test (-2,2) comparison performed in A; the Transforming Growth Factor β (TGFβ), came out in this IPA network as a central hierarchical dominant hub. "Migration of tumor cell" and "Invasion of tumor" came out as main biological functions related with this network. **C.** Impairment of TGF-β serum level in mice treated with the quadruple combination, in both orthotopic and heterotopic models.





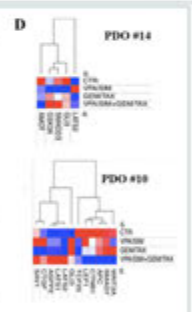
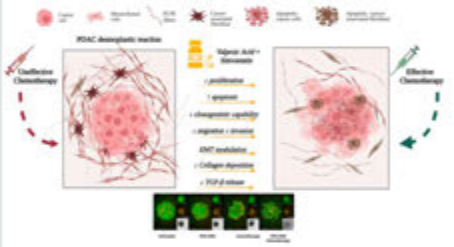
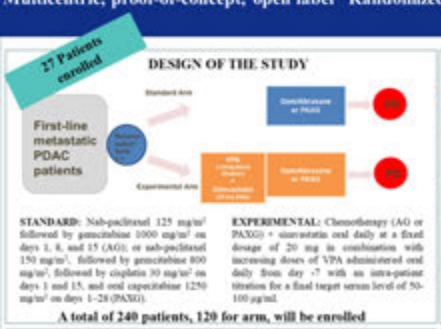


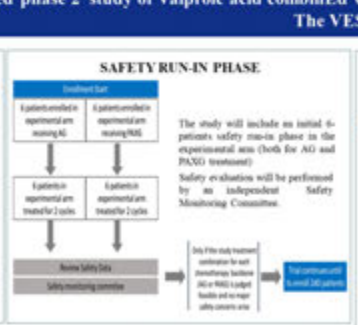
Figure 5. A. Network generated by IPA searching for known target of VPA and SIM (HDAC, HMOCR and YAP) and EMT markers (VIM and CD81) evidencing indirect and direct interactions between them. Migration and invasion were confirmed as biological function associated with this network and "Fibrosis" came out as new important function. **B.** Drug-induced apoptosis in patient-derived-organoids measured as Caspase 3 cleavage on PDO #14 (resistant to quadruple combination) and on PDO #10 (sensitive to quadruple combination). **C.** Volcano Plot of differentially expressed protein between PDO #14 and #10 at basal level. Proteins upregulated are highlighted in red (241 proteins) and downregulated protein is highlighted in light blue (3 proteins). **D.** Heatmap of Hippo pathway proteins modulated by treatment in resistant PDO #14 and sensitive PDO #10. PDO #14 resulted less enriched in proteins belonging to Hippo pathway, and less modulated by treatment.

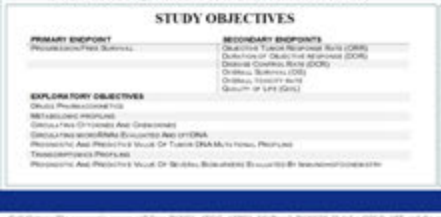
SCHEMATIC OVERVIEW OF PRECLINICAL FINDINGS



Multicentric, proof-of-concept, open label "Randomized phase 2 study of Valproic acid combinEd with Simvastatin and gemcitabine/nab-paclitaxel-based regimens in untreated mPDAC patients" The VESPA trial







METHODS

Cell Culture The pancreatic cancer cell lines PANC1_ATCC, ASPC1, MiaPaca2, PANC28, D-hpl + COLO_357, and the mouse pancreatic cancer cell lines KPC_11 e KPC_95 were maintained as monolayer cultures and cultured in Dulbecco's modified Eagle's medium (DMEM) containing 4.5 g/L glucose, glutamine, and nonessential amino acids and supplemented with 10% heat-inactivated fetal bovine serum and penicillin (100 IU/mL)-streptomycin (100 μg/mL). BxPC3 cell line were grown in RPMI (Roswell Park Memorial Institute)-supplemented with 10% fetal bovine serum (FBS, Cambrex, Belgium), heat inactivated, 50 units/ml penicillin (Cambrex, Belgium), 500 g/ml streptomycin (Cambrex, Belgium), and glutamine 4 mM. **Proliferation assay.** Cell proliferation was measured in 96 well plates in cells untreated and treated with described drugs as single agent or in combination. Cell proliferation was measured using a spectrophotometric dye incorporation assay (sulforhodamine B). Synergism, additivity, and antagonism were quantified after an evaluation of the CI, which was calculated by the Chou-Talalay equation with CalcuSyn software (Biosoft,Cambridge, UK). Cell proliferation of PDX-derived cell lines, 185 and 215, was measured using using Cristal Violet colorimetric assay and expressed as absorbance at 590 nm. **Microtissues** PANC1 cells were marked using a fluorescent probe cell tracker and cultured as microtissues by the ULA System (PerkinElmer). Cancer cells were co-cultured with human pancreatic stellate cells in a ratio of 1:1 as described in literature (Bocsaci V. et al. 2020) and untreated or treated with drugs for 96h. 3D microtissues were maintained in the incubator and photographed by Opera Phenix microscope (PerkinElmer) an objective magnification 5X. **In vivo.** All studies have been performed in accordance with "Directive 2010/63/EU on the protection of Animals used for scientific purposes" and made effective in Italy by the Legislative Decree DL 026 2014. Female athymic nude mice (NCI-nu), which were 6- to 8-weeks old, were purchased from Envigo Laboratories (Huntingdon, UK). The mice were acclimatized in the Animal Care Facility of CROM--Centro Ricerche Oncologiche di Mercogliano. To produce pancreatic tumors, PANC1_LUC cells were harvested from subconfluent cultures and resuspended in PBS solution. **RNA Seq** protocol was performed as differential gene expression analysis using Illumina sequencing. Computational analysis including quality control, quantification of gene expression, and differential expression was performing at Mario Negri Institute, Milan. **Patient Derived Organoids (PDO).** PDOs were generated from tumor surgical procedures of primitive pancreatic cancer specimens. Tumor tissue was processed mechanically then in digestion media and plated in matrigel and treated as indicated in the figure. To monitor the sensitivity to different treatments PDO were photographed with an objective magnification 10X and scored by CellEvent Caspase 3/7 Green (Invitrogen, Thermo Fisher Scientific). **Proteomic analysis** Differentially expressed proteins by Patient-derived organoids at basal level as well as upon treatment was performed by nano spectrometry (LC 360-MS) and quantified by Progenesis QI for proteomics v 4.2. Data were filtered using a global FDR < 9% and only proteins with at least one unique identical peptide sequence (p-value < 0.05) were considered identified.

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Repurposing a p53 reactivator for the treatment of pancreatic cancer

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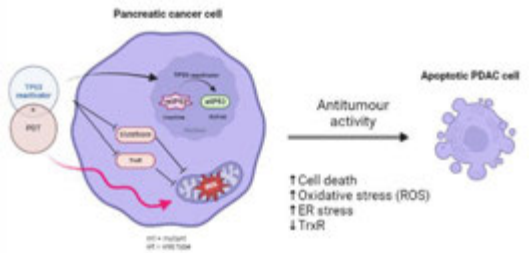
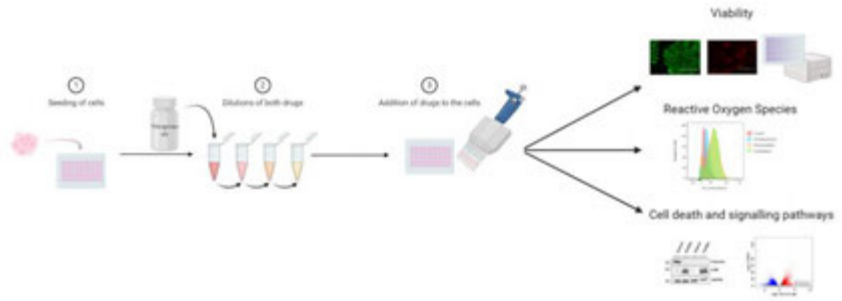
INTRODUCTION

TP53 mutations are linked with poor outcomes in pancreatic ductal adenocarcinoma (PDAC).[1] P53 wild type conformation can be restored using *TP53* reactivators. This restors P53 tumour suppressor functions and induces oxidative stress, killing cancer cells. This approach has showed promising results in other types of cancer, while its potential for PDAC remains underexplored. This study evaluates the potential of repurposing a *TP53* reactivator in combination with ROS-mediated therapies as a new therapeutic strategy for PDAC.



MATERIALS AND METHODS



1. Assess the effect of mono- and combination therapy in pancreatic cancer cells viability by MTT and Live/Dead assays
2. Study changes in ROS levels exert by the proposed therapy using flow cytometry
3. Evaluate the cell death type induced after therapy and signalling pathways regulated by the P53 reactivator anticancer activity

RESULTS

1 Metabolic Activity (MTT)

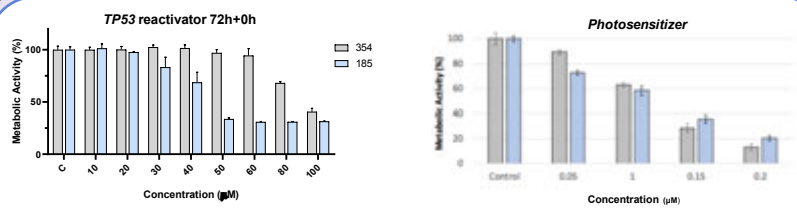


Figure 1. Dose-response assays showed a concentration dependent effect induced by both the *TP53* reactivator and the photosensitizer (PS) in patient-derived PDAC models. Cells were treated for 72h with the TP53 reactivator and for 24h with the PS. Illumination: 2.5 J/cm^2.

Viability after Combination Treatment

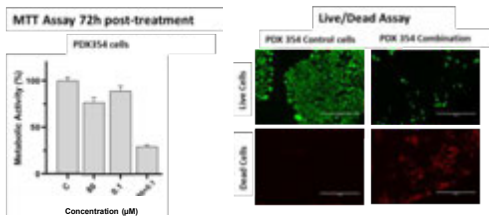


Figure 2. The combination of a TP53 reactivator + a PS induced a synergistic anti-tumour effect on PDAC cells. Green: live cells. Red: dead cells.

2 Quantification of ROS generation

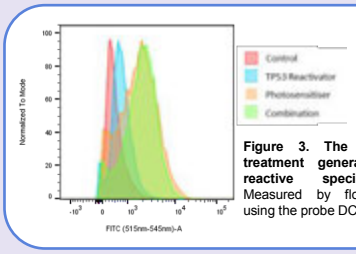


Figure 3. The combination treatment generated oxygen reactive species (ROS). Measured by flow cytometry using the probe DCFDA.

3 Induction of cell death and altered signalling pathways

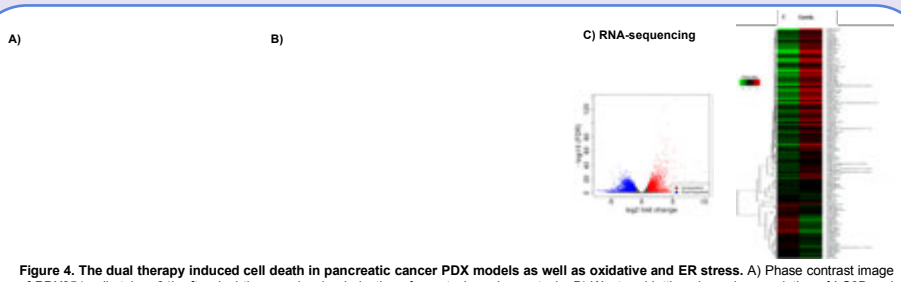


Figure 4. The dual therapy induced cell death in pancreatic cancer PDX models as well as oxidative and ER stress. A) Phase contrast image of PDX354 cells taken 24h after dual therapy showing induction of apoptosis and paraptosis. B) Western blotting showed upregulation of LC3B and Atg5 proteins. C) RNA-seq confirmed activation of oxidative and ER stress pathways and a cellular response to unfold proteins.

CONCLUSIONS

- The repurposing of a TP53 reactivator seems a promising strategy to treat PDAC. Its combination with ROS-mediated therapy induced a synergistic anti-tumour effect on pancreatic cancer models.
- The dual therapy increased ROS levels subsequently inducing oxidative stress and cell death (paraptosis and apoptosis).

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1. Pan, M., Jiang, C., Zhang, Z., Achacoso, N., Alexeeff, S., Solorzano, A. V., Tse, P., Chung, E., Sundaresan, T., Suga, J. M., Thomas, S., & Habel, L. A. (2023). TP53 Gain-of-Function and Non-Gain-of-Function Mutations Are Associated With Differential Prognosis in Advanced Pancreatic Ductal Adenocarcinoma. JCO precision oncology, 7, e2200570. https://doi.org/10.1200/PO.22.00570

Dose rationale for tebipenem in paediatric typhoid fever

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BACKGROUND

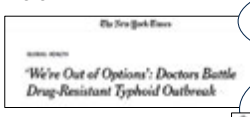
Context

Typhoid fever is an infection that affects 21 million people yearly, featuring unmet medical needs and challenges which are common to other paediatric diseases.

A critical aspect in the repurposing of antibiotics is the dose rationale, as to avoid resistance or treatment failure

Problem

Currently, only one oral drug, i.e. **azithromycin** is deemed efficacious and safe for the treatment of resistant typhoid fever.



What if azithromycin failed?

Hospitalisation injectable carbapenems

New therapies are urgently needed, **low cost**, and **easily manageable**. Repurposing offers an appealing option here.

Repurposing proposal

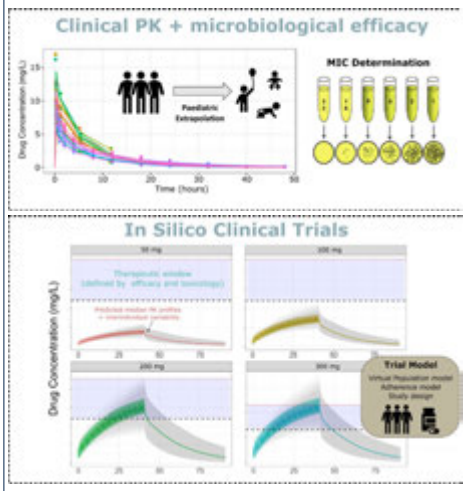
Tebipenem[2] (TBPM) is the only marketed carbapenem allowing for **oral formulation.** It has previously shown *in vitro* activity against the disease[3]

Aims

- To apply translational pharmacology principles as the basis for the dose selection and prediction of the efficacy of TBPM in children affected by typhoid fever
- To investigate the feasibility of a new age appropriate formulation for TBPM

METHODS

In silico dose regimen optimization



1 **PK Model choice**	Literature was reviewed to select a suitable PK model to perform clinical trial simulations.
2 **PK Model reparametrisation**	If necessary, model parameters were adjusted to reflect PK in the paediatric population
3 **Clinical trial simulations**	Different dosing regimens were tested across simulations scenarios, including paediatric patients
4 **f(T)>MIC computation**	Tebipenem features time-dependent pharmacodynamics[3]. The PKPD index that best links drug exposure to its antibiotic activity is f(T)>MIC
5 **Regimen selection**	Efficacious regimens should provide f(T)>MIC for at least 40% relative to the dosing interval[4]

Formulation investigation

Screening was performed over 30 different oral suspensions. They were tested for their ability to resuspend after sedimentation and pH stability

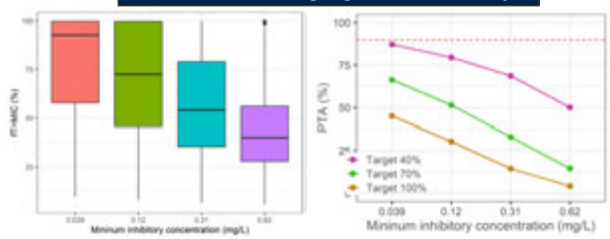
Initial formulation screening

The first three candidate formulation were carried forward to in vitro performance testing for sedimentation rate, pH and drug stability.

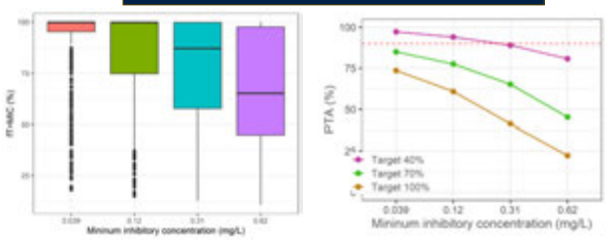
Formulation testing with TBPM

RESULTS

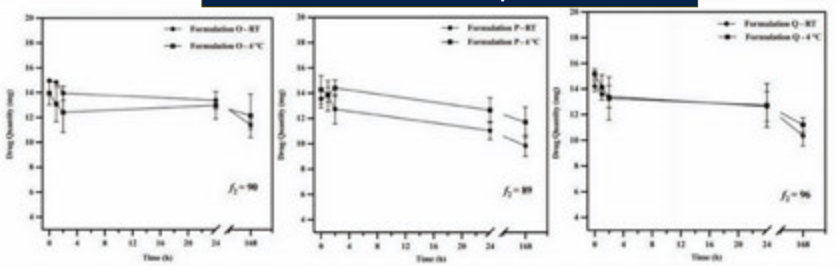
Scenario 1 – 6 mg/kg two times daily



Scenario 2 – 6 mg/kg three times daily



Final candidate suspensions



API/Excipient	Formulation 'O'	Formulation 'P'	Formulation 'Q'
Tebipenem	100 mg	100 mg	100 mg
Sodium lauryl sulphate	40 mg	40 mg	40 mg
Glycerol	-	200 mg	100 mg
Xantham Gum	25 mg	15 mg	25 mg
Sucrose	200 mg	200 mg	200 mg
Potassium sorbate	20 mg	20 gm	20 mg

CONCLUSIONS

- **Integration of *in vitro* microbiology data with *in silico* methodologies provided evidence of a suitable regimen (6mg/kg t.i.d. TBPM) for the treatment of typhoid fever in children.**
- **This regimen aligns with safety and toxicology data available for TBPM. Moreover, it sheds light into the anticipated efficacy profile of TBPM.**
- **While challenges related to the long-term stability of suspensions were noted, the utilization of single-use dispersible sachets is anticipated to address these issues effectively**

REFERENCES
[1] DOI: 10.2196/27268
[2] DOI: 10.1080/14787210.2018.1496821
[3] DOI: 10.1128/AAC.00603-19
[4] DOI: 10.3389/fphar.2022.833189

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CURE ID: Identifying infectious diseases for drug repurposing through a WHO collaboration

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CURE ID & WHO Collaboration

Background

- CURE ID: a global, publicly available website/mobile app to collect real-world clinical use of drug repurposing; run by U.S. Food and Drug Administration (FDA) and the National Center for Advancing Translational Science (NCATS/NIH)
- CURE Drug Repurposing Collaboratory (CDRC) run by Critical-Path, FDA, and NCATS aims to convene stakeholders to collect clinical data for CURE ID
- 2019: 5-year collaboration agreement between World Health Organization (WHO) and FDA to support the CURE ID program

Collaboration Goals

- WHO conducted landscape analysis to identify infectious diseases with high unmet need to prioritize for the CURE ID program
  - Drug-resistant sexually transmitted infections
  - **Implantation mycoses**
  - WHO fungal priority pathogens/diseases

Global Collaborative Project

Implantation Mycoses

- A group of pathogenic fungi that gain access through cutaneous or mucosal wounds or by contact
  - Four infections prioritized: Sporotrichosis, chromoblastomycosis, eumycetoma and actinomycetoma
- Collaborative efforts by WHO, FDA, and CDRC on project to capture real-world data (RWD) on use of repurposed drugs
  - WHO conducts a global online survey (WHO Dataform tool)
    - ➢Results published as a WHO report and a PLOS NTD article in 2023
  - CDRC/CURE ID teams collect case reports for CURE ID
    - ➢Conducted a systematic literature review of global case reports in PubMed
    - ➢Performed outreach to gather clinician-submitted case reports

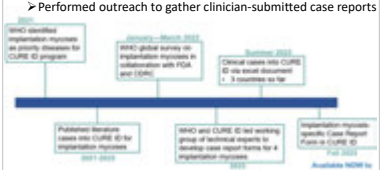


Figure 1. Timeline of implantation mycoses collaborative project

Results: Comparisons of WHO & CURE ID Data

WHO Global Survey on Implantation Mycoses

- Captured diagnostic methods, non-pharmacological interventions and pharmacological treatments used by respondents
- 142 respondents from 47 countries completed the survey
  - 97 respondents treat sporotrichosis, 101 respondents treat chromoblastomycosis, 114 respondents treat eumycetoma, 102 respondents treat actinomycetoma
- Confirmation that drug repurposing is occurring for fungal diseases beyond itraconazole as first choice (85–90%) and terbinafine for refractory cases (44–56%); newer generation azoles used by 27-41% of respondents for eumycetoma and chromoblastomycosis

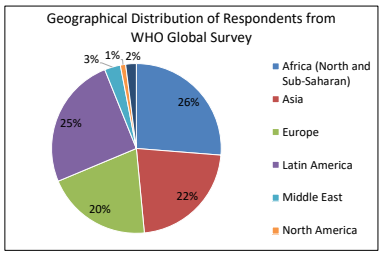


Figure 2. Geographical distribution of the respondents that completed the WHO global survey

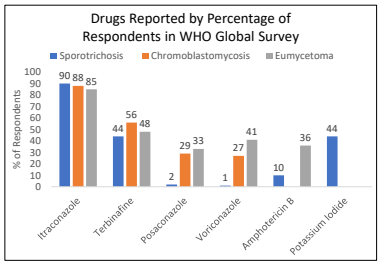


Figure 4. Percentages of respondents that treat sporotrichosis, chromoblastomycosis and eumycetoma with each medicine

CURE ID Cases Reports for Implantation Mycoses

- 546 published case reports were entered into CURE ID
  - 259 published cases on sporotrichosis, 198 published cases on chromoblastomycosis, 58 published cases on eumycetoma, 61 published cases on actinomycetoma
- 140 cases were submitted by clinicians into CURE ID
  - 114 cases on sporotrichosis, 19 cases on chromoblastomycosis, 1 case on eumycetoma, 6 cases on actinomycetoma
- Itraconazole was the most frequently used drug for sporotrichosis, chromoblastomycosis and eumycetoma; newer generation azoles reported for eumycetoma and chromoblastomycosis

Figure 3. Global distribution for published case reports from literature review for sporotrichosis, chromoblastomycosis and eumycetoma

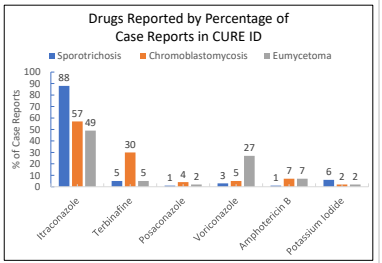


Figure 5. Percentages of case reports that treated sporotrichosis, chromoblastomycosis and eumycetoma with each medicine

Implantation Mycoses CRFs

Development of CRFs

- Collaboration with technical experts, clinicians, and CDRC working groups helped develop implantation mycosis-specific case report forms (CRFs) for CURE ID
  - Experts determined relevant data to collect for each CRF
  - Four CRFs are now available in CURE ID for clinicians to submit their cases of implantation mycoses
    - ➢Sporotrichosis
    - ➢Chromoblastomycosis
    - ➢Eumycetoma
    - ➢Actinomycetoma

Collection of RWD

- WHO, FDA, and CDRC are jointly working to collect RWD of cases of implantation mycoses treated with repurposed drugs
- Continuous efforts to get more clinicians to submit their use of repurposed drugs on the implantation mycosis-specific CRFs

Share your experiences treating implantation mycoses!

CURE ID
Visit us at https://cure.ncats.io

Continued Collaborative Efforts

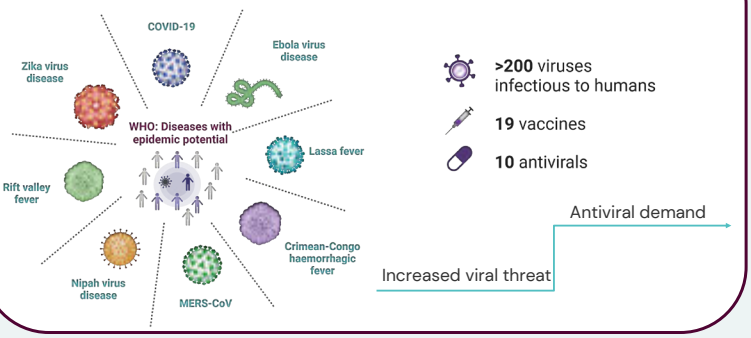
- CRFs available on CURE ID to collect RWD on implantation mycoses, which can add to the results from the WHO Global survey and the current case reports in CURE ID on implantation mycoses
- Similar collaborative approach can be utilized for STIs
  - Current development of a CRF for *Neisseria gonorrhea* treatment failures; pilot project with three National Agencies in USA, Canada, UK
- Selection of two WHO-listed fungal priority pathogens/diseases for piloting in CURE ID is ongoing
- Overall, there is a need to capture large volumes of RWD for hypothesis generation and informing clinical trials about efficacy signals to support regulatory decisions, especially with neglected tropical infections
  - ➢Collaborative efforts and systematic approaches such as the WHO Global Survey and the data collection of published cases and RWD in CURE ID can play an important role

Exploring the morphology of host cells for innovative drug repurposing in viral infections

Marianna Tampere[1,4], Adelinn Kalman[2,4], Jonne Rietdijk[2,4], Hanna Axelsson[3,4], Duncan Njenda[1,4], **Elin Asp**[1,4], Maris Lapins[2,4], Kun Qian[3,4], Flavio Ballante[3,4], Ola Spjuth[2,4*], Jordi Carreras-Puigvert[2,4*], Brinton Seashore-Ludlow[1,3,4*] and Päivi Östling[1,4*]

Affiliations: [1] *Karolinska Institutet*, [2] *Uppsala University*, [3] *Chemical Biology Consortium Sweden (CBCS)*, [4] *Science for Life Laboratory (SciLifeLab)*
*equal contribution

Ten antivirals vs hundreds of viruses



>200 viruses infectious to humans

19 vaccines

10 antivirals

Antiviral demand

Increased viral threat

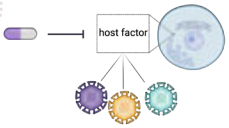
Exploiting the virus dependency on host cell pathways

Host-directed antivirals

- ⊕ Larger target repertoire
- ⊕ Broad spectrum opportunity
- ⊕ Reduced drug resistance
- ⊖ Increased risk of toxicity

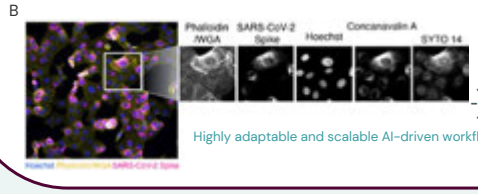
Elevating possibilities for viral infections by drug repurposing

- ✓ Cost-benefit
- ✓ Time-benefit
- ✓ Lower safety-risk

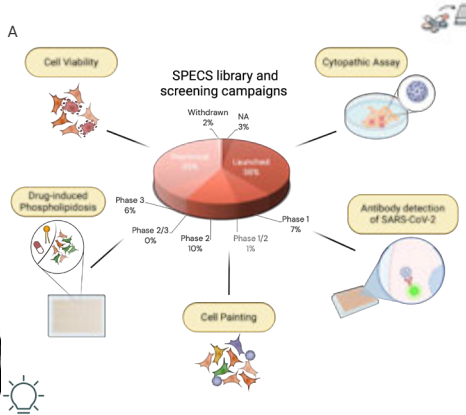


Morphological profiling unveils antiviral compounds

- SPECS library screenings identifies 324 compounds with antiviral activity
- Cell Painting creates a unique fingerprint with >2000 morphological parameters
- SARS-CoV-2 induces a unique phenotype, reversed by reference antivirals
- Cell Painting pinpoints 36 potential SARS-CoV-2 repurposing candidates



Highly adaptable and scalable AI-driven workflow!



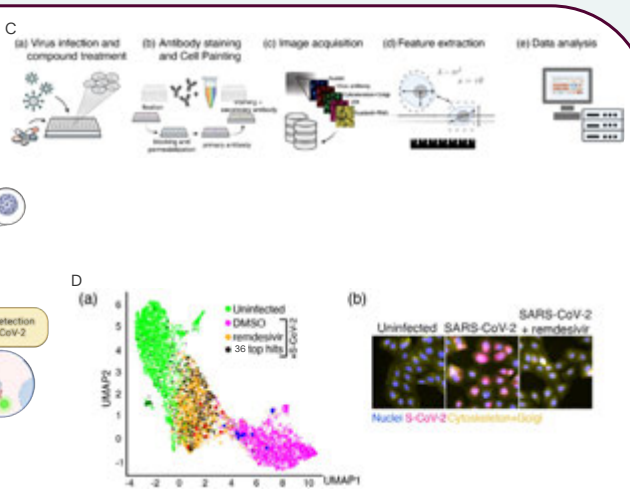
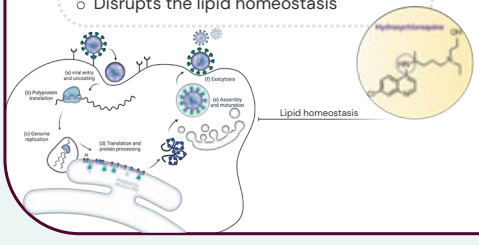


Fig. 1. (A) Overview of the screening methods using SPECS drug library of 5275 compounds. (B) Representative picture of fluorescent dyes with SARS-CoV-2 Spike antibody. (C) Cell painting workflow. (D) Cell Painting summary and representative images. UMAP plot representing populations of uninfected cells (green) and infected cells treated with DMSO (pink), remdesivir (orange) and screening hits (black).

Drug-induced phospholipidosis

- Predominantly induced by cationic-amphiphilic drugs
- Characterized by accumulation of the drug in cellular compartments
- Disrupts the lipid homeostasis



- Confounds drugs for SARS-CoV-2
  - Correlation with SARS-CoV-2 inhibition in vitro
- Does not reflect specific target-based activities of the drug
- Cell-line specific activity
- 157 compounds in the SPECS library (3%) induce phospholipidosis
- 61 antiviral compounds (19%) induce phospholipidosis

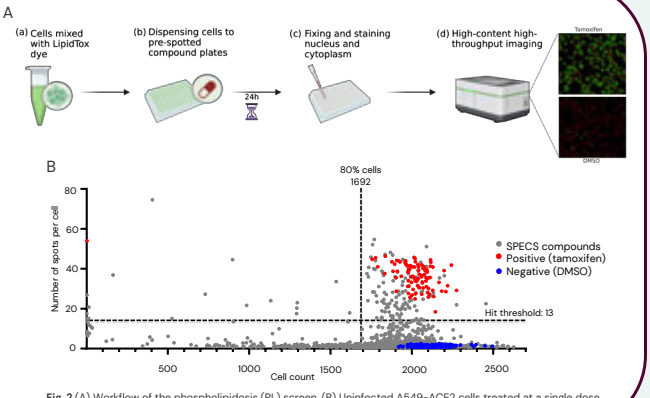


Fig. 2 (A) Workflow of the phospholipidosis (PL) screen. (B) Uninfected A549-ACE2 cells treated at a single dose screened for PL. Displayed are SPECS compounds (gray), positive control (red), and DMSO (blue).

Conclusions and future outlook

- Cell Painting enables unbiased morphological profiling for finding repurposing antiviral candidates
  → Applicable for emerging viruses to combat future pandemics
- Several antiviral compounds have phospholipidosis activity
  → Future research is required to understand the importance of phospholipidosis in viral drug discovery

Next step: Explore antiviral drug targets and drug combinations

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442

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Acknowledgement: Analysis of data for figure 2 made by Kun Qian (CBCS)

UPPSALA UNIVERSITET

MMAtt-DTA: A MULTIMODAL ATTENTION-BASED APPROACH TO PREDICT DRUG-TARGET AFFINITIES ACROSS SEVEN TARGET SUPERFAMILIES

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FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

Drug-target affinity (DTA) prediction is key for drug discovery and repurposing. This study introduces a multimodal, attention-based method to predict DTAs for human proteins across seven superfamilies (Figure 1). We explored nine descriptor sets to identify optimal representations for drug-target pairs (Figure 2). Using independent testing, our method showed promising performance in three prediction scenarios and outperformed several state-of-the-art solutions (Figure 3). We applied our models to predict the complete interaction matrix between 3492 FDA-approved drugs and 1251 human proteins (Figure 4). The data and models are freely accessible via the provided QR-code.

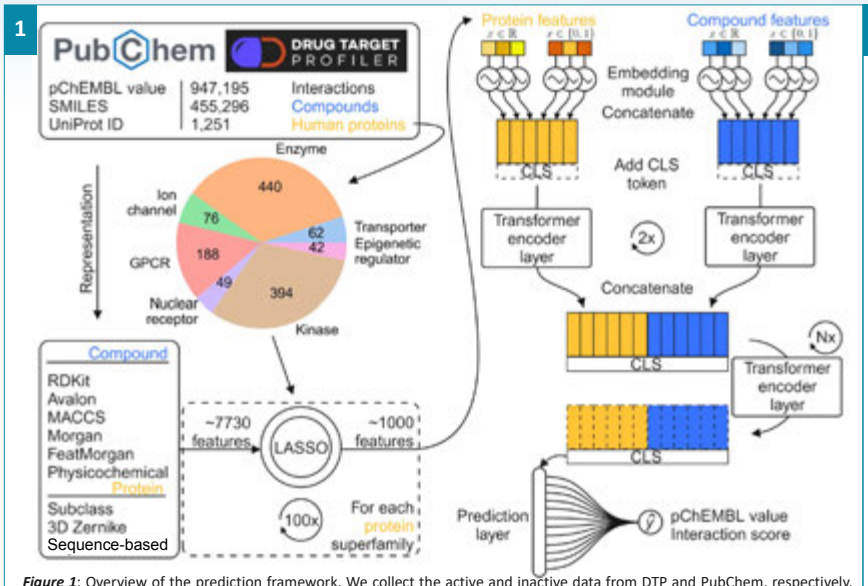

Figure 1: Overview of the prediction framework. We collect the active and inactive data from DTP and PubChem, respectively. We generate a high-dimensional feature vector and select the best descriptors with LASSO separately for each protein superfamily. We separate each descriptor set into protein and compound features, and further divide them into continuous and binary variables. The grouped features are passed into the predictive model to yield pairwise binding affinity point predictions.

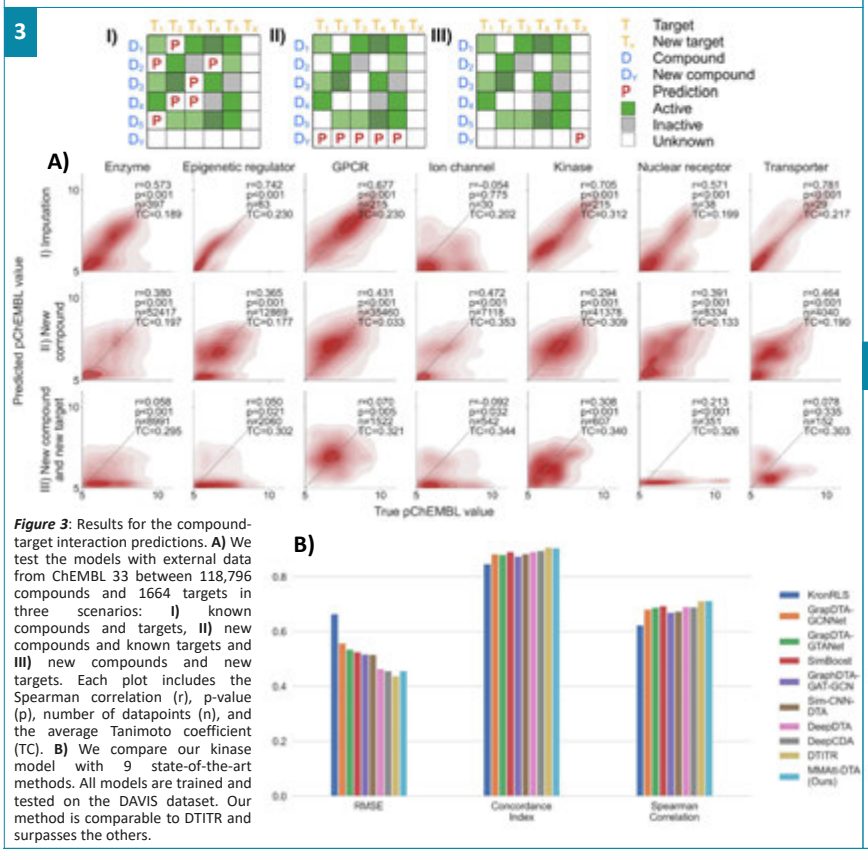

Figure 3: Results for the compound-target interaction predictions. **A)** We test the models with external data from ChEMBL 33 between 118,796 compounds and 1664 targets in three scenarios: **I)** known compounds and targets, **II)** new compounds and known targets and **III)** new compounds and new targets. Each plot includes the Spearman correlation (r), p-value (p), number of datapoints (n), and the average Tanimoto coefficient (TC). **B)** We compare our kinase model with 9 state-of-the-art methods. All models are trained and tested on the DAVIS dataset. Our method is comparable to DTITR and surpasses the others.

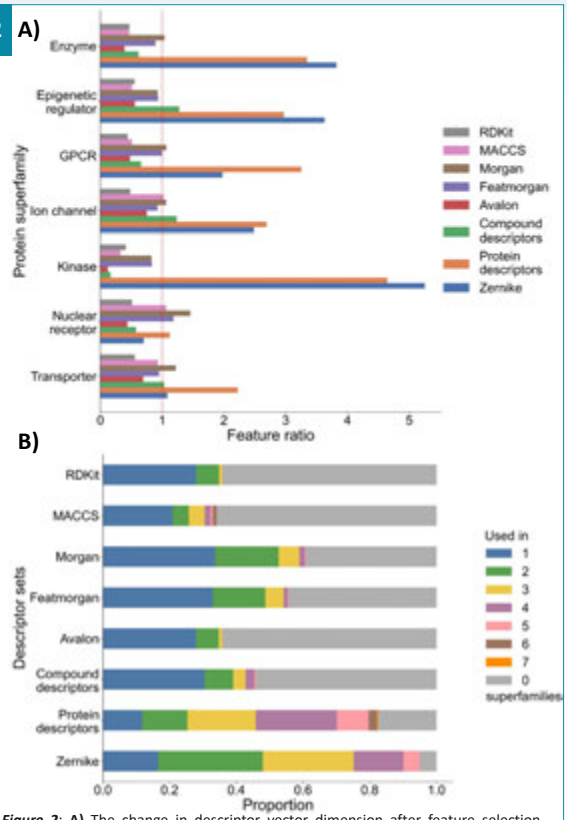

Figure 2: **A)** The change in descriptor vector dimension after feature selection. Originally, each compound-protein pair was represented by a 7719-dimensional vector. We reduced the dimension to 1000 with LASSO. The selected descriptors are different across superfamilies. Bars that cross the dotted reference line indicate an increased contribution of a descriptor set to the overall composition of a feature-selected vector than to the original vector. **B)** Proportions of how often individual descriptors belonging to a set are selected by LASSO into a model for each protein superfamily. The descriptors are grouped by their generality, i.e., how often they are selected for different superfamilies. Protein subclass labels are always included in the descriptor vectors and are thus omitted from the figure.

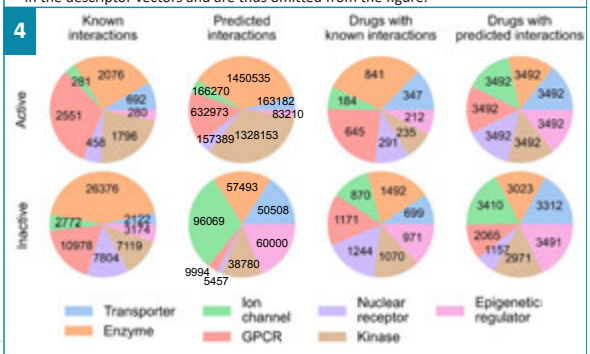

Figure 4: The proportions of known and predicted interactions by protein superfamily for the completed interaction matrix between 3492 FDA-approved drugs and 1251 human proteins. An interaction with pChEMBL value of 5.0 or smaller is considered inactive. For the predicted values, we set the inactivity threshold at 5.1 due to the regression model predicting many values close to, but not exactly, 5.0.

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pharmb.io

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Morphological profiling as a powerful approach for drug repurposing and disease modelling

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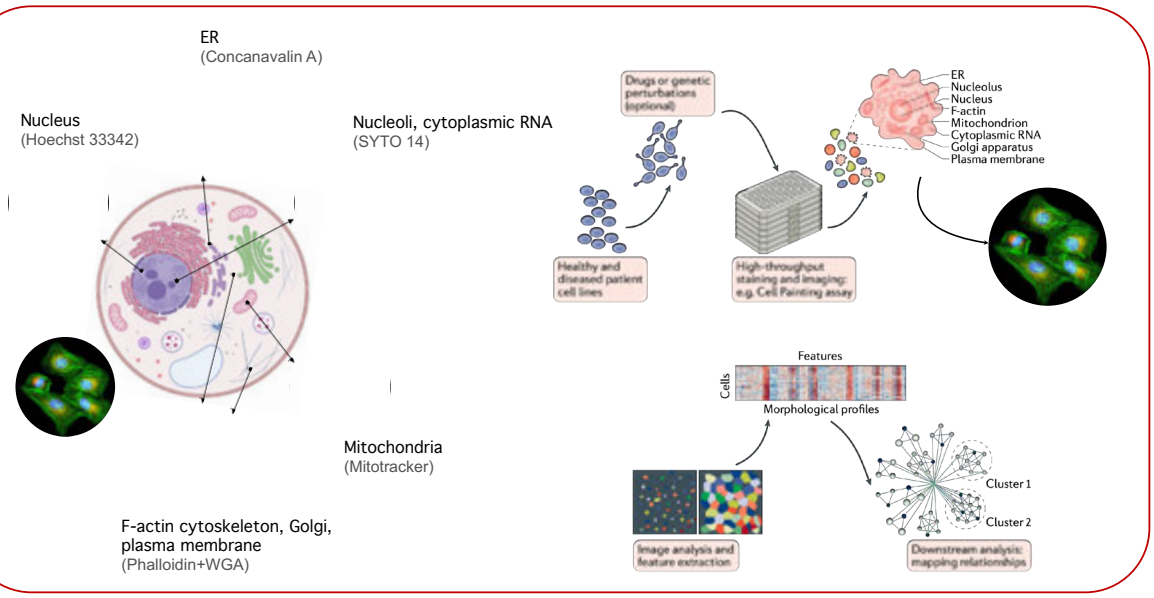
1. Department of Pharmaceutical Biosciences and Science for Life Laboratory, Uppsala University, Sweden 2. Chemical Biology Consortium Sweden (CBCS), Uppsala node

Untargeted morphological profiling

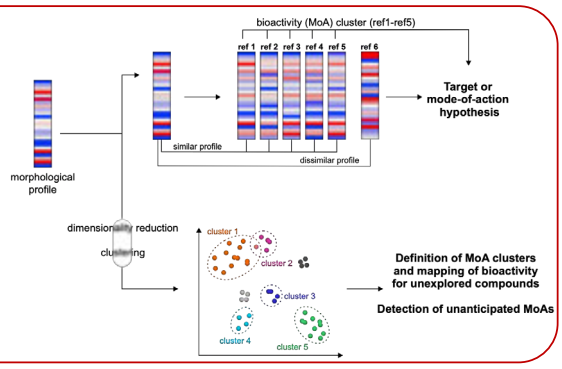


Cell Painting

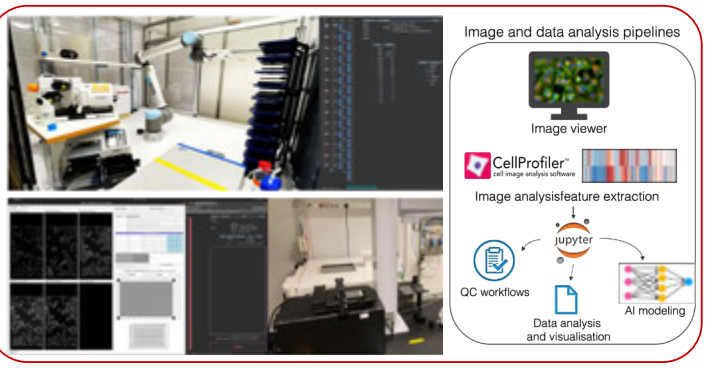
The technique includes a cocktail of fluorescent reagents to stain 8 different organelles (nucleus, nucleoli, cytoplasmic RNA, f-actin cytoskeleton, Golgi, ER, mitochondria and plasma membrane. High content imaging and image analysis are used to extract cellular features, which are then used for morphological profiling

MoA identification

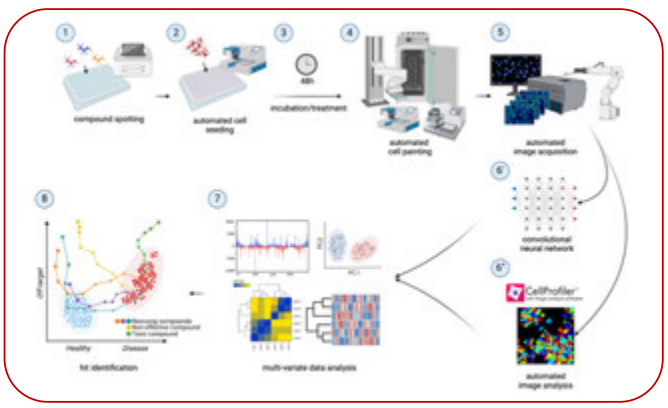
By comparing morphological profiles of query compounds with those of a reference compound library, the mechanism of action (MoA) of the query compound can be estimated



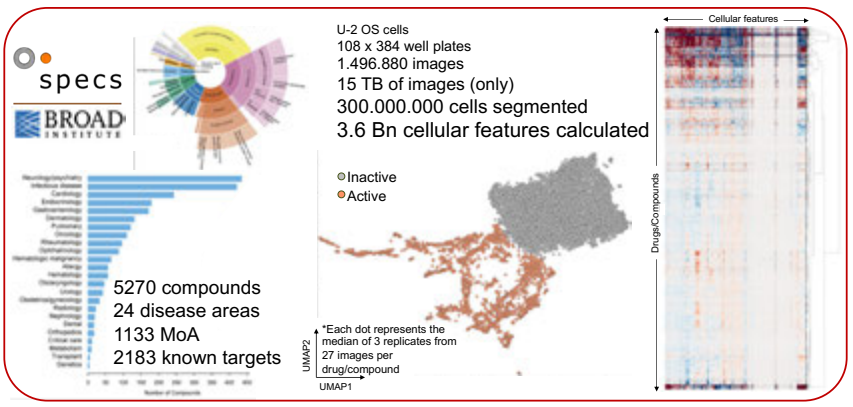
Infrastructure



Automated cell painting



Morphological profiling of 5270 reference drugs



SciLifeLab

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Challenges and solutions in the set-up of an international, cross-boundary, repurposing clinical trial for Osteogenesis Imperfecta

Mahboobeh Haji Sadeghi[1], Judith Cohen[1], Luca Sangiorgi[3], Bronwen Williams[1], Sarah Sumpter[1], Laura Simms[1], Chao Huang[1], Keith Pugh[2], Francesca Gurioli[3], Maria Gnoli[3], Alice Moroni[3], Martina Piccini Leopardi[3], Clara del Coco[3], Nicholas Bishop[2]
1 HYMS, University of Hull, UK. 2 Sheffield Children's NHS Foundation Trust, UK. 3 IRCCS Istituto Ortopedico Rizzoli, Italy

INTRODUCTION

Matrix-directed therapy in older adolescents and adults with osteogenesis imperfecta – the "MOI-A" project within the REMEDi4ALL Consortium – is assessing the repurposing of losartan in adults and older adolescents with osteogenesis imperfecta, an inherited form of bone fragility caused in the majority of cases by mutations in one of the two genes encoding type I collagen. We present the challenges we have encountered during the set-up of this international study due to the variation in regulatory processes across national boundaries.

FACING CHALLENGES

RDT Meetings

- As a demonstrator project in REMEDi4ALL we have a Research Development Team (RDT) assigned to our project, including expertise across the regulatory pathway for drug development
- We presented our challenges at these meetings, detailing discussions between study team, regulators and Sponsors and they helped to facilitate solutions

Sponsorship Agreement

- We had to decide whether to have one sponsor with a legal representative or a co-sponsorship agreement
- The co-sponsorship agreement was determined to be the best practice to ensure a clear outline of responsibilities for different aspects of the study in their representative countries
- There were challenges in preparing a co-sponsorship agreement because of lack of harmonization between UK & EU regulations.

Protocol preparation and regulatory approval

We will use one master protocol across both countries ensuring the same procedures for treatment and outcome measures are followed in both countries

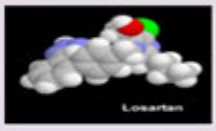
Reporting of SUSARs approaches

To ensure that we can comply with pharmacovigilance guidance we decided:

- The UK Sponsor will report all the study SUSARs to the MHRA
- The Italian Sponsor will report all the study SUSARs to EVCTM/AIFA
- Co-CIs will each inform the other immediately of any such events

Availability of the IMP

- We were unable to source one IMP product available in both countries
- Agreed to use two different IMP brands
- Agreed to use one of the SmPCs as the reference safety information in both countries



Database arrangements

- Patients will be randomised from one central randomisation system
- Data will be collected in one central database to streamline study oversight
- Having the one central database would be the best way to collate safety events centrally for reporting to the regulatory authorities

CONCLUSION

By presenting the current status of each of these areas we have demonstrated the complex regulatory environment when working cross-boundaries, and the advantages of the input of a RDT within the REMEDi4ALL Consortium. We hope that the details of the discussions between the RDT, study team, regulatory authorities and eventual solutions will help future studies to be able to proceed more swiftly.

Matrix-directed therapy in older adolescents and adults with osteogenesis imperfecta – the "MOI-A" study
IRAS NUMBER: 1006449 Trial Registration: ISRCTN13317811 Funded by: EU Horizon programme REMEDi4ALL, UKRI (underwritten UK partners)

Engaging the patient community to ensure successful drug repurposing

Judit Baijet[1], Abby Stock-Duerdoth[2], Claudia Fuchs[1], Eve Hewitt[2], Virginie Hivert[1], William May[2], Rick Thompson[2]
1. EURORDIS- Rare Diseases Europe, Paris, France. 2. Beacon: for rare disease, Cambridge, UK.

PATIENT ENGAGEMENT IN REMEDI4ALL

Introduction

Drug repurposing interest is steadily increasing in a variety of areas such as policy, regulation, funding and research.

Although a huge amount of progress has been made in pushing forward this innovative opportunity in the drug development field, we frequently lack meaningful, efficient and effective patient-centric perspectives to address unmet medical needs.

Patients in a partnership role

REMEDi4ALL is positioning the **patient's voice and experience** at the heart of every repurposing project and empowering them as true **co-creators**.

To deliver on this mission, REMEDi4ALL is **embedding patient engagement** in all its four demonstrator projects as a core and essential principle for a patient-centric approach to drug repurposing.

- **Patient Champion**
- **Patient Advocacy Group**
- **Patient Engagement Plan**
- **Multi-stakeholder meetings**

PATIENT CHAMPIONS

A **REMEDi4ALL patient champion** has been defined as a **non-profit stakeholder developing or gathering evidence and expertise in order to accelerate the repurposing of a medicinal product for their target condition.** A champion may be a patient organisation representative, patient, carer, or advocate tied to collaborative groups such as umbrella charities or a European Reference Network (ERN).

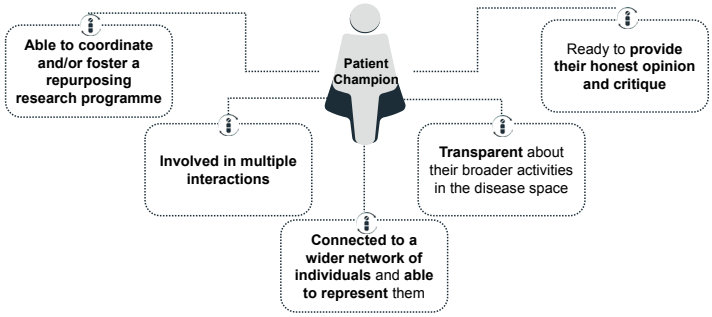


Fig. 1 Patient champion characteristics

PATIENT ADVOCACY GROUP (PAG)

PAGs are set up to **provide the Patient Champion and Project Team with an additional source of patient insight** at key points within the project.

Their main purpose is to help all relevant parties access a more representative selection of patient experience as well as ensuring that the repurposed drug can **address the true need of the patient's community**.

PAGs are a **group of patients, relatives, carers or individual experts,** generally disease-specific, who **advocate for their community in different ways;** e.g., by providing training and education, participating in research projects, and by being involved in high-level discussions on treatment approvals with regulators and other stakeholders.

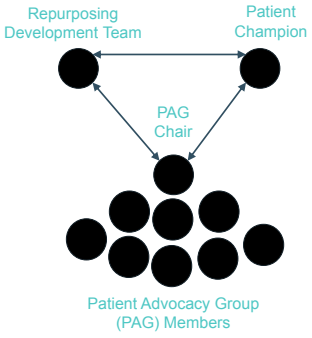


Fig. 2 Patient Advocacy Group governance and interactions

PATIENT ENGAGEMENT PLAN

The REMEDi4ALL Patient Engagement Plan is a living document developed to **help the project principal investigators and teams identify and implement patient engagement activities.**

This tool allows to ensure meaningful and continuous engagement throughout the project

This plan includes:

- **Challenges related to patient engagement**
- **Potential solutions to the identified challenges**
- **Assessment of every step of the project**

MULTI-STAKEHOLDER MEETINGS

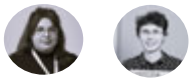
Multistakeholder meetings are regularly organised to **gather diverse stakeholders and tackle subjects relevant to the patient community**.

Patient centricity runs as the core narrative in all the multistakeholder meeting sessions ensuring that each stakeholder is considering the patient perspective in their current and future work.

Multi-stakeholder meetings aim at sharing information and advance learning, promoting dialogue and constructive interaction between all relevant stakeholders, and facilitating collaborations between all stakeholders.

Fig 3. Participants of the 1st REMEDi4ALL Multi-stakeholder meeting: Drug repurposing, an attractive strategy in pancreatic cancer treatment?

Patient Engagement Team



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This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.
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Exploiting real-world data to assist drug repurposing. Safety profiling of valproic acid and simvastatin combination treatment.

Alessia Antonella Galbussera[1], Laura Fiorenza[1], Adrià Fernández-Torras[2], Jordi Quintana[2], Alessandra Leone[3], Alfredo Budillon[3], Mauro Tettamanti[1] and Maddalena Fratelli[1]

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

ABSTRACT

REMEDI4ALL is studying the repurposing of valproic acid (VPA) and simvastatin (SIM), administered on top of standard-of-care chemotherapy for metastatic pancreatic cancer.[1] The two drugs are widely used and generally safe. However, we decided to evaluate the safety aspects of their combination using real-world data (RWD).

We analysed Lombardy Region's administrative database (10 M inhabitants). Healthcare in Italy is public, so the data are acquired for administrative and reimbursement purposes. Subjects that acquired at least one package of VAL or SIM in 2015-21 without any package in the previous 5 years entered the cohort. More than 7,000 patients were treated with both drugs. Hospital admissions and outpatient visits showed no significant increase in these patients as compared to those in patients taking either drug individually. We also analysed drug discontinuation rate, assuming that any side effects would lead to interruption of the treatment. The discontinuation rate of SIM was only slightly higher in patients with prior use of VAL than in those taking SIM only (HR 1.05, 95% CI 1.01-1.09). Conversely, there was a considerable decrease in the discontinuation rate of VAL in patients who were already taking SIM (HR 0.77, 95% CI 0.74-0.79).

In parallel, we explored the post-marketing reports of adverse events (AEs) from four databases, which have been standardized, de-duplicated and corrected for masking effects in the CLARITY PV platform. Reassuringly, AE levels were generally lower in patients taking both VAL and SIM, when compared to monotherapy, in agreement with the lower discontinuation rate observed in Lombardy.

We conclude that there are no increased safety concerns in the patients taking both drugs. These results underline the impact of the use of real world data in drug repurposing.

METHODS

Data sources

Data were obtained from the administrative database of Lombardy Region. Lombardy, located in Northern Italy, has approximately 10 million inhabitants: we had access to data on subjects 40 years and older (more than 6 millions). Healthcare in Italy is public, so the data are acquired for administrative and reimbursement purposes. Records contain information on sex, age, drug dispensation, hospital admissions together with primary and secondary diagnoses, ambulatory specialist visits and exemption registries. Drugs were classified according to Anatomical Therapeutic Chemical (ATC) Classification while hospital diagnoses were classified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification. All data were managed according to the current Italian law on privacy.

Study cohort

Subjects that acquired at least one package of valproic acid (ATC N03AG01) or simvastatin (ATC C10AA01) from 2015 to 2021 without any package of the same active principle in the previous five years entered the cohort. Beginning time was date of first dispensation of valproic acid or simvastatin and exit time was date of last dispensation, plus 60 days to allow for drug consumption of enclosed drug in last package(s). We considered that subjects had a co-prescription (valproic acid and simvastatin) when both drugs were dispensed in the same solar year. For this subjects beginning time date of dispensation of the second active principle and exit time last dispensation of the same active principle plus 60 days. For these three cohorts we analysed hospitalization, access to emergency room, and ambulatory specialty visits, We calculated a proxy for a comorbidity index using drug prescriptions, the Drug Derived Complexity Index (DDCI) (except for the C10 class, since it was directly included in the analysis).

Statistical analysis

The characteristics of patients included in the analyses were described with mean and standard deviation for continuous variables and numbers with percentages for categorical ones. Kaplan Meier curves were plotted and a log-rank test was performed to assess differences among groups. Cox proportional hazard model were fitted to analyze the interruption of drug assumption and survival, reporting the hazard ratio and 95% confidence intervals as risk estimation. We fitted also a competing-risk regression model based on Fine and Gray method for interruption of drug assumption and competing risk of death. Statistical analysis was performed using SAS software, SAS Institute Inc., Cary, NC, USA.[2]

Adverse drug reaction post-marketing reports

Post-marketing reports of adverse events (AEs) were estracted from four databases (VigiBase[3], FAERS[4], VAERS[5] and JADER[6]), which have been standardized, de-duplicated and corrected for masking effects in the CLARITY PV technology platform.[7]

To identify statistically significant AEs, we used the proportional reporting ratio (PRR), which quantifies the extent to which an AE is more frequently reported with a given drug than with other drugs. More specifically, we focused on those AEs that were detected by CLARITY PV as signals of disproportionate reporting at some point during the lifetime of the drug (PRR > 2), either for valproic acid or simvastatin

RESULTS AND CONCLUSIONS

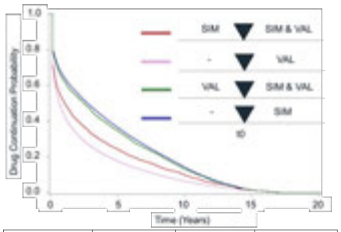
Drug, age, sex and tumor exemption distribution in the Lombardy Region study cohort

2005-2021	VAL	SIM	VAL + SIM
N	67407	656847	7397
45-49	12265 (18.2%)	32045 (4.88%)	491 (6.64%)
50-59	18647 (27.66%)	129696 (19.75%)	15 (20.48%)
60-69	13678 (20.29%)	205623 (31.3%)	2020 (27.31%)
70-79	12281 (18.22%)	201435 (30.67%)	2125 (28.73%)
80-89	8664 (12.85%)	81958 (12.48%)	1135 (15.34%)
90-99	1840 (2.73%)	6032 (0.92%)	111 (1.5%)
100+	32 (0.05%)	58 (0.01%)	-
M	31475 (46.69%)	304712 (46.39%)	3521 (47.6%)

Exemption for Tumor (exc_id=048 e 0043) Dates intervals	VAL	SIM	VAL + SM
end ex < study entry	1315 (1.95%)	11389 (1.73%)	176 (2.38%)
start ex <=study entry<=end ex	4806 (7.13%)	42716 (6.50%)	544 (7.35%)
study entry<=start ex <=study exit	1812 (2.69%)	36725 (5.59%)	430 (5.81%)
start ex>study exit	3020 (4.48%)	40115 (6.11%)	145 (1.95%)

- A total of 7397 subjects have been taking both VAL and SIM between 2005 and 2021.
- 1295 subjects among them had a tumor (tumor exemption from medical care expenses) before (first row), after (last row), or during the study interval (central rows).
- No patients had chemotherapy treatment in concomitance with VAL+SIM assumption.

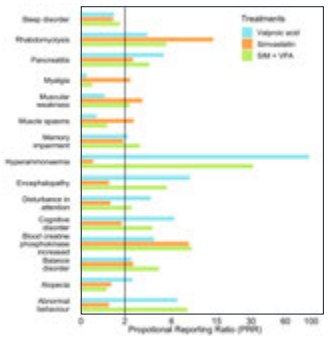
Discontinuation rate as a proxy of adverse effects



HR(95% C.I.)	Unadjusted	Sex and age adjusted	Sex, age and *DDCI adjusted
SIM/VAL vs VAL only	0.85 (0.82; 0.88)	0.78 (0.76; 0.81)	0.77 (0.74; 0.79)
VAL/SIM vs SIM only	1.04 (1.00; 1.08)	1.07 (1.03; 1.11)	1.05 (1.01;1.09)

- There is no increase in the discontinuation rate of either drug, whether treatment was started with or without prior treatment with the other.
- The very slight increase, although significant after adjustment for sex, age and DDCI (HR1.05 CI 1.01-1.09). Rather, there is a decrease in the discontinuation rate of valproate in patients who were already taking simvastatin.

Adverse Drug Reaction post-marketing data (CLARITY PV)



- Reassuringly, except for balance disorder, the proportional reporting ratio (PRR) levels are not higher in patients taking both valproic acid and simvastatin, when compared to monotherapy use of the two drugs. Rather, in most cases, they are lower

Despite the possible metabolic interactions, **no signs of increased safety concerns are evident in the population of patients taking both these drugs**.

We are currently exploring the possibility of accessing similar data in **Campania**, another Italian region, and in **SERMAS**.

This indication of a lower drug toxicity, deriving from two independent sources and data types may be due to a **lower drug bioavailability**, consequent to a metabolic interaction with simvastatin, and warrants further investigations

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1) Roca, Maria Serena, et al. "Repurposing of valproic acid and simvastatin in pancreatic cancer: in vitro and in vivo synergistic antitumor interaction and sensitization to gemcitabine/nab-paclitaxel via inhibition of TGFβ-EMT signaling pathway." Cancer Research 82.12_Supplement (2022): 1840-1840.

2) https://www.sas.com/

3) https://who-umc.org/vigibase/

4) https://open.fda.gov/data/faers/

5) https://vaers.hhs.gov/

6) Pharmaceuticals and Medical Devices Agency. Japanese adverse drugevent report database. https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html (in Japanese).

7) https://claritypv.com/

AFFILIATIONS AND ACKNOWLEDGMENTS

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- We thank Zia Urrehman, Tero Aittokallio and the WP4 team, with whom we worked on the in silico tools survey that includes the adverse reaction post-marketing data reported here (paper under review).
- We also acknowledge the collaboration with Egidio Celentano (Istituto Pascale, Naples) and Ana Maria Alvarez Diaz and Maria Laura Garcia Bermejo (SERMAS, Madrid) to prospectively add Regione Campania and Ramon y Cajal Hospital patients' cohorts to this study.

First International Conference on Drug Repurposing (#iDR24), Barcelona, 06-03-2024

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442. Views and opinions expressed are those of the author(s) only and do not necessarily reflect those of the European Union, who cannot be held responsible for them. This presentation reflects only the author's view. The EU is not responsible for any use that may be made of the information itcontains.

In-depth exploration of assessment criteria for funding organizations involved in drug repurposing

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BACKGROUND AND OBJECTIVES

Conventional valuation strategies for new medical entities are often not appropriate as they do not capture all aspects of short and long-term value) to apply to drug repurposing (DR) [1], and there is a lack of broadly accepted methods for measuring patient and societal benefits [2].

REMEDI4ALL aims to create a range of incentives and funding opportunities to engage funders with DR projects. One activity to achieve this objective is **to create a standardized tool for the assessment of DR projects.**

Within this task, REMEDi4ALL partners join forces to develop **a flexible tool that can encompass a wide range of assessment criteria** relevant for DR. This tool is being designed to provide future REMEDi4ALL project partners (e.g., funders, venture philanthropies, biotech companies, pharmaceutical firms, HTA bodies and payers) the opportunity to make explicit and transparent selections of potential projects based on their perspectives and the specific attributes of individual DR projects. In addition, the tool will be also publicly available.

METHODS

We performed a systematic overview of two major information sources: **1) documents used by research funders** (e.g., funding call application evaluation forms); **2) published literature**.

Funders were identified from the Funders Network, established by ZonMw within REMEDi4ALL. Funders were specifically asked to share their potentially relevant publicly or internally available documents for the purpose of identifying assessment criteria.

Scientific and grey literature were queried using PubMed and Google Scholar with additional publications made available from other REMEDi4ALL activities.

To create the initial list of criteria, the raw texts were copied from the source documents. An iterative process with an inductive approach was applied to formulate concise criteria, which were reformulated throughout the process until a complete list of criteria covering all collected data was established. Finally, based on the available data, a definition was attached to each criterion, however, the definitions are not included to this poster.

COMPREHENSIVE LIST OF FUNDING ASSESSMENT CRITERIA

Eventually, the complete dataset included 330 criteria, which were processed and finally 35 criteria were defined.

- Aligned mission
- Clarity of objectives
- Phase of R&D
- Patent status of the investigated drug
- Infrastructure for development and production
- Patient involvement
- Patient centricity
- Equity in terms of process and impact
- Stakeholder mapping
- Competition in the environment
- Commitment of the pharmaceutical industry
- Project leadership
- Project team
- Approach, methodology and concept of the project
- Ethical principles
- Feasibility of the project and workplan
- Budget plan
- Innovative potential
- Risk management plan
- Social return on investment
- Financial return on investment
- Funding mechanisms
- Disease burden for the patients
- Disease burden for the close environment of the patients
- Disease burden for the society at regional or global level
- Disease burden for the health & social care system
- Availability / accessibility of scientific evidence
- Unmet need
- Benefits to patients / Added therapeutic value
- Benefits for beneficiaries beyond patients
- Benefits to society at regional or global level
- Benefits for the health & social care system
- Sustainability of the project
- Capacity building
- Dissemination plan

NEXT STEPS

In the process of creating a standardized tool for the assessment of DR projects, the following steps will be undertaken:

- Specifying metrics and methodologies to each criterion (Q2 2024)
- Validation of defined criteria with REMEDi4ALL partners and members of the REMEDi4ALL Funders Network (Q2-Q3 2024)
- Platform development for the tool (Q4 2024)
- Testing of the platform with Funders Network members (Q1-Q2 2025)

CONCLUDING REMARKS

The lack of broadly accepted methods and approaches for assigning quantifiable values to patient and societal benefit can be a major barrier to establishing a partnership or collaboration to enhance drug repurposing projects [3].

Therefore, the tool developed in REMEDi4ALL could not only help to evaluate and justify R&D funding decisions at an earlier stage but could also contribute to bridging discrepancies in value assessment across different stakeholders.

1. Petykó, Z. I., Kaló, Z., Espin, J., Podrazilová, K., Tesař, T., Maniadakis, N., Fricke, F. U., & Inotai, A. (2021). Development of a core evaluation framework of value-added medicines: report 1 on methodology and findings. Cost effectiveness and resource allocation: C/E, 19(1), 57.
2. Verbaanderd, C., Rooman, I., & Huys, I. (2021). Exploring new uses for existing drugs: innovative mechanisms to fund independent clinical research. Trials, 22(1), 322.
3. Krishnamurthy, N., Grimshaw, A. A., Axson, S. A., Choe, S. H., & Miller, J. E. (2022). Drug repurposing: a systematic review on root causes, barriers and facilitators. BMC health services research, 22(1), 970.

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ProfhEX
AI-driven platform enabling drug repurposing by in-silico polypharmacology estimations

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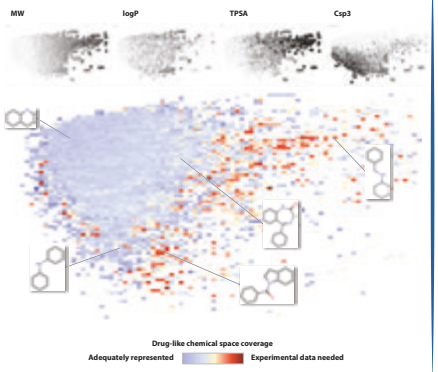
Repurposing is a viable strategy for uncovering novel indications for already approved drugs, as they have the potential to synergistically interact with multiple targets. However, assessing a drug's pleiotropic effect is strongly limited by the scarcity of experimental evidence on drug-target interactions. In-silico simulations play an important role in supplementing missing experimental annotations: ProfhEX is a suite of AI-driven models capable of estimating potential interactions between drugs and therapeutically relevant targets, thereby proposing new drug repurposing strategies.

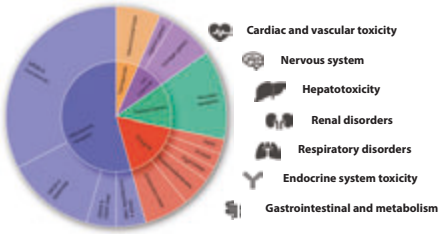
Platform

A first version of ProfhEX focusing on safety profiling has already been published [1], featuring >250K activity data over 46 targets. Models have been generated within the SASviya environment, leveraging state-of-the-art machine learning algorithms, chemistry-aware molecular descriptors "DompeKeys", consensus modelling, applicability domain, uncertainty evaluation and enhanced interpretability.

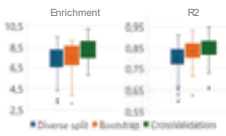
Applicability domain: >85 % of the drug-like chemical space is well-represented by ProfhEX models



Available models: each ProfhEX model is linked to a specific system organ class (SOC) toxicity, exploiting >1M drug-target side-effects annotations

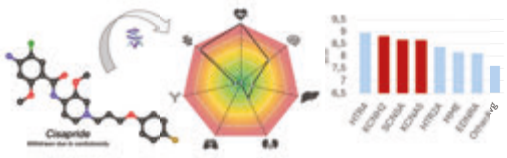


Performance: by coupling a comprehensive validation protocol and the FDA-certified SAS platform, ProfhEX models ensure the highest level of validation and transparency



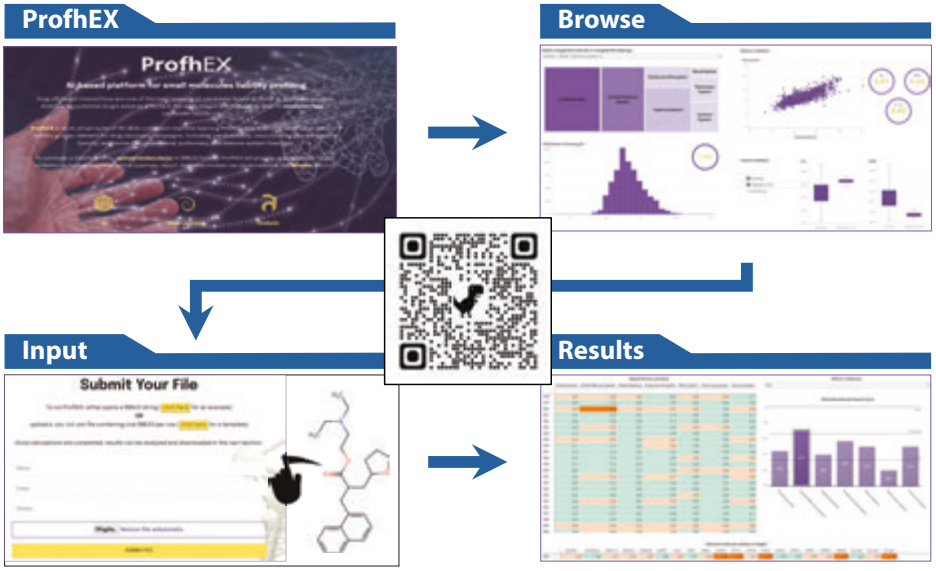
Encoding: DompeKeys [2] is a novel hierarchical-based descriptor for efficient chemical space mapping, structural moieties interpretation and machine learning

Interpretability: a compound's liability profile is associated to its polypharmacology, providing insights for MoA interpretation



Access

ProfhEX is freely available as webservice enabling high-throughput screening of molecules in a secure, code-free and intuitive cloud environment (https://profhex.exscalate.eu/)



R4ALL Impact

ProfhEX provides estimations for drug-target interactions involving >600 therapeutically relevant targets, offering researchers a freely accessible tool for evaluating new drug repurposing hypotheses. Additionally, the platform can estimate >30 ADME endpoints and identify the most probable metabolic pathways, enabling comprehensive polypharmacological molecule profiling. Therefore, ProfhEX is well-suited to empower R4ALL activities through in-silico driven discovery of new mechanisms of action.

[1] *"ProfhEX: AI-based platform for small molecules liability profiling"*, 10.1186/s13321-023-00728-6, Journal of Cheminformatics
[2] *"DompeKeys": a novel substructure-based descriptor for an efficient chemical space mapping and structural moieties interpretation in Machine Learning models, accepted paper, Journal of Cheminformatics.*

INTERNATIONAL DRUG REPURPOSING CONFERENCE

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