Title

Drug Repurposing in Chemical Genomics: Can We Learn from the Past to Improve the Future?

Title Page

TITLE:

Drug Repurposing in Chemical Genomics: Can We Learn from the Past to Improve the Future?

AUTHOR:

William H. Bisson*

Environmental Health Sciences Center
Department of Environmental and Molecular Toxicology
Oregon State University
1007 ALS
Corvallis, OR 97331
United States

*Address correspondence to this author at Oregon State University, Environmental Health Sciences Center, Department of Environmental and Molecular Toxicology, 1007 ALS, Corvallis, OR 97331 United States.
Tel: 1-541-207-5395; Fax: 1-541-737-0497
E-mail: bissonw@science.oregonstate.edu

Abstract

More needs to be done by the private sector to optimize the drug discovery and development pipeline. In addition, significant efforts should also be focused on the understanding of mechanism of diseases, on the characterization of unexplored biochemical pathways and on the validation of new protein targets. Chemical genomics, which uses chemical probes to help understand the complexity of biological systems at the gene and protein levels, has proven in recent years to be an important tool. Experimental and computational chemical genomic screenings have been used by the private sector and recently also by academia and non-profit institutions for drug repurposing or repositioning to find new indications for known drugs. A detailed overview of the current initiatives in drug repurposing, initiated by the major
govermental funding agencies around the world is reported. The push towards greater
efficiency is encouraging drug repurposing and other techniques in chemical genomics. Finding
the best ways to improve translational research and accelerate the regulation of clinical phases
means being able to launch safer drugs into the market faster.

**Keywords**

Chemical Genomics, Clinical Phase, Drug, High Throughput Screening, Repurposing,
Translational Research, Virtual Ligand Screening
1. INTRODUCTION

In the current post-genomic era, all the information obtained from Genome and Epigenome Projects in Human and other eukaryotic organisms must be translated from gene sequence level into 3D-protein space. More effort is needed to investigate and discover new intracellular biochemical pathways and protein targets linked to cancer and other diseases. Medicinal chemists have realized that the chemical space is biologically restrained. On the other hand, in the biological space, there is still much to be explored with the help of chemistry in order to better understand the mechanism of diseases and the action of current drugs.

Chemical genomics, which utilizes chemical probes to investigate the complexity of biological systems at the gene and protein levels, proved to be an important tool in the hands of interdisciplinary teams working in drug design and discovery, biomarker validation and protein target prediction [1-3].

Experimental and computational chemical genomics techniques have been implemented in pharmaceutical companies. Recently they have also entered in non-profit and academic institutions in the USA through NIH-funded initiatives involving Screening Centers such as the Scripps Research Institute and the Sanford-Burnham Medical Research Institute in California, the Vanderbilt University Medical Center in Tennessee and the Center for World Health and Medicine at St. Louis University. In Europe, the Lead Discovery Center GmbH in Dortmund, Germany and the recent SNF-funded Access facility of the NCCR Chemical Biology in Lausanne, Switzerland are successful growing realities.

An important concept fueling ideas, investments, initiatives and interdisciplinary collaborative efforts in chemical genomics is drug repurposing or repositioning, which has been extensively
applied in the last 5-10 years by the private sector and recently also in non-profit/academic efforts [4-6].

The idea behind drug repurposing is the use of old drugs (marketed FDA-approved drugs, FDA-non-approved drugs, or compounds which failed clinical trials) hitting the original or a different protein target for new indications. It started because of the need to speed up drug discovery and development pipelines which on average require 15 years and over a billion USD to bring a drug from a lab bench to the market and thus to the patients. Repurposed drugs would not only help make translational research steps faster but also would facilitate regulatory approval processes, increasing the chance of delivering drugs to the market [7, 8].

Successful experimental drug repurposing techniques involving High-Throughput-Screening (HTS) or an in vivo zebrafish model have been already described [9, 10]. In addition, funding agencies have been encouraging the recent role of non-profit and academic centers and institutions in the use of drug repurposing in finding novel targets against neglected diseases [11]. Virtual Ligand Screening (VLS) of commercially available or purchasable drug repurposing databases have been employed in computational drug repurposing approaches [12, 13]. Database mining in systems biology offers a great opportunity to study side effects (off-target side effects) of known drugs [14].

Pitfalls and limitations of drug repurposing have been considered and significant efforts to correct them has been made so far.

The intention of this article is to report the current initiatives on drug repurposing in the field of chemical genomics, outlining different frameworks around the world, as shown in Fig. (1).
2. DRUG REPURPOSING

2.1. Experimental

The case of Viagra was a successful repurposing case based on serendipity. Clinical trials for male erectile dysfunction were initiated by Pfizer because healthy volunteers taking Sildenafil, a phosphodiesterase (PDE) type 5 inhibitor, under clinical investigation to treat angina, were having spontaneous erections during treatment [15]. Other successful cases have been reported including hyaluronic acid [16] and thalidomide [17].

The first drug repurposing campaigns using HTS started in pharmaceutical companies because of the large number of active molecules stored in their freezers and the lowered cost of screening, which offered the promise of discovering new indications for existing chemistry. Sukhai et al. recently listed new drugs approved by the FDA for oncology in the period 2000-2009 [18]. Interestingly, Sukhai et al. mentioned that experimental drug repurposing opportunities can originate by the understanding of disease biology in a chemical genomics context. These types of studies consider specific mutations causing drug resistance, especially in cancer. The cases of successful kinase inhibitors such as Imatinib (Novartis) and Vemurafenib (Plexxikon-Roche) were reported [18].

Animal models can be also helpful in drug repurposing. The preclinical efficacy in vivo is key prerequisite for a molecule to enter human trials. Recently, the zebrafish model is becoming more attractive to the drug discovery community. This is due to the numerous advantages as a basic research model, per se, and for the variety of possible chemical genomics applications like protein target identification, genetic screens, phenotype-based target and lead discovery, Structure-Activity-Relationship (SAR) studies and toxicology prediction [19]. Since 2005, when
Zon et al. published their interesting article [10], considerable efforts by different academic groups possessing ”in house” zebrafish facilities have been made [19, 20].

A research domain for drug repurposing in academia is the study of neglected diseases [11, 21]. The non-profit network Global Alliance for TB Drug Development is an inspiring initiative dedicated to the finding of new treatments through chemical genomics approaches for tuberculosis [22]. This is one of the recent examples where academia can successfully collaborate with private organizations. Solid initiatives have been recently begun by the National Cancer Institute (NCI) in the USA, as explained below.

2.2 Computational

Experimental approaches in drug repurposing have been ongoing but significant steps have been also made using computational techniques. Repurposing databases for in silico VLS are commercially available [23]. Pharmaceutical companies with their ”in house” databases were the first to screen molecules computationally. In 2007, Bisson et al. published the first paper describing the successful use of in silico drug repurposing to find novel scaffolds inhibiting the Androgen Receptor (AR) [13].

Later, Brian Shoichet and colleagues at the University of California, San Francisco (UCSF), published the important use of FDA-approved database of compounds for VLS techniques in order to predict off-side protein targets. This information is critical when we try to combine clinically more than one drug hitting different targets but aiming for the same phenotypic effect/indication [24, 25].

In this particular context, database mining in systems biology might also represent other types of opportunities in drug repurposing. The publically available program PROMISCOUS is able to
combine data on drugs, proteins and side effects [14]. In this way, researchers can then identify prospective new uses for known drugs by looking at the predictive interaction points available in the PROMISCOUS databases [14].

3. DRUG REPURPOSING: CURRENT DEVELOPMENTS

3.1 USA
In January 2011 the US National Institutes of Health decided to create a strategic partnership between industry, government, academia and non-profit organizations to find future new treatments and cures [26]. The Learning Collaborative initiative combines the expertise of the NIH Chemical Genomics Center (NCGC) with its Therapeutics for Rare and Neglected Diseases (TRND) program, the Leukemia and Lymphoma Society (LLS) and the University of Kansas Cancer Center (KUCC) to discover and develop new drug therapies for rare blood cancers. The aims of this partnership are the discovery and the development of drugs for the treatment for rare blood cancer, whether new molecular entities (NME) or repurposed known drugs, whether approved or not [26].

In addition, the involvement of academia in drug discovery programs is considered an important step. The non-profit organization Partnership for Cures in Chicago, which joins several academic universities and medical centers in US and Canada, has initiated the research program Cure Within Reach based exclusively on drug repurposing [27].

Solid links between the academic research engine and the translational/regulatory expertise of governmental agencies and industry represents a new trend. This will help small biotech and academic startups ‘‘de-risk’’ early stage-drug discoveries of promising novel drug therapies to attract external capital. In less than 2 years the Learning Collaborative advanced Auranofin into
clinical trials as a new treatment for relapsed chronic lymphocytic leukemia (CLL) which shows what can be achieved with this type of public-private partnerships [26].

In 2011, Oprea et al. published an interesting article on drug repurposing reporting current experimental and computational NIH-funded academic screenings of known drugs [28]. Strengths and weaknesses of academic-based drug repurposing research are listed and ideas on how to overcome the so called "valley of death" by bridging basic and clinical sciences are proposed.

Asher Mullard recently reported NIH initiatives on drug repurposing started in April 2011 when pharmaceutical companies, government and academic institutions met in order to discuss the usefulness of drug repurposing [8, 29]. Again, the NIH catalyzed industry-academic partnerships like the Pfizer-Washington University deal which provides researchers access to over 500 compounds for repositioning opportunities.

Interestingly, several pharmaceutical companies, thanks to the joined effort of the NIH and the UK Medical Research Council (MRC), decided to share ideas on repurposing initiatives [29]. So far, Abbott, Astra Zeneca, Bristol Meyers Squibb, Lilly, Glaxo, Smith Kline, Johnson & Johnson, Pfizer and Sanofi have agreed to put together 58 compounds to be screened for 90 indications [30]. In addition, a subset of 12 candidates from the AZ assets is currently entering preclinical studies [31].

Most of the compounds involved in this initiative failed in the clinic due to lack of efficacy, selectivity and side effects. The fact that these molecules are available for the scientific community to find new indications highlights an important concept. Even if certain compounds are not suitable for treating disease, they can be still useful as chemical probes to understand mechanisms of diseases, to explain drug resistance, to validate new biochemical pathways and
protein targets. Fields like chemical genomics and chemical genetics emerged and exploit small chemical probes for example to elucidate signal pathways [32] or to discover new targets in cancer and other diseases [33,34]. A successful case is the one recently published by the group of Yi Zhong [35]. By using EGFR known inhibitors Erlotinib and Gefitinib, the authors suggested that amyloid-β may activate EGFR triggering a cascade of biochemical processes that damage neurons. Hence, EGFR is a preferred target for treating Aβ-induced memory loss [35].

The private sector is not interested in investing too much time and money in molecules that do not stand a chance of becoming a drug. Hence, this becomes an opportunity for academia to step in.

As previously mentioned, academic groups are pushing for drug repurposing and chemical genomics on rare and neglected diseases because the expected limited return on investments make the discovery of new chemical entities (NCE) in these fields very challenging. The National Clinical Guideline Centre (NCGC) created the NCGC pharmaceutical collection of non-redundant approved molecules ready for both experimental and computational chemical genomics screenings [36]. Inspired by the previous successful repurposing stories of sildenafil (Viagra) and thalidomide, particular attention will not be focused on the interaction of a drug with its intended target but instead on a different organ and/or the action of a drug on a different target (“off-target” effects) [36, 37].

3.2 Taiwan

Asia in general has a history based on the study of pharmaceutical active properties of natural substances in herbs, plants and rare animals for the cure of a variety of diseases. The idea of repurposing in drug discovery and development is supported by the large amount of information present in Asian Pharmacopoeias like the Chinese one, which is currently available online, also
in English. [38] Among all the classics, Bencao Gangmu, also known as Compendium of Materia Medica, is the most famous. The compilation of this encyclopedia was supported by the government (the Ming Dynasty) and Shizhen Li is the major editor and author.

In 2008 Lin et al. [39] published the biological effects of statins in the inhibition of specific HDAC isoforms. These drugs are broadly used for the control of hypercholesterolemia and to treat certain cancers. In this article, Lin and colleagues reported the \textit{in vivo} inhibitory epigenetic properties of lovastatin on HDAC and proposed new indications for this particular family of drugs in cancer therapy and chemoprevention.

Following up the success of these findings Jung-Hsin Lin and colleagues from the National Taiwan University and Institute of Biomedical Sciences of the Academia Sinica focused their attention in protein target prediction given a particular chemical scaffold. Identification of targets of small organic molecules through experimental and computational chemical genomic screenings is essential in drug discovery but also in unravelling novel mechanism of diseases. The program IdTarget developed and published in 2012 is an available online as a web server for the identification of protein targets of small chemical molecules through VLS also using repurposing databases [40]. IdTarget screens rapidly against all protein structures deposited in the Protein Data Bank (PDB) [40].

\textbf{3.3 Switzerland}

In May 2012 the official opening of the NCCR (National Centre of Competence in Research) Chemical Biology \textquote{Access} facility took place with a short high profile Symposium at EPFL campus in Lausanne [41]. With this initiative, Switzerland showed within the European context that is willing to take a step forward in the development of academically independent screening
centers. A variety of SNF-funded projects covering different areas of chemical genomics are in the pipeline.

The presence of two big pharmaceutical companies, Novartis and Roche, in Switzerland allows the establishment of solid links between the private and the academic sectors in drug discovery [42]. Michel Aguet from the Swiss Federal Institute of technology in Lausanne (EPFL), who started a spin-off company in Zurich in 1998, said "Ten years ago it was easier to start a biotech with no compound in hand. Today you don’t attract investors and funds if you don’t have a compound with successful preclinical and at times phase 1 clinical data“.

The fact that the bar now is higher should be considered as a unique opportunity for academia to push good candidate molecules into clinical trials. In order to do this, creativity and originality are needed and most of all risks must be taken. Future successful academic examples in drug discovery will build the trust of the government and the investors.

In Switzerland, it is still controversial as to what extent drug discovery should be carried out in academia. Initiatives like the “ACCESS” facility of the NCCR Chemical Biology might lower hurdles and generate demand for indentifying chemical probes and hits for early stage targets, and opportunities to repurpose known drugs.

Howard Riezman from the University of Geneva and Director of the NCCR Chemical Biology said “we are creating tool compounds in an academic setting in order to control and visualize biological processes.” Databases of marketed drugs are included in the screening to characterize novel active scaffolds independently whether the target is known or not. "We are all aware of the NIH initiatives to improve Translational Research” Riezman continues “but we want to remain basic. We are a government funded basic-research centre with the possibility of creating healthy spin-offs, of course.” Based on innovative and promising ideas, the ”Access” platform supported
by the NCCR Chemical Biology in Lausanne and the NCCR Trans-cure in Bern may create new demand for academic drug discovery projects in the future. This is also thanks to the quality of Swiss Universities and the nearby solid expertise of Novartis and Roche in particular domains usually and historically not covered by academia.

### 3.4 EU

The EU FP7 emphasis on translational research (translation of basic discoveries in clinical applications) was a source of inspiration for innovative approaches in chemical genomics.

Chris Rundfeldt, Consultant, Preclinical Drug Development at Drug-Consult.Net said “Drug repurposing is not a primary goal for EU Funding but it can be the base for individual proposals. At the moment, the EU is waiting to see the rate of success of drug repurposing campaigns initiated in US. There is still too much risk involved and the general concern that the use of old drugs for new indications will not produce a significant increase in the number of drugs into the market”.

A current example of EU individual initiative on drug repurposing is the one of the Innovative Medicine Initiative (IMI) where particular known drugs are screened for new uses based on partnerships between academia and the private sector.

In Sweden, AstraZeneca is part of the list of companies willing to provide and share known drugs for repurposing initiatives supported by the NIH and MRC [31]. The Swedish Foundation for Strategic Research (SSF), the Swedish Innovation Agency (Vinnova) and other funding agencies are encouraging academic efforts and the initiation of spin-offs around successful ideas. One repurposing example is the currently on-going clinical trial for the treatment of stroke in which a drug commonly used to treat leukaemia (Glivec®) has shown promise in improving the therapeutic outcome [43].
Michael Sundstrom, VP Drug Discovery Karolinska Development AB says “in Sweden we commonly follow EU Funding RoadMaps but at the same time we try to promote innovation by independent decisions and other funding sources. Especially, if that means taking significant steps towards optimal research and regulatory affairs which benefits public health in the country”.

4. PITFALLS IN DRUG REPURPOSING: CAN WE DO SOMETHING ABOUT IT?

Drug repurposing may play an important role in optimizing and speeding up drug discovery and development pipelines. In addition, drug repurposing will help with the use of known compounds as chemical probes to understand mechanisms of diseases and to find novel protein targets.

As any other approach, drug repurposing faces a number of pitfalls. Some of them have been totally or partially sorted out but others certainly demand more effort from governments and the private sector.

In 2004 in the first big review, Ashburn et al. listed a number of disadvantages in drug repurposing [4]. These include public accessibility of data, regulatory standards, IP protection issues and required novel designs for clinical trials in case of new indications for a known compound.

Compared to only 5 years ago, the fact that several pharmaceutical companies decided to share data publically regarding a number of drugs was a significant step forward. ”There is certainly still much to do to render clinical and physiological data on drugs accessible to researchers all over the world” says Ruben Abagyan of the University of California, San Diego (UCSD). ”This would definitely help the development of more precise experimental and computational toxicity
prediction tools and to reinforce target and biomarker validation”. This and many other topics were discussed at the Workshop “Computational Chemogenomics to understand System Biology & Computational Medicinal Chemistry” organized and chaired by Profs. Bisson and Scapozza at the University of Geneva [44].

Asher Mullard, in his recent analysis talks about “new use” Intellectual Property (IP) and ”composition of matter” IP. There are patent arrangements getting in the way of delivering new drugs [8, 36]. The IP issue remains a challenging topic and it is still difficult getting all parties to agree upfront in big research programs. For this reason, it is preferable to address the reader to specific articles talking about the subject in more detail.

The Pfizer-Washington deal in 2010 made possible through the joined effort of both NIH and MRC (full access to over 500 Pfizer compounds) is an example of how to overcome, at least in the US, legal, regulatory and commercial barriers to initiate repurposing campaigns [8, 36].

There are three common paths available to obtain approval for drug products in the US: 505(b)(1), 505(j) and 505(b)(2) [18]. Existing differences between US, Canada, Australia, Japan and Europe, for example, in regulatory pathways and mechanisms ultimately delay new indication approvals/withdrawals. Overall, regulatory agencies now accept data from literature and drug product monographs to catalyze trials of drug repurposing, [18].

The exploration of novel target for repurposing opportunities through chemical genomics screening will likely require new dosing, means of delivery and safety controls for selected candidates. Drug repositioning obviously brings up new regulatory and IP issues. A promising starting point to work on these issues is the optimization and acceleration of translational
research and subsequent clinical trials through solid collaborative networks between governmental agencies, academia and industry [28].

CONCLUSIONS
The present article highlights the importance of drug repurposing in drug discovery and development and reports on the current status of repurposing in different regions around the world.

Solid networks between academia and the private sectors, sponsored by government agencies, focused on repurposing to address cancer, neurological and other diseases have been initiated.

Experimental and computational chemical genomic techniques linking chemistry and biology can help promote drug repurposing and other approaches to catalyze translational research in academia.

Considerable efforts have been made to overcome current pitfalls in drug repositioning but there is still much work to do to properly address these issues.

Delivering successful drugs to patients faster and safer should be the main target for scientists, managers and politicians involved in drug discovery.

ACKNOWLEDGMENTS
I sincerely acknowledge Dr. E. Wade for his critical reading of the manuscript. I thank Dr. A. Orry for his help and corrections.

REFERENCES


[31]. Available from: http://www.mrc.ac.uk/Fundingopportunities/Calls/MoD/compounds/index.htm


[44]. Available from: http://www.unige.ch/sciences/pharm/pb/events/

**Figures**

Fig. (1). The realities described in the article and shown on the map are: Unites States (US), United Kingdom (UK), European Union (EU), Switzerland and Taiwan.