Establishing the UM Re-Targeting Discovery Platform: Creating Pilot Translational Infrastructure for Drug Repurposing

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Executive Summary: This exploratory biosciences initiative seeks to build a pilot drug-repurposing resource for the University of Michigan that will capitalize on its strenths in biomedical and clinical research to rapidly address unmet medical needs. This resource will consist of a drug repurposing compound collection that can be used across campus in drug discovery efforts and a corresponding informatics platform to catalog all compounds and associated clinical trial data, pharmacokinetics/metabolism, mechanism of action, all with links to the scientific literature, patents and regulatory databases.

The ultimate vision for building this resource is to acquire and curate all clinically-evaluated compounds (~10,000 total) from commercially-available sources where possible (~5,000) and synthesize the remaining portion (~5,000). An additional part of this resource is to build a compound quality control infrastructure and develop ongoing data mining procedures for new clinical compounds to ensure the library remains current. While this is a beyond the scope of an exploratory BSI, herein we seek to demonstrate the utility of our approach by building a pilot repurposing library of 1,000 compounds.

The traditional drug development process has a timeline of 11–18 years and costs approximately $1–3 billion dollars to bring a novel drug to market. This results in decades-long delay between advances in basic biomedical science and effective therapies for unmet medical needs. Additionally, over the past 30 years across all therapeutic areas, only 9% of drugs evaluated in clinical trials are ever approved. This situation presents a unique opportunity for drug repurposing - to leverage the wealth of compounds that have entered clinical trials for new/alternate indications with the goal of dramatically shortening the drug development timeline. Discovering new uses for existing drugs can offer the shortest path from the drug discovery phase to clinical use as well as reduced cost of development and reduced risk in commercialization. This approach has numerous advantages that rely on existing knowledge about the drug. The most important of these advantages include a known safety profile, reduced regulatory burden for entry into clinical trials, and knowledge of drug manufacturing and formulation.

In vitro screening of FDA-approved drugs libraries has been widely available for several decades and have led to many successes in repurposing. An example that underscores the potential for drug prepurposing is thalidomide. Originally approved for insomnia (and notorious for causing birth defects when given to pregnant women to treat nausea), thalidomide has been repurposed as an immuno-oncology drug with global total revenue of $2.8 billion.

While FDA-approved drug libraries can produce interesting lead molecules, a considerable and untapped resource for drug repurposing is in the expansion of bioactivity-based chemical libraries to include clinical candidate compounds that have either failed for their primary indication or are in clinical development. Indeed, there are over 10,000 drugs that have reached the clinic in the US and Europe, but no complete collection

exists, and less than half of clinical candidate molecules are commercially available. Even though half of these molecules are commercially available as individual compounds, a comprehensive library formatted for bioassay screening is not currently available and this poses a considerable hindrance to drug repurposing efforts. Existing drug repurposing libraries are out-of-date and omit the most recent and most valuable compounds (developed against targets within the past 5-years).

In this proposal, we will address this critical gap in drug repurposing by developing a comprehensive database containing the structures, mechanism of action/target, associated pre-clinical safety, and phase-I clinical trial outcomes. With chemo/bioinformatics support, we will prioritize the list of clinically evaluated compounds (approximately 10,000) for acquisition and synthesis to generate a drug repurposing library of 1,000 compounds that represent maximal diversity in biological activities and chemical structure. This resource will be housed in the Center for Discovery of New Medicines (CDNM) within the Life Sciences Institute and will be screened as a first step in most high-throughput screening campaigns to deliver early and highly translatable “hits”, and can help to connect molecular targets with clinically relevant outcomes in phenotypic screening.

The overarching goal of this drug repurposing platform is to provide basic and clinical researchers at the University of Michigan with a readily accessible resource for drug repurposing. Positive “hits” from this compound collection can lead to numerous beneficial outcomes including: translatable hits that can be evaluated directly for efficacy in Phase-II/Phase-IIB clinical trials, connecting new molecular targets/pathways with diseases to enhance basic science understanding of disease etiology and offer new avenues for exploration, and will provide researchers with a pilot screening platform to evaluate their in vitro assays in a highly annotated, biologically active context.