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feature

Nonprofit drugs as the salvation of the world's healthcare systems: the case of Antabuse (disulfiram)

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The effort to repurpose old drugs for new uses is not sufficient; even drugs that have been used clinically for decades must undergo expensive clinical trials. This process requires the pharmaceutical industry to fund the repatenting of old drugs. Because inexpensive drugs are necessary for people around the world, attempts should be made to develop nonprofit drugs through clinical trials of generic drugs that are funded by governments and charities. Evidence supports the use the old anti-alcoholic drug Antabuse as a new nonprofit drug for cancer.

Drug repurposing: with or without repatenting?

The 'repurposing' or 'repositioning' of approved drugs as treatments for other diseases based on their 'promiscuity' is currently a hot topic in industry, academia and government [1]. According to Francis Collins, who is the Director of the National Institutes of Health (NIH; http://www.nih.gov/), research in this direction should be 'an important focus of the NIH's proposed National Center for Advancing Translational Sciences' [2]. The current process of translating potential research targets into marketable drugs is frustratingly slow. In 2007, discovering and developing a new molecular entity required approximately 13.5 years. During the 1990s, the failure rates for oncology drugs were 70% in Phase II and 59% in Phase III clinical trials [3]. Even with approved drugs, unknown targets in the human body can emerge as primary sites of action, making 'off-target' drug actions the cause of 'on-target' effects [4]. The notion of 'drug repurposing' includes the search for 'off-target' effects of approved drugs to treat other diseases, such as the use of a drug, which was originally approved as an aversion therapy for alcoholics (Antabuse), in cancer treatment. Drugs that are already in use can be rapidly evaluated in Phase II clinical trials, and drug developers can avoid approximately 40% of the overall cost that is incurred to bring the drug into clinical settings [5]. On the basis of current estimates, 8850 unique drugs are available to screen for new therapeutic uses [6].

One way to repurpose a drug is to secure patent protection for the new uses of the drug. Historically, old drugs have been repatented through method-of-use patents (which are not applicable in EU countries, according to [7]) or composition-of-matter patents. This is the case for thalidomide, which has been repositioned for use in erythema nodosum leprosum and multiple myeloma [8]. Recently, several publications have reviewed the repositioning of existing drugs from the perspective of the pharmaceutical industry [9–11]. However, it seems that the patent system has a particularly important role in the expenses and ineffectiveness of current strategies in biomedical innovation [12]. Repatented and repurposed drugs remain costly and inaccessible for most people worldwide. Even in wealthy countries, healthcare costs are rapidly increasing and the fastest-growing costs are for pharmaceutical products [Drug Expenditure in Canada 1985–2008: http://secure.cihi.ca/cihiweb/products/dex_1985_to_2009_e.pdf].

Repurposing alone might not be as fruitful as it appears at first glance. We must significantly lower the costs of global healthcare systems to enable people in need to obtain the drugs that will cure them. Furthermore, we need inexpensive cures for seriously ill people more than we need expensive treatments that will only briefly prolong life. Tito Fojo and Christine Grady have clearly stated this point in the case of cancer therapy [13]: 'We must deal with the escalating

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price of cancer therapy now. If we allow a survival advantage of 1.2 months to be worth $80,000, and by extrapolation survival of 1 year to be valued at $800,000, we would need $440 billion annually – an amount nearly 100 times the budget of the National Cancer Institute – to extend by 1 year the life of the 550,000 Americans who die of cancer annually. And no one would be cured.'

Thus, the question is whether we can effectively repurpose a drug for clinical trials without repatenting it. The answer is simple: yes, we can. The nonprofit pharmaceutical proof-of-concept has already been established by the Institute for OneWorld Health (iOWH; http://www.oneworldhealth.org/), whose mission is to develop safe, effective, and affordable medicines for people with infectious diseases in the developing world [14]. With the licensing of paromomycin in 2007 as an effective treatment for visceral leishmaniasis (VL, black fever) in India, the iOWH has demonstrated how nonprofit companies can fill unmet needs and increase patient value. Paramomycin is no longer used as an antibiotic against Gram-negative and many Gram-positive bacteria, but it is a well-tolerated and affordable drug to cure VL at a dose of 11 mg/kg (base) for 21 days. The price of the drug for a 21-day course for a 35 kg patient is only €4.19 [15].

In India, approximately 100,000 VL cases with clinical symptoms, such as fever, progressive anemia, and weight loss are estimated to occur annually. If left untreated, this disease is always fatal [16]. In the district of Bihar, which is a state comprising 85% of VL cases in India, household expenditures for VL treatments can significantly contribute to increasing poverty [17]. A Phase III clinical trial for injectable paromomycin for VL was conducted between June 2003 and November 2004 in Bihar, and was financed by grants from the Bill and Melinda Gates Foundation (http://www.gatesfoundation.org/Pages/home.aspx) to iOWH and additional funding from iOWH and the Special Program for Research and Training in Tropical Diseases of the United Nations Development Program, the World Bank (http://www.worldbank.org/), and the World Health Organization (http://www.who.int/en/) [18]. Paromomycin is a success story of an unpatentable drug that had been repurposed by a nonprofit drug company with philanthropic funding. This nonprofit company model is slightly different from my proposal of the nonprofit drug model [19,20], as discussed below.

Beyond the patent system: GlobalCures and Antabuse

The repurposing of unpatentable drugs should avoid focusing only on developing countries as a way to help the poorest people. Governments and charities in the developed world can simultaneously help all nations worldwide. We can repurpose drugs to improve our healthcare systems and simultaneously develop nonprofit drugs for people worldwide. The best example is cancer, one of the most-feared diseases. In the USA, approximately 40,000 women died from breast cancer in 2010 [21]. However, the highest estimated age-standardized mortality rates due to breast cancer (in 2002) were not in the USA, but – in addition to Canada, European countries or Argentina – in Pakistan, Botswana, Cameroon and Nigeria [22]. The cost of chemotherapy exceeds the healthcare budgets of low-resource countries [23]. If our governments and charities help to cure breast cancer effectively and inexpensively in the developed world with a nonprofit drug, they will also help to cure breast cancer in the developing world.

An experience with breast cancer is the motivation for the inception of GlobalCures (http://www.global-cures.org/), which is a Boston-based initiative to develop nonprofit drugs to fight cancer. Vidula Sukhatme, who is the founder of GlobalCures, explains: 'In June 2004, my friend Jennifer was diagnosed with a recurrence of breast cancer. As she failed one chemotherapy agent after another, I frantically searched the web for 'alternative' treatments – treatments that were not in her doctor's medical bag. While I found quite a few 'remedies' online, trying to find the few potentially 'promising' ones became an overwhelming task. I would bring some of these remedies to my husband Vikas, a physician and cancer researcher at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston, MA. While helping me to evaluate the scientific basis for these treatments, he began to sound like a broken record: 'This looks interesting, but we need rigorous clinical studies to carefully evaluate toxicities and efficacy.' . . . Thus we discovered a 'gap'. Promising therapies would languish in the realm of the 'unproven' unless a different drug development model was used. A nonprofit drug development organization funded by the public, without a profit incentive, seemed to be the only way and so GlobalCures was born.' The comparison of the business model of GlobalCures and the for-profit pharmaceutical model is provided in Table 1.

The clinical cost for an approved drug is hundreds of millions of dollars [5]. Thus, the danger in the clinical development of nonprofit drug is the billions of dollars from governments and charities that are wasted because they are spent on failed clinical trials. A suitable candidate for the potential 'success story' of a nonprofit drug must be carefully identified. The evidence for this candidate should come from the experience of physicians [24] and patients [through disease-oriented social networks, such as Genetic Alliance (http://www.geneticalliance.org/), PatientsLikeMe (http://www.patientslikeme.com/), and MyDaughtersDNA (http://www.mydaughtersdna.org/) [25]], retrospective epidemiological studies, and new models of pharmacovigilance [26].

TABLE 1

The unique business model of GlobalCures, a not-for-profit initiative to find new uses for old drugs without repatenting them. *Motto* 'Yesterday's Medicines, Tomorrow's Cures, Available Today!'

For-profit pharmaceutical	GlobalCures
Mission	
Create shareholder value	Create patient value
Funding	
Investments	Philanthropy
Scientific screen	
Potential patient benefits (yes)	Potential patient benefits (yes)
Strength of existing data (yes)	Strength of existing data (yes)
Knowledge of disease pathway (yes)	Knowledge of disease pathway (yes)
Quality of existing treatments (yes)	Quality of existing treatments (yes)
Commercial screen	
Patent rights (yes)	Patent rights (no)
Market size (yes)	Market size (no)
Income of affected patients (yes)	Income of affected patients (no)
Expected return on investment (yes)	Expected return on investment (no)
Perceived risk of clinical development (yes)	Perceived risk of clinical development (no)
Business model	
Test, commercialize, and market 'profitable' therapies	Test clinical benefit of the most 'promising' therapies

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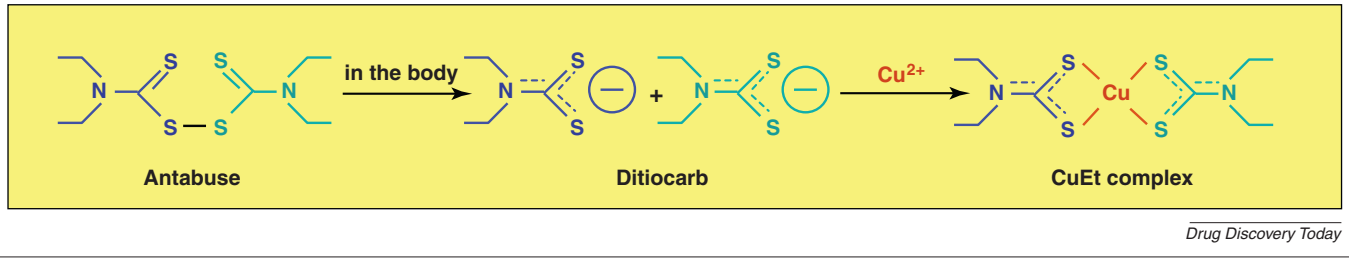

FIGURE 1

Antabuse is rapidly metabolized to ditiocarb (diethyldithiocarbamate) in human body. Ditiocarb as a strong cooper chelator reacts with copper forming Cu(II) diethyldithiocarbamate complex (CuEt).

I propose that the old antialcoholic drug Antabuse (disulfiram), which has been tested in several Phase I clinical trials as an anticancer drug, represents an effective example of a repurposed drug [27,28]. The maximum daily dose of Antabuse in current clinical practice is 500 mg [29]. Through PharmacyChecker.com (http://www.pharmacychecker.com/compare-drug-prices-online-pharmacies/ANTABUSE-500+mg/38005/67830/), a patient with cancer can obtain one tablet of 500 mg Antabuse for US$1–2 on average. Thus, one year of Antabuse-based therapy (500 mg per day) costs approximately US$550 per patient (the estimated cost of cancer therapy per year per person could be as high as $800,000, according to [13]).

Several pieces of evidence suggest that Antabuse is a potent anticancer drug. The anticancer activity of Antabuse has been known for decades from experiments that have been performed in carcinogen-fed rats [30,31]. This effect is not caused by the interference of Antabuse with the metabolism of the carcinogen [32]. Current studies have shown that Antabuse suppresses breast cancer xenografts in mice through a copper complex (CuEt), which is a potent inhibitor of the cellular proteasome [33,34]. Therefore, I expect that there are unpublished cases of 'spontaneous' remission of breast cancer in alcoholics on Antabuse. At least one case was published by Dr Lewison from Johns Hopkins Hospital (http://www.hopkinsmedicine.org/) in Baltimore in 1977 [35]: 'A 35 year-old female was operated upon for breast cancer in 1956 ... severe back pain developed as the result of metastases to the spine, ribs and pelvis ... in 1961 she became a severe alcoholic ... and Antabuse (disulfiram) was started. Over the next ten years – from 1961 to 1971 – complete resolution of all bone lesions in the spine, skull, pelvis and ribs gradually occurred and the patient remained clinically free of cancer with no further hormone therapy, chemotherapy, or radiation therapy.'

Surprisingly, this case report has not been cited in an article on a relatively successful Phase II clinical trial of an Antabuse metabolite that is known as ditiocarb (Fig. 1) in breast cancer patients [36]. In this double-blind trial, 64 women with breast cancer were treated with sodium ditiocarb (diethyldithiocarbamate) or a placebo. The overall survival after six years was significantly higher in the ditiocarb group than in the placebo group (81% versus 55%, respectively). The disease-free survival rates were 76% and 55% in the ditiocarb and placebo groups, respectively. Ditiocarb, which is the main Antabuse metabolite in the human body that is responsible for its mechanism of action [37,38], was believed to be a potent immunomodulator that could be used to treat AIDS [39–41]. As further clinical trials of ditiocarb in patients with AIDS have failed and key study has shown no ditiocarb-dependent immunomodulatory activity in patients, ditiocarb and its anticancer activity in breast cancer patients have been forgotten [42]. This situation might illustrate a challenge for the repurposing of old drugs: reports of their activity or the activity of their metabolites might be lost in the thousands of articles that have been published in the field of biomedicine during the past century. For example, the anticancer potency of Antabuse is most probably caused by CuEt (Fig. 1) that forms in the blood after taking Antabuse [28]. The early evidence of the strong copper-binding capacity of Antabuse *in vivo* is from the 1930s, when Antabuse was used in human patients against intestinal worms inhibiting their copper-containing respiratory enzymes by binding copper ions [37]. Further evidence is provided in a study that was published in 1997. The authors showed that a rat injected with 500 mg/kg ditiocarb and sacrificed after 30 min later had exhibited a detectable concentration of CuEt in the brain homogenate [43]. Antabuse might be more effective in future clinical trials with breast cancer patients if patients have copper-enriched diets.

Antabuse seems to be active in other solid cancers. A woman with stage IV metastatic ocular melanoma of the liver was cured by Antabuse and zinc gluconate. She was clinically well and physically active after 53 continuous months of therapy [44]. This observation led to the current Phase I clinical trial of Antabuse and copper gluconate in patients with all types of liver-delivered cancers. The design of the trial (http://www.cancer.gov/clinicaltrials/search/view?cdrid=614004&version=HealthProfessional&protocolsearchid=6900494) is as follows: 'Copper gluconate containing up to 8 mg elemental copper would be given in the morning a half hour before breakfast, and disulfiram would be consumed with the evening meal. The rationale for separating administration of the two agents in time is to avoid producing gastrointestinal toxicity, such as mucositis from complexation of copper by disulfiram in the gut. Administered orally, both disulfiram and Cu^{2+} will probably achieve high hepatic concentrations before distribution to other body tissues. This might suggest a utility of disulfiram and Cu^{2+} in treating primary hepatic tumors such as hepatomas, or secondary hepatic metastases from common malignancies such as colonic adenocarcinoma.' We need many of these types of trials, especially for terminally ill oncological patients without hope of prolonged life through standard treatments. Antabuse is a cheap, safe and widely available drug for patients in every country with any type of cancer, and new case reports can be generated to demonstrate the potential efficacy of Antabuse with or without copper in various cancers.

Concluding remarks

We have sufficient evidence of efficacy to conduct a large clinical trial (Phase III) for Antabuse in breast cancer patients. Successful trials might alter the global mentality and lead to new regulatory policies regarding the development of nonprofit drugs to reduce the price of their development. As a result, millions of people

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worldwide would have access to inexpensive and affordable drugs for otherwise fatal diseases, and healthcare systems would not waste money on overpriced, ineffective drugs. I recommend that the National Center for Advancing Translational Sciences (http://feedback.nih.gov/index.php/faq-ncats/) devote a portion of their funding to the development of nonprofit drugs and use Antabuse as a pilot case.

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