Drug repurposing and it’s implications in therapy: an overview

Blessy Mariyam Babu * 
Department of pharmacy practice, Amrita School of Pharmacy, AIMS Health Sciences Campus, Amrita Vishwa Vidyapeetham University, Ponekkara, Kochi-682041, Kerala, India

*Corresponding Author
Name: Blessy Mariyam Babu
Phone: +91-8943764867
Email: blezenmariyam1996@gmail.com
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INTRODUCTION

The repurposing (repositioning, therapeutic switching, drug re-tasking or re-profiling) of medicines is the technique of finding new healing targets for present drugs. Drug re-profiling has advantages over typical drug development because it reduces the actual price for the medication, as a result of the that they have already undergone tests and clinical trials. Need already been undergone toxicity and alternative tests like clinical trials. The prospect of further marketing and extending the patent life of a drug is one reason behind repositioning drugs. Another aim is to treat rare or neglected diseases; such conditions are typically difficult to address for financial reasons, yet some safe and active molecules already produced for other indications may exist.

Drug repositioning is potentially one of the most significant tools to enhance our discovery and understanding of new biology. It can be an important research strategy, as many new drugs have high absorption, distribution, metabolism and excretion data, previously passed clinical trial data and post-marketing surveillance data (Ashburn and Thor, 2004; Tobinick, 2009). These are expensive and time-consuming to obtain.
The benefits of drug repositioning

Finding new indications for the existing drugs will benefit patients who will see a potential new therapy sooner. Repositioning is usually done by accident and in a limited manner. Drug repositioning is often studied beyond financial sense in terms of its patent protection scenarios and potential intrinsic restriction due to off-label use of such products in their new indications.

Often, when repositioning a drug, it is always a good idea to include a new dosage, formulation or route of administration, if medically necessary. These systematic approaches could also be divided into method approaches and experimental approaches, every of that is additional and more obtaining used synergistically.

Discovery of a candidate molecule for a given indication (generation of the hypothesis); mechanical assessment of the drug's effects by pre-clinical models; and efficacy review in phase II trials are the three steps involved in drug repurposing process.

Drug Repositioning has two profiles: on target and off-target. In ‘off-target’, the drugs bind to targets that are not always the ones they were initially designed for. But in reality, the drugs are completely ‘on target’, binding precisely to what they are capable of binding.

MINOCYLiene

Minocycline has been in use since 1972, and it is a semi-synthetic tetracycline analogue having broad-spectrum activity against a wide range of gram-positive and gram-negative bacteria. Its clinical applications include susceptible microorganism infections and rheumatoid arthritis (Ochsendorf, 2010). Many research studies showed its non-antibiotic role, such as anti-inflammatory, antioxidant, anti-apoptotic, neuroprotective, and anti-cancer properties. The significant anti-inflammatory and immunomodulatory effects of minocycline in the management of COVID-19 patients can offer potential benefits, especially for its respiratory complications, such as acute respiratory distress syndrome and multiorgan damage. Minocycline prevented the human immunodeficiency virus (HIV) induced cytopathic effects in a study conducted by Lemaitre et al. (1990). Minocycline reduced HIV replication as well as reactivation in primary human CD4+ T cells in a study by Szeto et al. In this study, anti-HIV effects of minocycline were found to be mediated by the modification of cellular environment rather than direct drug-induced antiviral effects (Szeto et al., 2010).

VALPROATE

Valproate (VPA) is widely used as a mood-stabilizing and anti-epileptic agent. Being an inhibitor of histone deacetylases (HDAC), VPA is also modulating epigenetic changes. VPA can inhibit NF-κB, TNF-α, and IL-6 production in human cells stimulated with lipopolysaccharides in vitro studies (Ichiyama et al., 2000). VPA has also been shown to decrease the expression of nitric oxide, down regulate the macrophage response, and block macrophage migration by inhibiting pro-inflammatory cytokines; pathogen-associated molecular pattern receptors of toll-like receptors, retinoic acid-inducible gene-1, phosphatases; and transcriptional modulators (Suliman et al., 2012; Guo et al., 2007). Differentiation of T cells towards Th2 / M2 instead of Th1 / M1 is possible through VPA, and also a generation of regulatory T cells are stimulated through VPA, thereby reducing the percentage of CD8 + T lymphocytes. In another study conducted on rats by Fukudome et al., haemorrhage-induced acute lung injury (ALI) is prevented by VPA in rats by decreasing the expression of cytokine-induced monocyte chemoattractant protein-1 (Fukudome et al., 2012). In response to sepsis-induced lung injury, VPA administration 6 hours before the inflammatory stimulus inhibited NF-κB activation and neutrophil infiltration in the lungs observed by Ji et al. (2013) in a retrospective study on patients with subarachnoid haemorrhage, 521 patients who received VPA for seizures had reduced incidences of pneumonia and sepsis-related ALI compared to the 1042 patients who received other anticonvulsants. The difference in respiratory failure could be due to the epigenetic mediated anti-inflammatory effects of VPA, postulated by the authors (Liao et al., 2018).

ASPIRIN

For the treatment and prevention of atherosclerotic diseases, aspirin is commonly used. COX-1 and COX-2 are the pharmacological targets of aspirin (Smith et al., 1996). Thromboxane A2 (TXA2) in platelets are produced from COX-1, which promotes platelet aggregation and platelet adherence to tumour cells. Being a rapidly inducing enzyme during inflammation, COX-2 produces prostaglandin E2 (PGE2) primarily in tumour cells compared to COX-1, and it is suspected that PGE2 plays an essential role in promoting cell proliferation and tumour growth. Aspirin administered at low doses (50–100 mg daily), and high doses (>325 mg daily) selectively irreversibly blocks COX-1 and COX-2, respectively. In 1972, the anti-tumour effect of aspirin was first reported in a tumour bearing mouse (Gasic et al., 1972).
survival time and decreased primary tumour vol-

ume in mice with a strongly metastasizing breast cancer cell line (Jiang et al., 2010).

**METFORMIN**

Metformin, the biguanide antidiabetic drug typically prescribed for type 2 diabetes (T2D) Metformin (N, N-dimethyl biguanide) is derived initially from galegine (isoamylenguanidine), a guanidine derivative found in the French lilac Galeagofficinalis (Bailey, 2017). By increasing peripheral glucose absorption and reducing basal and postprandial glucose, it decreases hepatic gluconeogenesis and improves insulin sensitivity (Zhou et al., 2007). Metformin is orally delivered and has a bioavailability of 40–60 per cent. Metformin is distributed systematically within 6 hours of absorption, which occurs primarily in the upper small intestine, following a single oral dose of 0.5 g, with limited absorption in the large intestine (Graham et al., 2011).

**METFORMIN AND CANCER**

Cancer is the number one cause of morbidity and death worldwide. A recent lifespan risk assessment by the British population showed, at some point in their lifetime, more than 50 per cent of adults under the age of 65 will be diagnosed with the disease (Ahmad et al., 2015). Various studies show that metformin can change the inflammatory pathways which are known to play a role in the development of cancer. It was stated that metformin blocks the transcription factor nuclear factor activity, which results in reduced pro-inflammatory cytokine secretion by the senescent cells (Moiseeva et al., 2013). A recent mouse model study showed that metformin protects CD8+ lymphocytes that invade the tumour from apoptosis and functional exhaustion (Eikawa et al., 2015). Metformin has been demonstrated to enhance the efficacy of an experimental anti-cancer vaccine by enabling T-cell survival in memory, also a promising one (Pearce et al., 2009). The ability of metformin to prevent complex I and prevent oxidative phosphorylation has recently been emphasized as a significant prerequisite for inhibiting tumorigenesis. Metformin reduces the intermediate cycle of tricarboxylic acids suggesting impaired complex I activity in a metabolomic study of a neoplastic-transformed breast epithelial cell line and thus highlights the fact that this enzyme is a primary target.

**NELFINAVIR**

Nelfinavir is used to treat patients with HIV infection in conjunction with other antiretroviral medicines (Moyle et al., 1998). In 1997 it received approval from the US-FDA for an oral dosage scheme of 750 mg three times a day. It was later changed to a twice-daily 1250 mg. All regimens have been
proven equally effective (Marzolini et al., 2001).

Nelfinavir peak plasma level is around 8 μM, and it is established that the bioavailability is increased when taken with food (Bardsley-Elliot and Plosker, 2000). Since the early 2000s, researchers have been seeking possible anti-cancer activity of nelfinavir. The growths of Kaposis’s sarcoma (Sgadari et al., 2003), multiple myeloma (Ikezoe et al., 2004), prostate cancer (Yang et al., 2005), and breast cancer (Brüning et al., 2010; Shim et al., 2012) were confirmed to be inhibiting by nelfinavir. Nelfinavir exhibited wide-spectrum anti-cancer activity in vivo, being successful in several models of preclinical cancer.

Insulin resistance was a common side effect of nelfinavir. (Brunner et al., 2008) have recently conducted a Phase I clinical trial of nelfinavir and chemoradiation for locally advanced pancreatic cancer (Brunner et al., 2008). In this trial, during patients with pancreatic cancer, nelfinavir demonstrated potent radiosensitizing and anti-tumour activities without adding toxicity.

NITROXOLINE

Nitroxoline, an old antibiotic commonly used since the 1960s in countries like Europe, Asia and Africa for treating urinary tract infections (UTI). Nitroxoline is quickly absorbed into the plasma when injected orally and eventually excreted into urine (Mrhar et al., 1979). Due to its ability to chelate divalent metal ions such as Mg2+ and Mn2+ is the possible mechanism of nitroxoline antibacterial activity (Pelletier et al., 1995).

Anti-cancer activity of nitroxoline is initially reported in 2010. Many recent studies have also been supporting nitroxoline’s anti-cancer role.

A study conducted by Jiang et al. (2011) showed the anti-cancer activity of nitroxoline against lymphoma, leukaemia, pancreatic cancer and ovarian cancer cells (Jiang et al., 2011). Nitroxoline has been used as a UTI medication in several European countries for over 50 years, and no significant human toxicity has been recorded, making the drug an excellent candidate for repositioning of anti-cancer treatment.

CONCLUSION

Drug repositioning may be described as a process for finding and discovering new therapeutic uses for already approved drugs, outside the scope of the original pharmacological indication. Time and expense associated with drug development processes can be substantially reduced through drug repositioning. There are still lots of challenges following Phase II trials. Phase III studies include a significantly larger number of patients compared with Phase I and Phase II studies. Because of the size and relatively long duration, Phase III studies are the most expensive and time-consuming trials, and those hurdles have not changed over the years in Phase III studies. Intellectual property (IP) protection of repositioned drugs is another challenge that should be considered for drug repositioning. Especially for those drugs that are off patents. Both pharmaceutical and biotech companies have recognized the advantages of repositioning, and activity in the area has increased dramatically.

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Compliance with ethical standards

Conflict of interest

Authors declare that there is no conflict of interests in this study.

Statement of human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

REFERENCES

Ahmad, A. S., Ormiston-Smith, N., Sasieni, P. D. 2015. Trends in the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960. British Journal of Cancer, 112(5):943–947.

Ashburn, T. T., Thor, K. B. 2004. Drug repositioning: identifying and developing new uses for existing drugs. Nature Reviews Drug Discovery, 3(8):673–683.

Bailey, C. J. 2017. Metformin: historical overview. Diabetologia, 60(9):1566–1576.

Bardsley-Elliot, A., Plosker, G. L. 2000. Nelfinavir. Drugs, 59(3):581–620.

Ben-Zvi, I., Kivity, S., Langevitz, P., Shoenfeld, Y. 2012. Hydroxychloroquine: From Malaria to Autoimmunity. Clinical Reviews in Allergy & Immunology, 42(2):145–153.

Brüning, A., Friese, K., Burges, A., Mylonas, I. 2010. Tamoxifen enhances the cytotoxic effects of nelfinavir in breast cancer cells. Breast Cancer Research, 12(4).

Brunner, T. B., Geiger, M., Grabenbauer, G. G., Lang-Welzenbach, M., Manton, T. S., Cavallaro, A., Sauer, R., Hohenberger, W., McKenna, W. G. 2008. Phase
Jiang, P. D., Zhao, Y. L., Deng, X. Q., Mao, Y. Q., Shi, W., Tang, Q. Q., Li, Z. G., Zheng, Y. Z., Yang, S. Y., Wei, Y. Q. 2010. Antitumor and antimitotic activities of chloroquine diphosphate in a murine model of breast cancer. Biomedicine & Pharmacotherapy, 64(9):609–614.

Jutten, B., Keulers, T. G., Schaar, M. B., Savelkoul, K., Theys, J., Span, P. N., Vooijs, M. A., Bussink, J., Rouschop, K. M. 2013. EGFR overexpressing cells and tumors are dependent on autophagy for growth and survival. Radiotherapy and Oncology, 108(3):479–483.

Kim, E. L., Wustenberg, R., Rubsam, A., Schmitz-Salue, C., Warnecke, G., Bcker, E. M., Pettkus, N., Speidel, D., Rohde, V., Schulz-Schaeffer, W., Deppert, W., Giese, A. 2010. Chloroquine activates the p53 pathway and induces apoptosis in human glioma cells. Neuro-Oncology, 12(4):389–400.

Kolenich, J., Mansour, E., Flynn, A. 1972. Haematological Effects of Aspirin. The Lancet, 300(7779):714–714.

Lakhter, A. J., Sahu, R. P., Sun, Y., Kaufmann, W. K., Androphy, E. J., Travers, J. B., Naidu, S. R. 2013. Chloroquine Promotes Apoptosis in Melanoma Cells by Inhibiting BH3 Domain–Mediated PUMA Degradation. Journal of Investigative Dermatology, 133(9):2247–2254.

Lemaître, M., Guétard, D., Hénin, Y., Montagnier, L., Zerial, A. 1990. Protective activity of tetracycline analogs against the cytotoxic effect of the human immunodeficiency viruses in CEM cells. Research in Virology, 141(1):5–16.

Liao, W. I., Chien, W. C., Chung, C. H., Wang, J. C., Chung, T. T., Chu, S. J., Tsai, S. H. 2018. Valproic acid attenuates the risk of acute respiratory failure in patients with subarachnoid hemorrhage. QJM: An International Journal of Medicine, 111(2):89–96.

Marzolini, C., Buclin, T., Decosterd, L. A., Biolaz, J., Telenti, A. 2001. Nelfinavir Plasma Levels Under Twice-Daily and Three-Times-Daily Regimens: High Intertapatient and Low Intrapatient Variability. Therapeutic Drug Monitoring, 23(4):394–398.

Moiseeva, O., Deschênes-Simard, X., St-Germain, E., Igelmann, S., Huot, G., Cader, A. E., Bourdeau, V., Pollak, M. N., Ferbeyre, G. 2013. Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kB activation. Aging Cell, 12(3):489–498.

Moyle, G. J., Youle, M., Higgs, C., Monaghan, J., Prince, W., Chapman, S., Clendeninn, N., Nelson, M. R. 1998. Safety, Pharmacokinetics, and Antiretroviral Activity of the Potent, Specific Human Immun-
odeϑiciency Virus Protease Inhibitor Nelϑinavir: Results of a Phase I/II Trial and Extended Follow-up in Patients Infected with Human Immunodeϑi-ciency Virus. The Journal of Clinical Pharmacology, 38(8):736–743.

Mrhar, A., Kopitar, Z., Kozjek, F., Presl, V., Karba, R. 1979. Clinical pharmacokinetics of nitroxoline. International Journal of Clinical Pharmacology and Biopharmacy, 17(12):476–481.

Ochsendorf, F. 2010. Minocycline in Acne Vulgaris. American Journal of Clinical Dermatology, 11(5):327–341.

Olson, N. Y., Lindsley, C. B. 1989. Adjunctive use of hydroxychloroquine in childhood dermatomyosi-tis. The Journal of Rheumatology, 16(12):1545–1547.

Pearce, E. L., Walsh, M. C., Cejas, P. J., Harms, G. M., Shen, H., Wang, L.-S., Jones, R. G., Choi, Y. 2009. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. Nature, 460(7251):103–107.

Pelletier, C., Prognon, P., Bourlioux, P. 1995. Roles of divalent cations and pH in mechanism of action of nitroxoline against Escherichia coli strains. Antimicrobial Agents and Chemotherapy, 39(3):707–713.

Pugh, S., Thomas, G. A. 1994. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E2. Gut, 35(5):675–678.

Rothwell, P. M., Wilson, M., Elwin, C.-E., Norrving, B., Algra, A., Warlow, C. P., Meade, T. W. 2010. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. The Lancet, 376(9754):1741–1750.

Ruffin, M. T., Normolle, D., Vaerten, M. A., Peters-Golden, M., Brenner, D. E., Krishnan, K., Rock, C. L., Boland, C. R., Crowell, J., Kelloff, G. 1997. Suppression of Human Colorectal Mucosal Prostaglandins: Determining the Lowest Effective Aspirin Dose. JNCI Journal of the National Cancer Institute, 89(15):1152–1160.

Sgadari, C., Monini, P., Barillari, G., Ensoli, B. 2003. Use of HIV protease inhibitors to block Kaposi’s sarcoma and tumour growth. The Lancet Oncology, 4(9):537–547.

Shao, J., Jung, C., Liu, C., Sheng, H. 2005. Prostaglandin E2 Stimulates the β-Catenin/T Cell Factor-dependent Transcription in Colon Cancer. Journal of Biological Chemistry, 280(28):26565–26572.

Shim, J. S., Rao, R., Beebe, K., Neckers, L., Han, I., Nahta, R., Liu, J. O. 2012. Selective Inhibition of HER2-Positive Breast Cancer Cells by the HIV Protease Inhibitor Nelϑinavir. JNCI: Journal of the National Cancer Institute, 104(20):1576–1590.

Smith, W. L., Garavito, R. M., DeWitt, D. 1996. Prostaglandin Endoperoxide H Synthases. Journal of Biological Chemistry, 271:33157–33160.

Song, Y., Zhang, S., Guo, X., Sun, K., Han, Z., Li, R., Zhao, Q., Deng, W., Xie, Y., Zhang, J., Wu, M., Wei, L. 2013. Autophagy contributes to the survival of CD133+ liver cancer stem cells in the hypoxic and nutrient-deprived tumor microenvironment. Cancer Letters, 339(1):70–81.

Suliman, B. A., Xu, D., Williams, B. R. 2012. HDACi: molecular mechanisms and therapeutic implications in the innate immune system. Immunology & Cell Biology, 90(1):23–32.

Szeto, G. L., Brice, A. K., Yang, H.-C., Barber, S. A., Siliciano, R. F., Clements, J. E. 2010. Minocycline Attenuates HIV Infection and Reactivation by Suppressing Cellular Activation in Human CD4+ T Cells. The Journal of Infectious Diseases, 210(8):1132–1140.

Thun, M. J., Henley, S. J., Patrono, C. 2002. Non-steroidal Anti-inϑlammatory Drugs as Anticancer Agents: Mechanistic, Pharmacologic, and Clinical Issues. JNCI Journal of the National Cancer Institute, 94(4):252–266.

Tobinick, E. L. 2009. The value of drug repositioning in the current pharmaceutical market. Drug News & Perspectives, 22(2):119–119.

Yang, Y., Ikezoe, T., Takeuchi, T., Adachi, Y., Ohtsuki, Y., Takeuchi, S., Koeffler, H. P., Taguchi, H. 2005. HIV-1 protease inhibitor induces growth arrest and apoptosis of human prostate cancer LNCaP cells in vitro and in vivo in conjunction with blockade of androgen receptor STAT3 and AKT signaling. Cancer Science, 96(7):425–433.

Zhou, M., Xia, L., Wang, J. 2007. Metformin Transport by a Newly Cloned Proton-Stimulated Organic Cation Transporter (Plasma Membrane Monoamine Transporter) Expressed in Human Intestine. Drug Metabolism and Disposition, 35(10):1956–1962.