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Drug Repurposing for Cancer Therapy

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Keywords

drug repurposing; drug repositioning; cancer therapy

Background

In the mid-1980s, a French company geared its efforts toward developing a synthetic steroid capable of blocking the glucocorticoid receptor in order to potentially treat Cushing's syndrome. Preclinical studies revealed that the compound developed, termed RU-38486, was indeed a potent antiglucocorticoid agent [1], yet with a caveat: if given to pregnant animals, it terminated pregnancy [2–4]. Thus, a compound originally developed for treating one disease, rapidly acquired a different identity, was named mifepristone and investigated in depth for its abortifacient properties through the blockage of uterine progesterone receptors [4,5]. In other words, developed with one intended use, RU-38486 was repurposed for another modality of use even before gaining approval for medical usage. In the US, the Food and Drug Administration (FDA) approved mifepristone for chemical termination of early pregnancy in September 2000 [6]. It took 12 more years for the FDA to support mifepristone for its intended original use, the treatment of Cushing's disease. In February 2012, the FDA approved mifepristone to control hyperglycemia in adults with endogenous Cushing's syndrome and not eligible for surgery [7].

The case of mifepristone is an evolving example of many in drug repurposing, rescue, or repositioning efforts, which entail the development of a new modality of use for an existing therapeutic compound – i.e., giving a new use to an old molecule. There are many compounds that have been developed by pharmaceutical companies and academic institutions throughout the years, in addition to many natural compounds, that remain without a concrete clinical application; they are abandoned or underinvestigated compounds [8–10].

Many preclinical developments promise further repurposing for RU-38486, including other reproductive-related applications such as oral contraception, menstrual regulation, and emergency contraception; and the amelioration of psychiatric and endocrine disorders (reviewed in [11,12]). Furthermore, the compound is emerging as a treatment for endometriosis and uterine fibroids (reviewed in [13]). More recently, we and others have provided ample evidence for the potential effectiveness of RU-38486 in oncology by blocking the growth of several cancer cell types [14–18] (reviewed in [19]).

The case of RU-38486 is just one example depicting the potentiality of relatively rapid translation to the clinic applicable to many abandoned compounds or compounds developed for other purposes. For instance, metformin, a drug developed and approved to treat type II diabetes, is currently being intensively investigated to treat breast cancer [20,21]. Another, perhaps enigmatic case, is that of thalidomide, currently approved for the treatment of multiple myeloma (reviewed in [22–25]). Thalidomide was originally developed for the

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treatment of morning sickness in pregnant women; yet, it had devastating teratogenic side effects manifested with severe birth defects [26,27].

Discoveries in cancer biology facilitated the development of the first targeted therapy, imatinib mesylate (a.k.a. Gleevec), which blocks a constitutive active kinase uniquely expressed in chronic myeloid leukemia (CML) harboring the Philadelphia chromosome translocation [28]. Yet, the success of Gleevec has been limited by the fact that the disease evolves in response to the drug, developing new mutations in the Bcr-Abl protein kinase, making the continuous development of new drug derivatives a necessity [29,30]. However, the development of new drugs is extremely costly and there is certainly a gap between the resources invested in drug development and their translatability into longer survival for cancer patients. Repurposing existing drugs has to its advantage the fact that many toxicological studies have been already done, which reduces the time and cost of approving the compounds for clinical use. For example, the repurposing of RU-38486 was accelerated by the fact that all previous toxicological studies had been done before its approval for early termination of pregnancy. Thus, before being approved for Cushing's syndrome, the safety and efficacy of the drug was evaluated in a clinical trial of only 50 patients; this is because the compound had the backup of extensive literature on side effects when used for short term as a contraceptive agent, or for long term in clinical trials in patients with inoperable meningiomas that have taken the drug for several years and had mild toxicity considering the clinical benefits [31].

In order to cooperate in utilizing the existing resources to its maximum, the National Institutes of Health (NIH) recently created the National Center for Advancing Translational Sciences (NCATS) [10,32]. In terms of drug repurposing, the new Institute developed a funding mechanism to investigate potential new clinical applications, including cancer therapy, for a group of abandoned drugs in agreement with the companies holding the propriety rights [32]. NCATS just lunched in July 2012 a pilot NIH-Industry program for discovering new therapeutic uses of existing molecules in which the NIH will collaborate with several pharmaceutical companies that will make a list of 58 drugs available to basic researchers [33]. This is good news for patients with so-named orphan diseases, i.e., those with low prevalence and for which R&D from traditional pharmaceutical companies is very limited. Within such orphan diseases, many cancer types can be included. There are additional signs of government-controlled institutions becoming more creative in the process of drug approval. For instance, going back to mifepristone and its relatively rapid approval to treat Cushing's syndrome (also an orphan disease with a prevalence of ~5,000 patients in the US), the FDA utilized an approach in which the pharmaceutical that develops the medicine, has the total right of access to the entire of patients being attended by endocrinologists in the US, and distributes the medicine via a centralized pharmacy. In this manner, the FDA made appealing to a small company one of the limitations which forces many pharmaceuticals to put back compounds in shelves—their reduced marketability. For instance, who would invest in developing a drug exclusively target ovarian cancer when it has a diagnosis rate of ~22,000 patients per year? Nevertheless 70% of those patients will die of the disease within 5 years of diagnosis due to a lack of alternative treatment approaches. Together, academic institutions, the government, and the pharmaceutical industries should work in coordination to become more creative and provide solutions to members of society that did not choose to develop an orphan disease, such as many cancers.

Researchers have now access to high throughput screenings to test old drugs and natural compounds for their potential anti-cancer properties; however, researchers should also have access to such chemicals. The NCATS is paving the way towards the access of these drugs, and the initiative is welcome. Still, as a society, we should enhance the process of discovery by creating a more dynamic feedback system between academics, clinicians, patients,

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patient advocates, funding institutions, and the private pharmaceutical sector. Bedside observations in terms of signs and symptoms of patients being treated for a special condition may underscore off-target effects of a drug. Some of these observations could lead to the use of certain compounds for preventing cancer development. For example, it is well documented by epidemiological studies that women who have used progestin-based contraceptive pills continuously for at least 5 years, have reduced risk to develop ovarian cancer for 20 years [34,35]. Clinicians should develop new hypotheses based on observations and interviews with patients, and basic researchers should go back to the bench to test compounds with anticipated anti-growth properties. Let's not forget that the most popularly used anticancer agent, platinum, was discovered serendipitously when microbiologists were investigating the behavior of bacteria upon changes in voltage and observed growth inhibition due to electrolysis products from a platinum electrode [36–39]. Cancer patients deserve that we scientists utilize all tools at our disposal, from rational drug design for targeted therapy all the way to serendipitous observations in the laboratory, the clinic, and by the patients themselves. Hopefully, using all these resources, we will convert cancer into a treatable chronic disease. The current technological armamentarium provides cancer researchers with a unique opportunity to find new targets for old synthetic, abandoned compounds or newly discovered natural products.

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