Drug Repositioning
Approaches and Applications for Neurotherapeutics

Edited by
Joel Dudley
Laura Berliocchi

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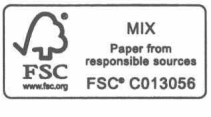

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Drug Repositioning

Approaches and Applications for Neurotherapeutics

FRONTIERS IN NEUROTHERAPEUTICS SERIES

Series Editors
Diana Amantea, Laura Berliocchi, and Rossella Russo

Drug Repositioning: Approaches and Applications for Neurotherapeutics
Joel Dudley, Mount Sinai School of Medicine, New York, New York, USA
Laura Berliocchi, Magna Græcia University, Catanzaro, Italy

Mapping of Nervous System Diseases via MicroRNAs
Christian Barbato, Institute of Cell Biology and Neurobiology (IBCN), Rome, Italy
Francesca Ruberti, Institute of Cell Biology and Neurobiology (IBCN), Rome, Italy

Rational Basis for Clinical Translation in Stroke Therapy
Giuseppe Micieli, IRCCS, Pavia, Italy
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Preface

A better understanding of many nervous system disorders and their effective treatment represents an important scientific challenge and an increasing concern for health systems worldwide, due to the chronic nature of some of these conditions and their high incidence especially in the increasing aging population. In spite of significant financial and professional investments, and great advances made during the past two decades, the fundamental etiology and pathophysiology of many diseases affecting the nervous system remain unclear, and effective disease-modifying therapies are still lacking. The reasons for such a failure in developing new effective therapeutics for nervous system disorders are several and of different nature. The intricate biology of the nervous system itself, together with the complexity and slow progression of these specific pathologies, made it difficult to understand the basic disease mechanisms and to identify appropriate end points and biomarkers, essential in achieving an accurate stratification of patients' populations. Indeed, patients' heterogeneity, lack of reliable biomarkers for both diagnosis and treatment, and slow progression are some of the factors responsible for the failure of many clinical trials. Furthermore, limitations related to the uncertain predictive validity of animal models seem to have interfered with the successful identification of safe and/or effective new candidate drugs, and contributed to the high rate of late-stage clinical trial failures, for instance in the case of drugs acting on the central nervous system.

In addition to the existing biological reasons, regulatory barriers seem to have contributed to make *de novo* drug discovery and development for nervous system diseases a lengthy, costly, and risky process. Although this is particularly true for drug development in the field of neuroscience, in recent years it has become more and more clear that, in general, the whole traditional paradigm of R&D needed some rethinking. Over the last decade, increasing pharma R&D costs were not paralleled by increased productivity. On the contrary, the relationship between the investments to develop new innovative drugs and the outcome in terms of the resulting medical and financial benefits dramatically decreased, and only very few new drugs were approved.

Among the possible alternative approaches to *de novo* drug discovery, drug repositioning seems to be one of the most promising strategies to develop therapeutic options for currently unmet medical needs. Drug repositioning or repurposing or reprofiling (the terms are sometimes used interchangeably) refers to a designed way to identify new applications for existing drugs, at any stage of their long developmental or clinical path. This also includes drugs that have been shown to be safe but not effective for the indication they were originally developed for or, to the extreme, drugs investigated but not further developed or even removed from the market for safety reasons (drug rescue).

Thanks to the most recent advancements in technologies, including *in vitro/in vivo* screening approaches and computational tools such as bioinformatics, chemoinformatics, network biology, and system biology, the drug repositioning concept has flourished and moved from casual discoveries to targeted strategies.

Repositioning shows several advantages over traditional *de novo* drug discovery, such as reduced development costs and shorter time to approval and launch, and is emerging as a particularly attractive approach for several pathologies including rare and neglected diseases. Although with some challenges, the recovery of failed compounds for new indications clearly represents an interesting business opportunity for the industry, as also shown by the creation of *ad hoc* partnerships between big pharma, academia, and governments. Also from a social standpoint, conveying existing data and knowledge toward new therapeutic applications stands as a highly ethical way to maximize the use of patient information, and several nonprofit organizations have launched programs specifically aimed to support drug repurposing projects and initiatives.

It is clear that collaboration between different entities is key to the success of this attractive and complex new strategy in improving and accelerating therapeutic development for nervous system disorders.

Renowned experts from different settings (academia, industry, nonprofit organizations) will discuss all these aspects in the present volume of the series Frontiers in Neurotherapeutics. The book aims to provide an overview of drug repositioning applications specific to neurotherapeutics and is organized in three sections, each composed of several chapters. *Section I* introduces the concept and rationale of drug repositioning, illustrates the different possible challenges in repurposing by analyzing the cases of Alzheimer's and Parkinson's diseases, and describes the contribution of nonprofit research organizations. *Section II* illustrates the evolution of drug repositioning from a serendipitous advance to a precise strategy, providing some examples of techniques and tools used for the identification of new applications for existing compounds. *Section III* focuses on drug repositioning relevance specifically for nervous system diseases, providing some historical examples and analyzing in individual chapters the status of some of the main nervous system conditions (Alzheimer's, Parkinson's, and Huntington's diseases; amyotrophic lateral sclerosis; spinal muscular atrophy; ischemic stroke; and psychiatric disorders).

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Editors

Dr. Joel Dudley is associate professor of genetics and genomic sciences and director of biomedical informatics at Mount Sinai School of Medicine, New York (NY, USA). Prior to Mount Sinai, he held positions as cofounder and director of informatics at NuMedii, Inc., and consulting professor of systems medicine in the Department of Pediatrics at Stanford University School of Medicine (CA, USA), where he participated in leading research to incorporate genome sequencing into clinical practice. Dr. Dudley's current research is focused toward solving key problems in genomics and precision medicine through the development and application of translational and biomedical informatics methodologies. His publications cover the areas of bioinformatics, genomic medicine, personal and clinical genomics, as well as drug and biomarker discovery. He received a BS in microbiology from Arizona State University and an MS and a PhD in biomedical informatics from Stanford University School of Medicine (CA, USA).

Dr. Laura Berliocchi is associate professor of pharmacology at the Department of Health Sciences, Magna Græcia University (Catanzaro, Italy). She is leading the Pain Unit at the Center of Preclinical and Translational Pharmacology (University of Calabria, Italy), whose research activity is focused on a better understanding of the neurobiology of pain for more effective clinical treatments. Her latest research activity is focused on the role of autophagy in neuronal dysfunction and on the identification of new strategies for pain management. She received a BSc (Hons) in biology from the University of Rome "Tor Vergata" (Italy), a specialization degree in biotechnologies from the same university, and a PhD in molecular toxicology from the University of Konstanz (Germany). She was a research associate at the Medical Research Council (MRC; Leicester, UK), working on the effects of synaptic and axonal damage on neuronal function and survival, then a London Pain Consortium (LPC) senior research fellow and a scientific visitor at University College London (UCL; London, UK), where she trained in experimental models of pain and worked on mechanisms of pain control. She is a *Deutscher Akademischer Austauschdienst* (DAAD) alumna.

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Contents

Section I

The Rationale and Economics of Drug Repositioning

1 Scientific and Commercial Value of Drug Repurposing

David Cavalla

CONTENTS

1.1 INTRODUCTION

Drug repurposing is a directed strategy to identify new uses for existing drugs, to be embarked upon at any stage in their developmental or clinical life. For pharmaceutical R&D, the benefits are clear: alongside reduced risk of developmental failure, there is demonstrable reduced cost and time of development. While historically many examples of repurposing arose from serendipitous clinical findings, modern repurposing has other skills in its toolbox; it may also derive from literature-based methods, deliberate *in vitro* or *in vivo* screening exercises, or *in silico* computational techniques to predict functionality based on a drug's gene expression effects, interaction profile, or chemical structure.

From the earliest times of medicine, doctors have sought further uses for available treatments. Traditional folk medicines are often proposed for the treatment of a bewilderingly wide range of purposes. The keystone in the process of new uses for existing drugs is the physician; they approach the issue using the principle of "clinical relatedness," whereby if a drug is useful for condition A, it is likely to be useful for a related condition B.