



ELSEVIER

 DRUG DISCOVERY
 TODAY
 THERAPEUTIC
 STRATEGIES

Drug Discovery Today: Therapeutic Strategies

Vol. xxx, No. xx 2011

Editors-in-Chief
Raymond Baker – formerly University of Southampton, UK and Merck Sharp & Dohme, UK

Eliot Ohlstein – GlaxoSmithKline, USA

Drug repurposing

theraTRACE[®]: a mechanism unbiased *in vivo* platform for phenotypic screening and drug repositioning

 Michael S. Saporito^{*}, Andrew G. Reaume

Melior Discovery Inc., 860 Springdale Drive, Exton, PA 19341, United States

Drug repositioning is an emerging strategy for filling the innovation gap in the pharmaceutical industry. Successful drug repositioning examples are nearly always explained by observations made in clinical settings or in *in vivo* therapeutic models. We have established an *in vivo* phenotypic platform, termed **theraTRACE[®]** that systematically evaluates and repositions drugs to new indications. This review article describes examples of drugs found using phenotypic models and the concepts behind the **theraTRACE[®]** approach.

Introduction

There has been a growing realization that complementary and alternative approaches to molecular target-based drug discovery are required to expand drug pipelines and bridge the pharmaceutical industry innovation gap. Repositioning of development stage and approved drugs to new indications has emerged as a productive but poorly exploited strategy for expanding these drug pipelines. For development stage and abandoned drugs, various strategies have been utilized to identify novel indications for existing drugs or candidates. These strategies include *in silico*, *in vitro* and cell-based biological systems. However, nearly all drug repositioning events can be attributed to therapeutic observations made *in vivo* biological settings including both preclinical animal and human clinical studies (Table 1). *In vivo* therapeutic activities,

Section editor:

Christopher A. Lipinski – Melior Discovery, Waterford, CT 06385-4122, USA

unlike *in silico*, *in vitro* or cell-based responses, are driven by factors that include the drugs pharmacokinetic (PK) properties, its known and unknown molecular target interactions and its effects on complex biological networks [1,2]. However, relying on detecting a serendipitous effect in the clinic is not the most efficient drug repositioning strategy. We have developed, and will describe in this review, an optimized preclinical *in vivo* efficacy platform that is an efficient and effective platform for rapidly and efficiently repositioning drugs and drug candidates to new indications.

Off-label prescribing as a metric for drug repositioning potential

Off-label prescribing rates are a good metric for describing the potential of drug repositioning. At least 20% of drugs are prescribed 'off-label' [3]. When examining cardiac and anti-convulsant drugs the rate of off-label prescribing rises to 80% [3]. Some well-known examples include the VEGF inhibitor and anticancer agent bevacizumab that is also used for macular degeneration; the anti-convulsant and analgesic agent gabapentin that is also used for bipolar disorder (among other disorders), and the anti-convulsant topiramate used for migraines, bipolar disorder and eating disorders [4–6]. These off-label data examples highlight the pleiotropic effects of biologically active compounds and the potential of drug repositioning as a strategy for increasing drug utilization.

^{*}Corresponding author.: M.S. Saporito (msaporito@melior-discovery.com)