Modern Strategies in Cancer Study: Drug Repositioning in Colorectal Cancer Treatment

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Abstract
Colorectal cancer is one of the most fatal cancers in the world because most of cases are diagnosed in advanced stages, when the development of resistance to chemotherapy is more frequent. To face this situation, new drugs and drug combinations would be necessary. Drug discovery is a very costly process; although efforts in drug discovery have been amplified in recent decades the success rate of approved FDA drugs continues being low. In response to this situation the repositioning of drugs proposes to delve into the genetic, epigenetic and metabolic differences to discover new targets and redirect drugs already approved to the treatment of other diseases and conditions. In this minireview we discuss the main avenues in which repositioning can occur and we cite some examples of repositioning drugs in colorectal cancer treatment that are being tested in clinical trials in the past years.

Keywords: Colorectal cancer; Drug repositioning; Clinical trials

Introduction
Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 [1]. CRC is often diagnosed at advanced stages, when the probability of development of distal or local recurrence due to chemotherapy resistance is more elevated [2,3]. The common protocol of CRC treatment consists in a primary surgical resection of the tumor, followed by radiotherapy and/or adjuvant chemotherapy. Since the 1950s, 5-fluorouracil (5-FU) remains the mainstay of chemotherapy [4,5]. In the recent years other drugs have been developed and used in combination with 5-FU such as oxaliplatin, irinotecan and capecitabine [6]. The use of new monoclonal antibodies such as Bevacizumab and Cetuximab has also allowed great advances in therapies [7]. However, almost half of patients with advanced CRC are resistant to chemotherapies based on 5-FU [8]. To counter this situation new strategies are being implemented; these include improved early diagnosis (down-staging), discovery of reliable predictive biomarkers and development of novel drugs/drug combinations.

The development of a new drug is a process that can take 10-15 years; the number of drugs approved by the FDA (Food and Drug Administration) has been declining since 1995 and investment in drug development has been gradually increasing, indicating that the cost of new drug development will continue to grow [9-11]. In this context, repurposing of drugs has emerged as an alternative to the classical pipeline of drug development and there has been increasing interest in analyzing anti-cancer activity of non-cancer drugs already FDA approved. The two main advantages of this strategy are the knowledge of the pharmacokinetics and toxicity of the drugs and their low costs and accessibility, since they are mostly generic [12]. In addition, repositioning of drugs is a strategy of special importance in low- and middle-income countries, where the conventional therapies are not economically accessible to the population in general due to their high costs [13,14].

Drug repositioning can take advantage of both computational and experimental methods. There are two main approaches in the selection of drugs to reposition: the first consists...
in propose a drug as possible anticarcinogenic based on prior information about it, such as the knowledge of its molecular target or the identification of its effects during the treatment of a clinical subpopulation that shows a lower incidence of certain disease. This approach is also called text mining-based since it is based on the literary and observational search of the mode of action and effect of the candidate drug and often the selection is follow by in vitro screening techniques. An example of this type is metformin, the postulation of this drug as a possible reposition drug arose as a result of a study of cancer incidence in patients with type II diabetes [15]. In this study it was observed that a group of diabetic patients treated chronically with metformin had a lower cancer incidence and cancer-related mortality. The drug was tested in vitro in cell lines of different types of cancer, including CRC, and due to favorable results also in animal models [16]. Preclinical studies determined that metformin affects cellular metabolism and suppresses oncogenic signaling pathways, such as receptor tyrosine kinase, PI3K/Akt, and mTOR pathway [17]. Metformin has been repositioned in combination with other compounds, showing synergistic action with EGFR inhibitors and other repositioning drugs such as propranolol [18]. Currently, our group is testing the combination of metformin and propranolol on in vitro and in vivo models of CRC, where we observed a decrease in cell proliferation and tumor growth, and the inhibition of metastasis related events associated with an effect on epithelial-mesenchymal transitions through the modification of E-cadherin and B-catenin levels (unpublished data). Metformin is actually in phase II to be approved by the FDA for CRC treatment (Table 1).

Within this same approach, other drugs were postulated to be repositioned based on their molecular target; an example is chloroquine, a drug used in the treatment of malaria. Chloroquine was proposed as a possible anticancer drug due to previous knowledge about its effects on parasite autophagy processes. It is known that chloroquine diffuses easily into lysosomes where it is known that chloroquine diffuses easily into lysosomes where it prevents the digestion of heme, killing the organism. In human cells, the accumulation of chloroquine in lysosomes produces the inhibition of enzymes such as phospholipase A2, hindering the breakdown of proteins and affecting cell signaling pathways [19]. The anticancer effects of chloroquine were corroborated in more than one type of cancer including CRC [20], leukemia [21] and breast cancer [22]. This drug is in phase II of preclinical studies for breast cancer treatment (NCT01446016) and in vitro stage for CRC treatment [23]. Other examples of repositioning drugs in CRC treatment with this approach is dehydroepiandrosterona (DHEA) [24], orlistat [25], pantoprazole [26], DCA [27] and raloxifene [28], all these are in in vitro stage. A second alternative approach for the search of putative drugs to be repositioned takes advantage of bioinformatic methods. During the past decade, the development of new technologies to study gene expression and the advances in sequencing machinery, such as microarrays and the whole transcriptome shotgun sequencing (RNA-seq), have allowed the emergence of gene expression databases (most of which are freely available) putting a large amount of information at the disposal of the scientific community. Some databases, like Gene Expression Omnibus (GEO) at the National Center for Biotechnology Information (NCBI) [29], Array Express [30] and EMBL-EBI Expression Atlas [31] are repositories of a great variety of gene expression studies including genetic expression of cell lines to human tissues, all of them under the most varied experimental conditions. The analysis of this new information has led to great advances in the acquisition of biological and chemical data pertaining to alteration of pathways in diseases, alteration in protein structures, drug-target interactions, mechanism of drug actions, disease-specific and drug-induced gene expression signatures [32-34]. In silico drug repositioning is an approach that takes advantage of this situation to relocate drugs using computational strategies [34]. A large amount of drugs to be repositioned have been proposed based on this approach, some of them for CRC treatment are itraconazole [17], tanshinone IIA [35], and fluspirilene [36], all these still are in in vitro tests stage, while others are already being tested in humans CRC as rapamycin and celecoxib (Table 1).

Table 1: Some repositioning drugs in clinical trial stage for CRC treatment.

| Drug       | Original Indication                  | Target in CRC          | Phase     | NCT Example                  | N° of CT Testing Drug |
|------------|-------------------------------------|------------------------|-----------|-----------------------------|-----------------------|
| Aflibercept| Wet macular degeneration treatment (DMAE) | VEGF pathway inhibitor | Approved (2015) | NCT01669720 NCT02181556 | 17                    |
| Aspirin    | Treatment of pain, fever and inflammation | TLR4 expression inhibitor | COX-2 inhibitor | Increase TGF-B1 secretion | NCT02394769 NCT02467582 NCT02647099 | 27     |
| Celecoxib  | Treat pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation | COX-2 selective inhibitor | III       | NCT00005094 NCT03645187 | 27                   |

Table 1: Some repositioning drugs in clinical trial stage for CRC treatment.
| Drug                  | Use                                                                 | Target Pathway/Activity                                                                 | Phase | NCT Numbers                |
|----------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------|---------------------------|
| Cyclosporine         | Immunosuppressant used to avoid rejection of transplants             | Wnt/calcium pathway modulator                                                          | II    | NCT00003950               |
| Doxycycline          | Antibiotic used in bacteria and certain parasites treatment          | Inhibitor of mitochondrial biogenesis                                                  | III   | NCT02201381               |
| Etodolac             | Non-steroidal anti-inflammatory drug (NSAID)                         | COX-2 inhibitor                                                                       | III   | NCT00888797               |
| Everolimus           | Immunosuppressant used to avoid rejection of transplants             | P13K/mTOR pathway inhibitor                                                            | II    | NCT00390364 NCT0154335 NCT01149434 |
| Indomethacin         | Non-steroidal anti-inflammatory drug (NSAID)                         | Non-selective COX inhibitor                                                            | I     | NCT01719926               |
| Lamivudine           | Treatment of HIV and Hepatitis B                                     | Under study. Is known to affect p53 metastatic CCR impairing cancer cells mutant grow| II    | NCT03144804               |
| Mebendazole          | Broad-spectrum anti-helminthic benzimidazole                         | Under study. Some known activities:                                                    | III   | NCT02201381               |
| Metformin            | Diabetes type 2 treatment                                           | mTOR pathway and IGF 1R protein inhibitor                                              | III   | NCT01930864 NCT0359681 NCT0359681 |
| Nelfinavir           | Antiretroviral of the family of protease inhibitors. HIV-1 and HIV-2 treatment | P13K pathway inhibitor                                                                | II    | NCT00704600               |
| Niclosamide          | Intestinal parasite infections treatment                             | Calcium-binding protein A4 inhibitor                                                   | II    | NCT02519582               |
| Nintedanib           | Idiopathic pulmonary fibrosis treatment                              | Approved                                                                               |       | NCT02780700 NCT02149108  |
| Pentamidine          | Antimicrobial used to treat African trypanosomiasis, leishmaniasis, babesiosis, and pneumocystic pneumonia treatment | PRL phosphatases inhibitor                                                             | II    | NCT00809796 NCT01378143  |
| Phenybutyrate        | Treatment of urea cycle disorders                                    | a) Inactivation of NF-kappaB                                                             | II    | NCT00002796               |
|                      |                                                                      | b) Histone deacetylase inhibitor (HCADi)                                               |       |                           |
Propranolol      β-blocker use for hypertension treatment     Under study. Some known activities: a) Lipins PAP activity inhibitor b) Affect β-adrenergic pathway     III     NCT00888797    1

Rapamycin      Immunosuppressant to prevent organ transplant rejection     mTOR inhibitor     II     NCT03439462    3

Simvastatin      Cholesterol treatment     HMG-CoA inhibitor     II     NCT02848443    4

Trifluridine      Anti-herpesvirus, antiviral drug, used primarily on the eye     Thymidine phosphorylase inhibitor     III     NCT02848443     NCT03274882    15

Valproate      Epilepsy, bipolar disorder and migraine headaches treatment     HDAC inhibitor     II     NCT01898104    2

CT: Clinical Trial
NCT: Clinical Trial Number

Conclusion

Drug repositioning is becoming one of the fundamental pillars of personalized medicine; aim to improve the productivity of current drug discovery pipelines. The recent advances in next-generation sequencing technologies are enabling personalized genomic studies which in turn provide insight into the heterogeneity between patients within a disease and, in the case of cancer, even within a same type of tumor. The identification of new important molecular pathways and their respective pharmacological targets have potential therapeutic utility in drug repositioning. The knowledge derived these kinds of approaches will result particularly useful for those patients that have developed pharmacological resistance to conventional treatment and/or suffer from tumors with reduced therapeutically options, especially in low- and middle-income countries.

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Conflict of Interest

The authors declare that they have no competing interest.

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