Drug Repurposing: Recent Advancements, Challenges, and Future Therapeutics for Cancer Treatment

Ika DM[3], Entonu ME[1], Emmanuel E[1], Barnabas CL[2], Gaiya DD[1,2,3] and Udu SK[1,2,3]

[1]Biology Unit Air Force Institute of Technology, Nigerian Air Force Base, Kawo, Kaduna State, Nigeria.

[2]African Centre of Excellence for Neglected Tropical Diseases and Forensic Biotechnology, Ahmadu Bello University, Zaria, Nigeria

[3]Department of Biochemistry, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

*Corresponding author:

Moses Edache Entonu
Biology Unit Air Force Institute of Technology,
Nigerian Air Force Base, Kawo, Kaduna State,
Nigeria, Phone: +2348061350442;
E-mail: moentos@yahoo.com

1. Abstract

Cancer is a prime public health burden that accounts for approximately 9.9 million deaths worldwide. Despite recent advances in treatment regimen and huge capital investment in the pharmaceutical sector, there has been little success in improving the chances of survival of cancer patients. Drug repurposing sometimes-termed drug repositioning is a strategy of discovery and redeveloping existing drugs for new therapeutic purposes. This novel approach is highly efficient, considerably cuts research and development costs, reduces the drug development timeline, maximizes therapeutic value and consequently increases success rate with minimum risk of failure. In this review, prioritizing drug repurposing to activate immune and inflammatory responses to target tumor cells through immune surveillance mechanism is a promising strategy for cancer immunotherapy. Cancer immunotherapy cover myriad of therapeutic approaches as cytokine therapy, immune checkpoint blockade therapy, cancer vaccines, natural killer cells, adoptive T cell therapies, monoclonal antibodies, oncolytic viruses, computational approach and host of others. In the current pipeline, drug repurposing is devoid of adequate funding and the necessary legal support for research and development by stakeholders. At the moment, immunotherapy strategies combine with computational biology could be considered the new milestone in drug re-profiling for cancer treatment.

2. Introduction

Cancer has been a major public health concern [19], being the second leading cause of death globally, and is responsible for an estimated 9.9 million deaths in 2020, with a projection of about 29.4 million new infections by 2024. The rising case of cancer incidence around the globe has placed a great burden on the world's economic, thereby, negatively affecting the survival rate among cancer patients, due to high costs in cancer treatment, putting many cancer treatments out of reach of patients and imposing strains on local health systems [33].

Recently, the use of cancer immunotherapy in the treatment of cancer has brought significant improvements in terms of survival and quality of life to cancer patients compared to other treatment approaches such as chemotherapy, radiotherapy, and surgery [7], due to its high success rate in clinical medicine [29]. However, many pharmaceutical industries have been faced with undesired challenges due to high failure rates during discoveries and production of new cancer therapeutic drugs (due to limited tumor specificity, immune related adverse effect, cost of production, etc.) which could not meet with the high demand of therapeutic drugs, these has made it crucial to explore new novel approach of drug repurposing in cancer immunotherapy which can serve as an alternative in cancer treatment using already approved drug agents [19, 29, 30].

Drug repurposing is a strategy of identifying and exploring new therapeutic potentials of existing or already approved drugs, beyond the scope of their original use in the treatment of new or existing diseases [21, 23]. For a better mastery of drug repurposing, knowledge of disease mechanisms and the identification of new

drug candidates is necessary. These can be achieve by combining both computational and experimental approaches involved in this process [23]. The novel computational approach in drugs repurposing takes different approaches, these includes: the target based, drug based and disease based approach [36, 46].

The unending spike in the database (genomic, proteomic, clinical, literature, and chemical structures) of knowledge available on the pharmacodynamics, pharmacokinetics, bioavailability, and toxicities of these drugs is crucial in the establishment of a well-defined protocols and dosing in drug repurposing process and clinical trials, these aid in optimizing the high cost, risk, and time involved, when compared to the traditional de novo approach of drug discovery [33, 36].

3. Immunotherapy to Treat Cancer

Exploiting the immune system in a way to target and destroy tumor cells has been the focus of research in cancer immunotherapy. During cancer invasion into a healthy tissue, immune and inflammatory responses are exert in a way to eliminate tumor cells through immune surveillance mechanism [25]. This serve as a monitoring mechanism system that targets surface antigens expressed on tumor cells, thereby elimination them from the body [32], showing the critical role played by monoclonal antibodies during the disease progression.

The use of immunotherapy as a regime to treat cancer has been given an optimal attention in recent times [37], and has stirred up a new and appealing stratagem in the treatment of cancer by enhancing the body's antitumor immune functions which leads to the destruction and death of the tumor cells. This approach has revolutionized the treatment of cancer among other models used, which include surgery, chemotherapy, radiotherapy and hormonal therapy.

4. Some Approaches in Cancer Immunotherapy

Immunotherapy in the treatment of tumor cells takes several approaches, this includes oncolytic viruses, cytokine therapy, cancer vaccines, natural killer cells, adoptive T cell therapies, monoclonal antibodies, and immune checkpoint blockade therapy etc., [9].

5. Cytokines Therapy

Cytokines, such as interferons, interleukins, lymphokines, monokines, chemokines, and growth factors, are cell-signaling molecules functioning as paracrine mediators that are produce naturally by numerous cell types [6, 25]. The immune cell activation properties (antiproliferative or pro-apoptotic activity and cytotoxic activity) of some of these cytokines have been investigate in oncology as a potential drug to resuscitate the body's immune system against tumor progression [9].

The antitumor activity of cytokines was first described by Ion Gresser and Chantal Bourali using the example of recombinant murine IFN-α in 1970. However, despite the promise on cytokines

as anti-tumor agent, IL-2 and IFN-α are the only two cytokines that has so far been approved by the Food and Drug Administration (FDA), showing mild clinical benefit by different studies [2, 9].

5.1. Oncolytic Viruses therapy

Oncolytic virus therapy (Oncolysis) is a novel approach that was develop in the treatment of cancer due to its ability to selectively replicate in cancer cells thereby causing tumor cell death [9, 36]. In this approach, the viral genome is modified in a way that will alter its virulence leading to an increase in anti-tumor activity. Promoters can be added into viral genes to reduce or delete the genes expressing pathogenicity [6, 7]. Also, some oncolytic virus expresses GM-CSF to enhance the production of granulocytes and monocytes that can stimulate cytokines production, required for T-cell activation and programmed to identify cancer cells in the body [8]. Although, from the clinical point of view, this approach is still at the infancy stage due to the possibility of some wild type virus to cause some adverse effect during replication in normal tissues [13].

Viruses such as adenoviruses, herpes viruses, measles viruses, coxsackie viruses, polioviruses, reoviruses, poxviruses, and Newcastle disease viruses, among others viruses have undergone some level of clinical studies as an antiviral agent [8, 13]. Among these viruses, herpes simplex-1 virus (HSV1) named "T-VEC again the resent approval by the FDA in 2015 to treat advanced melanoma. This virus was modified to express GM-CSF which further stimulates proliferation of the immune cells [6, 8].

However, the immune response exerted on the viral antigen has created some setback in this approach, reducing the effectiveness of the virus. This can be overcome by methods that prevent the virus from being recognized as an antigen. The process of using DCs, MSCs, T-cells, and cytokine-induced killers (CIKs) as host cell to load the virus or by modifying the viral genome genetically can protect the virus against immune neutralization [6].

6. Cancer Vaccines

Therapeutic vaccines are used in stimulating the immune system to fight and eliminate cancer cells from the body. They have the potential to recognize tumor antigens and augment antitumor T-cell responses against numerous cancer types [9, 39]. These vaccines are either dendritic Cell (DC) based vaccine; specialized in activating the immune system with targeted T cells to elicit an immune response against cancer cells (this helps in breaking the tumor tolerance that exist) [6], peptide-based vaccine or tumor cell-based vaccine, each exerting its own unique advantages and disadvantages. Clinical investigation on DNA-based, and nanocarrier-based vaccines are still under investigation [25].

The immune system is the first target of the therapeutic vaccine, this leads to an increase in attack on the cancer cells [47]. The validity of a target for a therapeutic cancer vaccine depends on the

ability of a tumor cell to process the Tumor-Associated Antigen (TAA) expressed by the vaccine in the context of a peptide–Major Histocompatibility Complex (MHC) for T-cell recognition or on the surface of the tumor cell for B-cell recognition [39].

6.1. Adoptive T cell Therapies

Adoptive T Cell Therapy is another type of immunotherapy that involves ex vivo manipulation of patient's T cells to initiate the expression of Chimeric Antigen Receptors (CARs) by genetic engineering [34], followed by the passive transfer of these cells into a lymphodepleted host. This leads to the production of a robust immune-mediated anti-tumor response of the T cells which recognize and attack tumor cells [37, 42].

This approach of genetically engineering T cells with chimeric receptors has shown remarkable effectiveness in the treatment of some hematological malignancies. However more clinical research need to be conducted to improve the efficacy of this approach [26].

6.2. Immune Checkpoint Blockade Therapy

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that inhibit factors that suppress T-cell function, by triggering the destruction and eradication of tumor cells. This approach acts by inhibiting several pathways use by tumor to escape immune surveillance. This aid in the down regulation of immune cells, thereby enhancing T cell activity, which ultimately results in increase in antitumor immunity [36]. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), [9, 47] are the most studied checkpoints receptor so far [1].

CTLA-4 is express on T cells and regulates the early activation of T-cells. It counteracts the activity of the T-cell costimulatory receptor CD28 by competing for its ligands B7.1 (CD80) and B7.2, thereby suppressing T cells activity. Ipilimumab is an anti-CTLA-4 antibody approved by FAD which blocks of CTLA-4 activity, resulting in prolonged T-cell activation, proliferation, and anti-tumor response [6, 36]. Similarly, PD-1 binds to programmed death ligands 1 and 2 (PDL1 and PD-L2), resulting in the down regulation of T-cell activity which cause a reduction in cytokine production and T-cell survival. This checkpoint receptor can be target-using Pembrolizumab [6, 44].

Immunomodulatory antibodies has demonstrated an effective anti-tumor response by targeting inhibitory T cell receptors in the treatment of various cancer type due to its long lasting treatment response in some patients [9]. Several drugs showing a positive result in clinical trial have been approved by FDA for treating various cancer diseases, these includes drugs like ipilimumab, pembrolizumab, nivolumab, and durvalumab [24].

6.3. Computational approaches in drug repurposing

Drug repositioning rely on data from existing drugs and diseases, the growth of publicly available biological, biomedical, and electronic health-related data along with the high-performance computing capabilities have accelerated the development of computational drug repositioning approaches. Multidisciplinary researchers have carried out numerous attempts, with different degrees of efficiency and success to computationally study the potential of repositioning drugs to identify alternative drug indications [20].

This strategy heavily relay on the wealth of large-scale genomic and proteomic data available, as well as data of small molecular compounds. It aids in timely and cost effectiveness in the production of new therapeutic agents for new or an existing disease through the utilization of a systematic drug-target-disease combination [15].

Computational approach in cancer drug repurposing has been successful through molecular docking, transcriptional signature, network analysis, data mining, machine learning and similarity analysis approaches

6.4. Drug repurposing approach to identify inhibitors of signalling pathway

Identification of molecular pathways that are deregulate in cancer will not only elucidate underlying tumorigenic mechanisms, but may also help to determine the classes of drugs that are used for treatment [11]. There is the need for novel efficacious and cost-effective strategies to identify efficacious modulators of oncogenic pathways in cells, the signatures associated with oncogenic activation of molecular pathways may offernew opportunities for targeted therapeutics discovery in cancer [4].

Expression signatures can be associated with oncogenic mutations and deregulated in tumours to predict the status of oncogenic signalling pathways that can be used to explore the biological basis underlying the differential patterns of expression [10]. Gene expression phenotypes have the potential to characterize the complex genetic alterations that typify the neoplastic state, whether in vitro or in vivo, in a way that truly reflects the complexity of the regulatory pathways that are affected [17].

Linking pathway deregulation with sensitivity to therapeutics that target components of the pathway provides an opportunity to make use of these oncogenic pathway signatures to guide the use of targeted therapeutics [3]. All successful cancer therapies are limited by the development of drug resistance. The increase in the understanding of the molecular and biochemical bases of drug efficacy has also facilitated studies elucidating the mechanism(s) of drug resistance. Experimental approaches that can help predict the eventual clinical drug resistance, coupled with the evolution of systematic genomic and proteomic technologies, are rapidly identifying novel resistance mechanisms [12]. Resistance to chemotherapy and molecularly targeted therapies is a major problem facing current cancer research. The mechanisms of resistance to 'classical' cytotoxic chemotherapeutics and to therapies that are designed to be selective for specific molecular targets share many features, such as alterations in the drug target, activation of

pro-survival pathways and ineffective induction of cell death [16].

Recent advances in computational biology suggest that any perturbation to the transcriptional programme of the cell can be summarised by a proper 'signature' a set of genes combined with a pattern of expression. Therefore, it should be possible to generate proxies of clinicopathological phenotypes and drug effects through signatures acquired [19].

Although the knowledge and technology of human diseases have developed substantially, the translation of these benefits into therapeutic innovations has been far slower than expected [25]. To solve this problem, drug repurposing (also known as drug repositioning, re-tasking or re-profiling) has emerged as an attractive and pragmatic way offering minimum risks failure, maximizes the therapeutic value of a drug and consequently increases the success rate [37].

In the past, drug repurposing has been largely accidental and serendipitous. The most successful examples so far have not involved a systematic approach. Nowadays, the boom of drugs, diseases and bioinformatics knowledge is offering great opportunities for designing novel drug repurposing approach [25].

Drug repurposing strategies uses a cost-effective way offers a rare opportunity for the treatment of human neoplastic disease, facilitating rapid clinical translation. With an increased understanding of the hallmarks of cancer and the development of various data-driven approaches, drug repurposing further promotes the holistic productivity of drug discovery and reasonably focuses on target-defined antineoplastic compounds [48]. The availability of several established clinical drug libraries and rapid advances in disease biology, genomics and bioinformatics has accelerated the pace of both activity-based and *in silico* drug repositioning. Drug repositioning has attracted particular attention from the communities engaged in anticancer drug discovery due to the combination of great demand for new anticancer drugs and the availability of a wide variety of cell- and target-based screening assays [40].

7. Challenges for Drug Repurposing

Despite clinical efficacy, advancing drug repurposing strategies in the clinical trial trajectory beyond early phase studies has been challenging mainly due to lack of funding and interest from the pharmaceutical industry. Also, Studies for drug repurposing usually enrolled relatively small numbers of patients, often with diverse treatment-refractory advanced malignances, which may have complicated data interpretation [21].

Another problem faced by drug repurposing is the issue of loss of operational revenue due the reproduction of generic version of expired patent at lower cost, this was seen to true, when a drug patent (celebrex) expired in 2014 [14]. Due to these implications, commercialization of repurposed drugs has little chance for success without patent protection that can attract funding and promise a reasonable return on investment [30].

Drug repositioning takes advantage of the reduced toxicity, side effects, and costs of clinical trials [33]. However, the financial support for drug repurposing approaches has been lacking, shorter patent duration. The Food and Drug Administration (FDA) offers only a period of three years exclusively for a new use of previously used drug for a new indication, which is very short period of time to regain the invested money and in case a loss for the pharmaceutical industry [41].

7.1. Perspectives and Future Direction

Pharmaceutical researches in recent years, and its utility has gone beyond bioactivity predictions and has shown promise in addressing diverse problems in drug discovery [5].

Broadly, there are three kinds of approaches, which are widely used in drug repositioning: computational approaches, biological experimental approaches, and mixed approaches. Data such as gene expression, drug-target interactions, protein networks, electronic health records, clinical trial reports, and drug adverse event reports has become accessible in standardized forms [43].

A multidisciplinary approach have also been seen to be successful when protein-protein interaction network was combined with CMap (Connectivity Map), project profiled human cancer cell lines exposed to a library of anticancer compounds with the goal of connecting cancer with underlying genes and potential treatments [46]. Many computational drug reposition methods based on transcriptomic data have been develop to identify potential new indications for drugs. Each method has applied techniques such as comparison of gene expression profiles between a disease model and the drug-treated condition [23].

The repository of knowledge and "omics" data available in pharmaceutical researches have led to the rise of some computational methods which are novel and exciting in the field of drug repositioning. These computational methods are capable of making high-level integration of all the knowledge and data that will enable the understanding of new signalling pathways and generate novel insights into drug mechanisms, side effects, and interactions which further speed up drug discovery [43].

8. Conclusion

In recent years, the concept of drug repurposing in cancer immunotherapy has attracted much attention, which validates it potential to improving the quality of life and survival of cancer patents. It is worth noting, prioritizing drug repurposing in cancer immunotherapy may be consider as one of many effective and reliable strategies that could be explore for cancer treatment. Drug repurposing in cancer immunotherapy would overcome the problem associated with high cost in research and development of new drug; prolong drug development timeline and loss of operational revenue. In this, present review, immunotherapy strategies combine with computational biology could be consider the new milestone in drug re-profiling for cancer treatment.

Reference

1. Anagnostou VK, Brahmer JR. Cancer Immunotherapy : A Future Paradigm Shift in the Treatment of Non – Small Cell Lung Cancer. 2015; 21(5): 976-85.

2. Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, et al. Cytokines in clinical cancer immunotherapy. British Journal of Cancer. 2019; 120(1): 6-15.

3. Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature. 2006; 439(7074): 353-7.

4. Carrella D, Manni I, Tumaini B, Dattilo R, Mutarelli M, Sirci F, et al. Computational drugs repositioning identifies inhibitors of oncogenic PI3K / AKT / P70S6K-dependent pathways among FDA- approved compounds. Oncotarget. 2016; 7(37).

5. Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug Discovery Today. 2018; 23: 1241-50.

6. Dong H, Markovic SN. The Basics of Cancer Immunotherapy. New York: Springer New York LLC. 2018.

7. Esfahani K, Roudaia L, Buhlaiga N, Rincon SV, Del, Papneja N. A review of cancer immunotherapy: from the past, to the present, to the future. 2020; 27: 87-97.

8. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: The beginning of the end of cancer? BMC Medicine. 2016; 14(1): 1-18.

9. Filin IY, Solovyeva VV, Kitaeva KV, Rutland CS, Rizvanov AA. Current trends in cancer immunotherapy. Biomedicines. 2020; 8(12): 1-36.

10. Freedman JA, Tyler DS, Nevins JR, Augustine CK. Use of gene expression and pathway signatures to characterize the complexity of human melanoma. American Journal of Pathology. 2011; 178(6): 2513-22.

11. Furge KA, Tan MH, Dykema K, Kort E, Stadler W, Yao X, et al. Identification of deregulated oncogenic pathways in renal cell carcinoma: An integrated oncogenomic approach based on gene expression profiling. Oncogene. 2007; 26: 1346-50.

12. Garraway LA, Jänne PA. Circumventing cancer drug resistance in the era of personalized medicine. Cancer Discovery. 2012; 2: 214-26.

13. Hemminki O, Dos Santos JM, Hemminki A. Oncolytic viruses for cancer immunotherapy. Journal of Hematology and Oncology. 2020; 13(1): 1-15.

14. Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, Molinski SV. Giving drugs a second chance: Overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. Frontiers in Oncology. 2017; 7: 1-13.

15. Hodos RA, Kidd BA, Khader S, Readhead BP, Dudley JT. Computational Approaches to Drug Repurposing and Pharmacology. Wiley Interdiscip Rev Syst Biol Med. 2016; 8(3): 1-46.

16. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. Nature Reviews Cancer. 2013; 13: 714-26.

17. Huang E, Ishida S, Pittman J, Dressman H, Bild A, Kloos M, et al. Gene expression phenotypic models that predict the activity of oncogenic pathways. Nature Genetics. 2003; 34(2): 226-30.

18. Huang J, Zhao D, Liu Z, Liu F. Repurposing psychiatric drugs as anti-cancer agents. Cancer Letters. 2018; 419: 257-65.

19. Iorio F, Rittman T, Ge H, Menden M, Saez-rodriguez J. Transcriptional data : a new gateway to drug repositioning ? Drug Discovery Today. 2013; 18(7-8): 350-7.

20. Jarada TN, Rokne JG, Alhajj R. A review of computational drug repositioning: strategies, approaches, opportunities, challenges, and directions. Journal of Cheminformatics. 2020; 1-23.

21. Kato S, Moulder SL, Ueno NT, Wheler JJ, Meric F, Kurzrock R, Janku, F. Challenges and perspective of drug repurposing strategies in early phase clinical trials. 2015; 2(6).

22. Ko Y. Applied sciences Computational Drug Repositioning: Current Progress and Challenges. 2020.

23. Lee SY, Song MY, Kim D, Park C, Park DK, Kim DG, et al. A proteotranscriptomic-based computational drug-repositioning method for Alzheimer's disease. Frontiers in Pharmacology. 2020; 10.

24. Lee Ventola C. Cancer immunotherapy, part 1: Current strategies and agents. P and T. 2017; 42(6): 375-83.

25. Li B, Dai C, Wang L, Deng H, Id YL, Guan Z, Ni H. A novel drug repurposing approach for non- small cell lung cancer using deep learning. 2020; 1–14.

26. Li D, Li X, Zhou WL, Huang Y, Liang X, Jiang L, et al. Genetically engineered t cells for cancer immunotherapy. Signal Transduction and Targeted Therapy. 2019; 4(1).

27. Li J, Zheng S, Chen B, Butte AJ, Swamidass SJ, Lu Z. A survey of current trends in computational drug repositioning. 2016; 17: 2-12.

28. Lim S, Park J, Shim MK, Um W, Yoon HY, Ryu JH. Theranostics Recent advances and challenges of repurposing nanoparticle-based drug delivery systems to enhance cancer immunotherapy. 2019; 9(25).

29. Mccabe B, Liberante F, Mills KI. Repurposing medicinal compounds for blood cancer treatment. Hematol, Ann. 2015.

30. Hulbert MB, Berghoff LLP. Why Method of Treatment Patents for Repurposed Drugs Are Worth the Investment | McDonnell Boehnen Hulbert & Berghoff LLP - JDSupra. 2020.

31. Meiliana A, Dewi NM, Wijaya A. Cancer Immunotherapy: A Review. The Indonesian Biomedical Journal. 2016; 8(1): 1.

32. Pantziarka P, Bouche G, Meheus L, Sukhatme V. Repurposing drugs in your medicine cabinet : untapped opportunities for cancer therapy? 2015; 11: 181-4.

33. Park K. A review of computational drug repurposing. Translational and Clinical Pharmacology. 2019; 27: 59-63.

34. Perica K, Varela JC, Oelke M, Schneck J. Adoptive T Cell Immunotherapy For Cancer. Rambam Maimonides Medical Journal. 2015; 6(1): e0004.

35. Peyvandipour A, Saberian N, Shafi A. A novel computational ap-

proach for drug repurposing using systems biology. 2018.

36. Rouzbahani FN, Dana H, Chalbatani GM, Mahmoodzadeh H. Immunotherapy a New Hope for Cancer Treatment : A Review Review Article Immunotherapy a New Hope for Cancer Treatment : A Review. 2018.

37. Rudrapal MJ, Khairnar S, Jadhav GA. Drug Repurposing (DR): An Emerging Approach in Drug Discovery. In Drug Repurposing [Working Title]. 2020.

38. Sambi M, Bagheri L, Szewczuk MR. Current challenges in cancer immunotherapy: Multimodal approaches to improve efficacy and patient response rates. Journal of Oncology. 2019.

39. Schlom J, Hodge JW, Palena C, Tsang KY, Jochems C, Greiner JW, et al. THERAPEUTIC CANCER VACCINES. Physiology & Behavior. 2019; 176(3): 139-48.

40. Shim JS, Liu JO. Recent advances in drug repositioning for the discovery of new anticancer drugs. International Journal of Biological Sciences. 2014; 10: 654-63.

41. Sindhu S, Murugan S. Review article: Challenges and Opportunities in Repurposing of Drugs: Mini Review. Medical Science. 2020; 19(03): 365-71.

42. Ti D, Bai M, Li X, Wei J, Chen D, Wu Z, et al. Adaptive T cell immunotherapy in cancer. Science China Life Sciences. 2020.

43. Uttam T, Subhashree S, Madhu P, Lingaraju C, Kesavan M, Kumar D. Drug repurposing approach to fight COVID-19. Pharmacological Reports. 2020; 0123456789.

44. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nature Reviews Immunology. 2020; 20(11), 651-68.

45. Würth R, Thellung T, Bajetto A, Mazzanti M, Tullio, Florio, FB. Drug-repositioning opportunities for cancer therapy: novel molecular targets for known compounds. Drug Discovery Today. 2015.

46. Yu J, Putcha P, Silva JM. Recovering drug-induced apoptosis subnetwork from connectivity map data. BioMed Research International. 2015.

47. Zhang H, Chen J. Current status and future directions of cancer immunotherapy. Journal of Cancer. 2018; 9(10): 1773-81.

48. Zhang Z, Zhou L, Xie N, Nice EC, Zhang T, Cui Y, Huang C. Overcoming cancer therapeutic bottleneck by drug repurposing. Signal Transduction and Targeted Therapy. 2020; 5(1).