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THERAPEUTIC DELIVERYVOL. 12, NO. 4EDITORIAL

Drug repurposing supported by nanotechnology: a promising strategy to fight cancer

- **Article title:** Drug Repurposing Supported by Nanotechnology: A Promising Strategy to Fight Cancer.
- **Short running title:** Drug Repurposing for Cancer Treatment.
- **Author names:** Mohammad Najlah *
- **Author affiliations:** Pharmaceutical Research Group, School of Allied Health, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Bishops Hall Lane, Chelmsford CM1 1SQ, UK
- **ORCID iD:** 0000-0001-7670-2859
- ***Author for correspondence:** Mohammad Najlah
mohammad.najlah@aru.ac.uk
- **Author Contributions:** Sole author, no other contribution to report.
- **Acknowledgements:** N/A
- **Financial disclosure:** N/A
- **Information pertaining to writing assistance:** N/A
- **Ethical disclosure:** N/A
- **Data sharing statement:** N/A

Published Online: 4 Mar 2021 <https://doi.org/10.4155/tde-2021-0009>

First draft submitted: 23 January 2021; Accepted for publication: TBC; Published online: TBC

- **Keywords:** drug repurposing, disulfiram, anti-cancer, copper, liposomes, PLGA.

Over the last few decades, cancer has been one of the major dangers to human health with more than 200 types of cancer diagnosed globally. According to the WHO, cancer diseases are expected to cause 21 million deaths worldwide by 2030 [1,2]. Furthermore, the impact on the global economy is excruciating with an expected global cost of \$200 billion by 2022 [3]. Despite the urgent need for efficient cancer therapy, the development of new anticancer drugs is yet gradual and expensive. This is mainly due to the high risk of toxicity associated with new druggable candidates. This has led to a predominant interest in repurposing licensed drugs into new use for cancer treatments [4,5]. With a currently massive library of

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non-toxic drugs and their derivatives, there is growing recognition for such a tremendous resource for drug repositioning [5].

Drug repurposing may become the most promising strategy in cancer treatment due to the high safety profile. More importantly, the potential feasibility of this strategy is to overcome challenges arising from traditional anticancer treatment such as multi-drug resistance and acquired chemoresistance [6-8]. Acquired chemoresistance, caused by repetitive exposure of cancer cells to anticancer drugs, is one of the main hurdles to successful chemotherapy. The resistant cancer cells are commonly cross-resistant to a wide range of anticancer drugs. Elucidation of pan-resistant mechanisms is of significant clinical importance and will identify novel targets for anticancer drug development [9].

On the other hand, similar to traditional anticancer drugs, repurposed drugs still have delivery and formulation challenges such as poor aqueous solubility, limited stability and/or unsuitability to the new route of administration. Nano-technology may play a key role in promoting the efficient use of drugs showing high anticancer activity but associated with delivery problems. Nano drug delivery systems have been investigated to circumvent challenges such as poor water solubility and multi-drug resistance [6-8].

Over last three decades, tens of nano-based drug delivery systems are approved by Food and Drug Administration (FDA) and used in clinic [10]. Doxil, approved 1995, represents the first nano-liposome encapsulated anti-tumor drug (doxorubicin) [11]. After a long journey of lab research and clinical trials, a perfect tuning of the liposome compositions and hydration conditions resulted in PEGylated non-liposomes enabling higher doses and less toxic effects compared to that of the free drug. Furthermore, the high passive targeting of Doxil to tumor tissues by “as yet unknown means” was the cherry on the top [11]. Hopefully, similar successful stories are expected with many of these “nano-drugs” are in clinical trials [10].

One of the most relevant examples of a potentially successful strategy is the combination between disulfiram and nano-technology. Disulfiram (DS), used safely for decades to treat alcoholism, has shown lethal activity against wide range of cancer cells including drug-resistant cancer stem cells (CSCs) [9]. Furthermore, DS entirely reverses the chemo-resistance and cross-resistance of cancer cells and blocks liver cancer cell migration *in vitro* and metastasis *in vivo*. DS has also a potent synergic anti-cancer activity with a wide range of first-line anticancer drugs such as cisplatin, 5-fluorouracil, paclitaxel, and others *in vitro*. Yet, DS was not toxic to normal cells in the kidneys, gut or bone marrow *in vivo* [12,13]. The anticancer activity of DS is dependent on the concentration of copper (II) (Cu^{+2}), which presents in cancer tissue at higher levels compared to normal counterparts. This might also explain the reported selectivity of DS to target cancer cells [5]. The chelation of DS with Cu^{+2} produces the complex diethyldithiocarbamate copper (II) (DDC-Cu), which has also shown potent anticancer activities [14]. The parenteral use of disulfiram for cancer treatment clinically is limited by its bio-instability in the bloodstream ($t_{1/2} < 4$ min). DS also undergoes extensive liver metabolism where its sulfhydryl group is blocked by methylation/glucuronidation. This might curtail the per oral administration of DS for cancer treatment. Therefore, the need to develop a long-circulating nano-drug delivery system to protect DS in the bloodstream and enable targeted delivery is undiminished [5,14].

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A wide range of nano-based drug delivery system such as liposomes, micelles, polymeric nanoparticles (NPs), and lipid-based NPs have been investigated as “shield carriers” of DS for cancer therapy. Despite the recent somewhat-successes in improving the stability DS in blood *in vitro* using nanotechnology [5,15,16], we are still far away from the “Trojan Horse” loading DS safely to cancer tissues. For example, liposomes provided enhanced stability of loaded DS compared to the free drug in horse serum. Further improvement was achieved upon PEGylation of DS-loaded liposomes with $t_{1/2} \sim 75$ min [5], whereas there have been conflicting reports on the extent of protection provided by PLGA nanoparticles [15,16]. It is unlikely that the half-life of DS-loaded PLGA exceeds 120 min [15]. Despite the fact that PLGA nanoparticles are considered biocompatible and might offer longer protection, liposomes may be more translational than any other nano-carriers based on the fact that liposomes have already found their way to the clinic [11]. For instance, Doxil[®], doxorubicin encapsulated in PEGylated liposomes, provided extended retention *in vivo* and improved therapeutic outcomes [11]. In contrast, PEGylated liposomes were unsuccessful for vincristine due to rapid leakage. Further extensive investigations including *in vivo* studies are therefore still needed for DS-loaded liposomes [5].

Another challenge that may hinder the use of DS is to ensure a sufficient supply of Cu^{+2} to cancer tissue. It could be suggested that Cu^{+2} may be given as an oral supplement during the treatment. Again, another dilemma arises in this context is how to create the perfect balance between using Cu^{+2} as a therapeutic agent and its toxicity. Some reports proposed the combined delivery of DS and Cu^{+2} in one nano-carrier [17], but the chelation reaction between DS and Cu^{+2} is instantaneous, therefore stability studies should be investigated in depth. The direct use of the complex DS-copper (DDC-Cu) in cancer therapy has been also investigated as an alternative to the split administration of both DS and copper. But, DDC-Cu is practically insoluble in water, limiting its anti-cancer studies. Recently, cyclodextrin inclusion complexes of DDC-Cu have been reported as a promising solution to facilitate further investigations on the potential use of this complex in the treatment of cancer [18].

This example shows the importance of a partnership between drug repositioning and nanotechnology as a strategy aiming to develop new therapies for cancer. Multidisciplinary collaborations bridging chemistry with biology are needed to develop such treatments from “bench” to “bedside”.

Financial and competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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