

## Article

# Drug Repositioning as a Pharmaceutical Strategy: The Obvious Benefits are Real but Beware of Pitfalls That May be Less Apparent

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## ABSTRACT

For the last 15 years the drug discovery strategy referred to as “drug-repositioning” has been a recognized approach towards bringing new therapeutics to market and has continued to grow in popularity over this time frame. Melior Discovery is a company with a founding mission centered on drug repositioning. The author shares his perspective on lessons learned over 15 years of conducting drug repositioning efforts, complete with advantages and disadvantages that he has encountered using this approach and why, overall, this means of drug discovery provides a compelling business rationale.

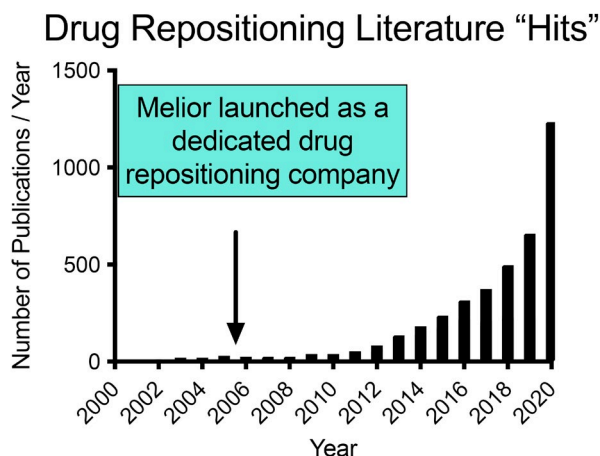
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## DISCUSSION

The concept of drug-repositioning (aka drug repurposing, drug reprofiling, indications discovery) emerged in the early 2000’s as a strategy to address the pharmaceutical “innovation gap”—a phenomenon which was first identified around the opening of the 21<sup>st</sup> century wherein, despite increases in R&D investment, research productivity, as measured by new drug approvals, was declining. The basic notion is simple enough; if one can take an existing drug and find a new therapeutic application for it then the savings in time and money could be enormous compared to the years of preclinical and clinical research and millions of dollars associated with just getting a drug up to the clinical stage. For example, consider the journey of a drug candidate, down the long path that it must cross before becoming a marketed drug. In the pre-clinical stage alone, many thousands of compounds will be tried and will fail for a wide range of reasons, from having poor solubility, to poor stability, to a host of reasons associated with toxicity – and this is over and above the challenges in identifying compounds that by some measure have achieved the efficacy goals set in place in the preclinical stage. The compound that makes its way through the gauntlet of hurdles and actually becomes a clinical candidate then truly is a “privileged” compound with rarified attributes by chemical matter standards.

However, as has been well-documented, even then only about one in ten compounds that enter the clinic will ever clear the additional clinical hurdles that lie ahead to go on to become a marketed drug. About half of the drugs that are discontinued in the clinic are stopped because of some safety or tolerability issue that had not been identified pre-clinically. Imagine if one could start off with compounds that had already traversed all of these stage gates and were known to be reasonably safe and well-tolerated in humans not to mention having all of the other properties that we look for in a drug-like molecule: favorable solubility, stability, ease of synthesis etc., and we found a new therapeutic use for it. The business rationale for this approach seems compelling indeed. In fact, this approach is increasingly being appreciated as a viable drug discovery strategy as evidenced by its increasing presence in the industry literature (Figure 1).

Melior Discovery was launched in 2005 as a company with a core mission around drug repositioning. From our more than 16 years of pursuing this strategy we are able to provide perspective on the pros and cons of the approach. While we have found patentable new therapeutic uses for more than half a dozen clinical stage candidates, MLR-1023 represents our lead compound that has advanced furthest. Therefore, for the purposes of this discussion, I will focus my attention on that program.



**Figure 1.** The prevalence of drug repositioning in the literature. This graph shows the number of papers published on the topic of drug repositioning by year as judged by PubMed search using the criteria “drug reposition\*[Title/Abstract]) OR drug reprofil\*[Title/Abstract]) OR drug repurpos\*[Title/Abstract])” and the publication year. Melior Discovery as a drug repositioning-focused company was founded in January of 2005.

In regards to the core attributes of drug repositioning as a discovery approach MLR-1023 has achieved these benefits and illustrate it well. The compound was first identified by Melior as an ideal repositioning candidate based upon our familiarity with its history. It was a discontinued Pfizer gastric ulcer candidate that had been run up through Phase 2a studies in subjects with gastric ulcer. With 187 patient exposures with a cumulative of 7.5 patient-years, the safety and tolerability appeared to be excellent. Otherwise, the drug seemed to have all of the features that one looks for in a desirable candidate with favorable physical-chemical properties, good oral bioavailability etc. Although the drug was discontinued by Pfizer due to lack of efficacy in gastric ulcers it was clearly biologically active as judged by the animal data that preceded the clinical studies (i.e. the drug was doing something). This compound pre-dated the era of target-based medicinal chemistry where one originates a chemistry program by screening chemical libraries against a molecular target of interest, such as an enzyme or receptor that is believed to be important in a disease process. Instead, this compound was identified as a compelling candidate by screening a series of compounds in an animal model of gastric ulcer. As such, the molecular target of MLR-1023 was not known by Pfizer.

In our first year of operation Melior took MLR-1023, along with two other drug repositioning candidates, and screened them in our proprietary phenotypic screening

platform (*theraTRACE*) which is comprised of an array of animal models of disease representing broad therapeutic area spectrum. MLR-1023 presented a clear pattern of activity in models related to metabolic disease including improved glycemic control in an oral glucose tolerance test, reduced weight gain on high fat diet and improved tolerance to cold environment (Figure 2). A series of follow-on studies over the next year and a half revealed that MLR-1023 was an insulin sensitizer that worked through a previously undescribed mechanism of action, lyn kinase activation<sup>1, 2</sup>. Melior secured exclusivity for the use of MLR-1023 as a diabetes therapeutic with the issuance of method-of-use (MOU) patents in countries around the world representing all of the global major pharmaceutical markets. Eventually, Melior filed an IND for clinical investigation of MLR-1023 in diabetic subjects and was able to take the compound directly into type 2 diabetic subjects without having to first run through Phase 1 studies in healthy volunteers as is the normal sequence of clinical candidate progress. The results of the clinical studies recapitulated the established animal pharmacology for metabolic disease thereby validating the novel drug discovery approach that we had used to uncover MLR-1023 (Figure 3). In these ways, our experience with MLR-1023 achieved all of the promise of a drug repositioning strategy. We were able to identify a clinical candidate with about 6-9 months of work with less than \$500,000 of cost and progress to IND-ready within a year for less than \$ 2 million invested. The compound was then able to shortcut the clinical trial process with the years in time savings and cost savings of several million dollars of investment. Moreover, we had high confidence that our clinical candidate would not be discontinued due to safety and tolerability issues as about 50% of clinical candidates are. Finally, despite the belief of some critics that method-of-use (MOU) patents do not provide a rigorous exclusivity strategy, I believe that we have proven, by way of our advanced discussions with several multinational pharma candidate partners, that in the context where a drug has not had previous market exposure, MOU patents do indeed provide a sound exclusivity mechanism.

But to describe our experience of drug repositioning in an objective and balanced way I have to point out the challenges. One thing that I omitted in the brief summary provided above was timelines. Although the discovery of a new use of MLR-1023 was fast and our scientific description of its mechanism was also relatively fast and cost-effective by industry comparables, in fact we did not have an approved IND until about 4 years later and our clinical study did not recruit the first patient until about 9 years after patent filing. These delays were partly inherent to the repositioning approach. The example of drug repositioning benefits that I described above involving

## MLR-1023: *thera*TRACE® Dashboard

			Dose (mg/kg)		
			1.2	6	30
<b>Metabolic Diseases</b>					
	Oral Glucose Tolerance Test				
	Standard Diet-Food intake				
	Standard Diet Weigh Gain				
	Western Diet-Food intake-Chronic				
	Western Diet-Body Weight Gain				
	Western Diet-Leptin levels				
	Cold sensitivity				
	Stress-induced corticosterone				
	Food intake after 2 hour fast				
<b>Neuropsychiatric</b>					
	Forced Swim Test				
	Tail Suspension Test				
	Open Field				
	Pentylenetetrazole-induced seizure				
	Maximal Electroshock seizure				
<b>Modified Irwin Battery (3 strains)</b>					
	In-cage observations				
	Suspended tests				
	Autonomic responses				
	Fecal pellet #				
<b>Neurodegenerative</b>					
	Experimental Autoimmune Encephalomyelitis				
	MPTP dopamine				
	MPTP Open Field				
<b>Pain and Analgesia</b>					
	Hot Plate				
	von Frey w/ carrageenan				
	Formalin test				
	Carrageenan paw inflammation				
<b>Inflammation and Immunological</b>					
	LPS-induced IL-6				
	LPS-induced TNF- $\alpha$				
	Collagen-induced Arthritis				
	Delayed-type Hypersensitivity				
	OVA Pulmonary Inflammation-induced MCP1				
	Monocyte infiltration MCP1				
<b>Gastrointestinal</b>					
	Colonic Propulsion Test				
	Morphine-induced constipation				
<b>Urogenital</b>					
	Diuretic-induced stress (micturition)				
<b>Cardiovascular</b>					
	Bleeding time				
	Aldosterone				
	Angiotensin I/Angiotensin II				
<b>Sexual Health</b>					
	Testosterone				
<b>Dermatology</b>					
	Sebum Production				

<b>PK Summary</b>		
Route of Administration	i.p.	
Dose Frequency	b.i.d.	
AUC (blood, ng x hr/ml)	4,777	
Cmax (ng/ml)	6,545	
Tmax (hr)	0.25	
% i.p. Bioavailability	53.9	
% Brain penetrance	1.3	
MTD (mg/ kg)	100	

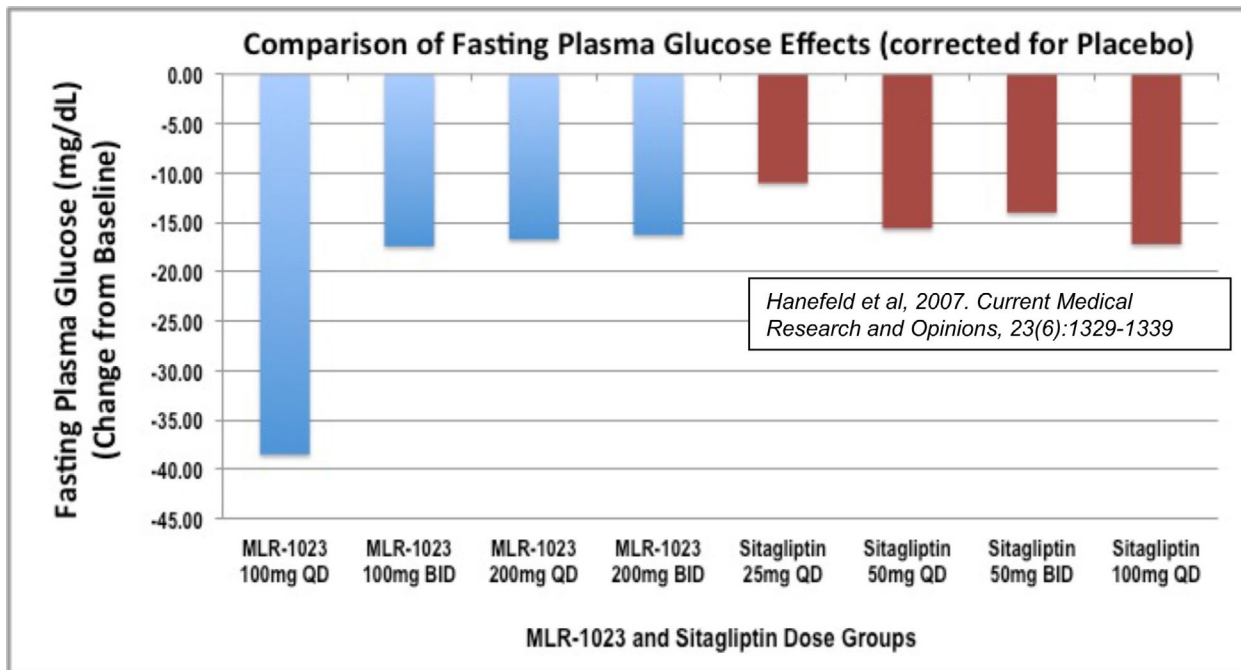
<b>Key</b>	
	Inactive
	Linear Trend
	Statistically significant vs. vehicle
MED	Minimum effective dose

**Figure 2.** The original phenotypic screening data for MLR-1023. This dashboard or heat map view of data from 35 different animal models covering a broad therapeutic area spectrum across 3 dose levels reveals a pattern of activity that was observed around models related to metabolic disease.

clinical development shortcutting that was achieved by working with a clinically experience drug would not have been possible without first accessing the clinical dossier from the originator, Pfizer. This however, took a considerable period of time to negotiate and ultimately procure files from deep archives of a large bureaucratic organization. In addition, although I made the statement above that we have shown that MOU patents, on a drug for which composition-of-matter (COM) patents have expired, provides a rigorous exclusivity strategy, it nonetheless has proven to represent an impediment insofar

that there are still licensing executives in this industry who do not, or at least did not, clearly understand this. This created an added challenge when entering partnering or investor discussions, thereby slowing our progress to bring on the needed capital necessary for initiating clinical trials.

There are other challenges associated with bringing a drug to market for which the drug repositioning strategy did not provide any advantages. The first of these that we encountered could be summarized under the heading “The world changes faster than our programs can evolve”.



**Figure 3.** MLR-1023 phase 2a study: Toplevel results comparison with sitagliptin. This figure shows data for the primary endpoint of this 4-week study: Change from baseline of fasting plasma glucose levels compared to placebo. The sitagliptin data come from the Hanefeld et al (2007) published data<sup>3</sup>. In addition to benefits on glycemic control, MLR-1023 exhibited benefits towards adiposity and lipid levels as well, consistent with animal model results.

In our case we committed ourselves to pursuing MLR-1023, and directed our company resources, toward type 2 diabetes in late 2005. By 2008 the FDA, in response to issues that arose with the drug rosiglitazone (Avandia<sup>®</sup>), issued new guidelines for developing drugs in type 2 diabetes which would significantly increase the time and expense to complete these clinical programs. Almost overnight, type 2 diabetes went from an indication that was favored by venture capitalists to being shunned. Most mid-sized and smaller pharma companies exited the area while the large multi-nationals that remained became much more risk-averse as a result of this decision by the FDA. This had the effect of increasing our “headwind” on a program that we now felt committed to given our years of time invested and committed capital—not to mention that we firmly believed that the drug had a unique and compelling profile that needed to be pursued.

The list of challenges that I have cited so far (procuring a dossier, overcoming misperceptions of MOU protected therapeutics, pursuing an indication that has fallen out-of-favor with investors) all contributed to slowing our rate of progress. In turn, this contributed to another major challenge for which a drug repositioning strategy could not serve to mitigate really—the shrinking exclusivity window. By 2018 we had achieved a successful Phase 2 study with MLR-1023 in diabetic

subjects and achieved proof-of-concept for a novel class of insulin-sensitizer that was not associated with the liabilities otherwise associated with all other existing insulin-sensitizers. We entered into partnering discussion with prospective large pharma companies interested in this product. Their scientific due diligence teams were encouraged by the clinical safety and efficacy profile. Their patent attorney teams were satisfied with the patent portfolio. Commercial assessment that we conducted around this time projected potential peak sales opportunity, because of its unique profile, of greater than \$1 billion /year. And yet, the net present value calculations conducted by Melior and our prospective pharma partners at this time both came up with values that were hovering around break even because of the short market exclusivity that was remaining for a product which probably would not be launched until around 2026. The lesson that is clearly illustrated here is that, as difficult as it is to achieve favorable clinical safety and efficacy for a drug candidate, those attributes alone are necessary but not sufficient to reach market approval.

But to end this story on a more hopeful note I will point out that there is still light at the end of this tunnel. In the course of our investigating the role of MLR-1023 in diabetic mouse models, we uncovered tremendous pancreatic beta cell preservation qualities of the drug and

filed patents for this use. That aspect of the story has continued to develop to the extent that within the last couple of years, independent investigators have shown that MLR-1023 is capable of inducing beta cell proliferation in beta cells harvested from human cadavers—a cell type previously not thought to be proliferation competent. Type 1 diabetes (T1D) is an autoimmune disease wherein the immune system attacks pancreatic beta cells; cells responsible for the production of insulin. While frank T1D occurs when total beta cell mass is depleted below a threshold capable of producing sufficient amounts of insulin to maintain glycemic control, about 30% of stable type 1 diabetics have demonstrable amounts of beta cell mass as determined by detectable amount of the insulin synthesis byproduct, C-peptide. Our belief is that if C-peptide positive type 1 diabetics are treated with MLR-1023 then we will be able to expand their beta cell mass thereby reducing their insulin requirements and perhaps even curing their diabetes. As a pre-clinical proof-of-concept, the investigator who has found that MLR-1023 causes proliferation of human beta cells in cadavers has also cured diabetes in a mouse model of T1D. The MOU patents which claim treatment for beta cell preservation extend to 2031 before patent term extension, and most likely to 2036 with patent term extension. This, coupled with the fact that clinical trial program requirements for T1D are shorter and significantly less costly than for T2D, drastically lowers the hurdle rate for commercial requirements. Our net present value estimates of MLR-1023 in T1D are currently much better than T2D even though T1D is a much smaller patient population.

Our 16 years of experience in the field of drug repositioning have taught us that this is indeed a viable drug discovery approach that basically provides the benefits that people normally associate with drug repositioning with its de-risking advantages, clinical program

short-cutting, and inherent cost savings. But in an endeavor as complicated as drug discovery and development, bearing so many operational aspects, the true picture is never so simple. For example, true regulatory short-cutting may be dependent upon availability of clinical dossiers. Developing a rigorous exclusivity strategy is often more involved than some newcomers appreciate. And of course, if one proceeds expeditiously into the clinic, with rigorous MOU coverage, there are still many daunting challenges to bringing a drug to market that are not mitigated by a drug repositioning strategy. Our story shows that an important tactic to incorporate into any drug development program is speed: i) to partner the program or raise money before the field or regulatory environment changes “beneath one’s feet”, ii) to provide as much market exclusivity given a fixed patent term, and iii) although not illustrated by our story, to beat possible competitors to market and possibly gain first-in-class benefits. If executed thoughtfully and carefully drug repositioning can provide this element of speed needed to achieve great success.

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