Drug Repurposing Guidebook

Building Block I454

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Combinations of drugs
References	• Drug combination and repurposing for cancer therapy: the example of breast cancer: DOI: 10.1016/j.heliyon.2021.e05948 • Drug Combinations: A New Strategy to Extend Drug Repurposing and Epithelial-Mesenchymal Transition in Breast and Colon Cancer Cells; DOI: 10.3390/biom12020190 • Evaluation of synergism in drug combinations and reference models for future orientations in oncology; DOI: 10.1016/j.crphar.2022.100110 • Combinational Drug Repurposing from Genetic Networks Applied to Alzheimer's Disease; DOI: 10.3233/JAD-220120 • The repositioned drugs disulfiram/diethyldithiocarbamate combined to benznidazole: Searching for Chagas disease selective therapy, preventing toxicity and drug resistance; DOI: 10.3389/fcimb.2022.926699 • Synergistic drug combination effectively blocks Ebola virus infection; DOI: 10.1016/j.antiviral.2016.11.017 • Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria; DOI: 10.1038/emi.2016.123 • Combining biomedical knowledge graphs and text to improve predictions for drug-target interactions and drug-indications; DOI: 10.1142/9789811215636_0041 • Therapies for rare diseases: therapeutic modalities, progress and challenges ahead; DOI: 10.1038/s41573-019-0049-9 • Drug Repurposing for Glioblastoma and Current Advances in Drug Delivery-A Comprehensive Review of the Literature; DOI: 10.3390/biom11121870 • Drug Repositioning in Glioblastoma: A Pathway Perspective; DOI: 10.3389/fphar.2018.00218

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Description	Drug combination is a strategy consisting of the administration of two or more drugs. It may allow for enhanced therapeutic activity by targeting multiple pathways in the condition of interest. Additive or synergistic drug combinations using approved drugs identified from drug repurposing screens might be more effective overcoming the problem of limited activity of individual drugs or the emergence of resistance. Examples of scientific literature on drug combination is provided, illustrating different approaches.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development resource
Geographical scope	International
Availability	Applicants interested in drug repurposing in areas where there is a strong scientific rationale for combine two or more medicines
Scope of use	This BB provides examples to explore drug combination as a new strategy to extend drug repurposing
Stakeholders involved	• Drug developers including pharmaceutical companies • Academic researchers • Clinical researchers
Enablers/ Requirements	Understanding of drug interactions, understanding the pathology of the condition which allows for scientific rationale for combination therapy
Output	A tool to explore drug combination as a new strategy to extend drug repurposing opportunities
Best time to apply and time window	At the beginning of the clinical development
Expert tips	**PROS:**

ITEM	DESCRIPTION
	• Drug combination may be more effective than monotherapy, providing additional patient benefits. **CONS:** • Tolerability and adverse events may be an issue • Clinical trials may be required to test combinations of potential repurposed agents to demonstrate efficacy and determine the risks / side effects, need to understand potential drug-drug interactions and to find new optimal dosing and formulation. • Could be a higher economic burden associated with combination therapy in the rare disease context • Strategy increasingly evaluated in anti-tumor and anti-viral therapies but less explored in the rare disease field.