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### Mini Review

## MODULATING MULTIPLE DRUG RESISTANCE VIA CO-DELIVERY OF NANOPARTICLE

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### ABSTRACT

When various mechanisms in cancer causing cells show resistance towards one or many chemotherapeutics, it hinders the efficacy of chemotherapy. This is referred as multidrug resistance. There are several factors that contribute in MDR. This research specifically focuses on modulate resistance towards multiple drugs by co-delivery of the nanoparticle. This research review has highlighted several delivery systems of nanodrug for overcoming the mechanism followed by MDR. This is done by exploiting, evading or neutralizing the pumps of drug efflux. The research essay has specifically discussed five different system categories. These categories are Mdr-1 and survivin-targeting, Docetaxel and siRNA, Paclitaxel and curcumin, Doxorubicin and paclitaxel and Doxorubicin and PSC 833. Based on the overall discussion, a brief summary is provided.

**Keywords:** Drug resistance, nanomedicine, co-delivery, drug delivery.

### INTRODUCTION

Cancer is a major factor contributing to several deaths across the globe. There has been development of several therapeutic strategies such as biological treatments to specific pathways of a cell.<sup>1-3</sup> However, acquired and inherent multidrug resistance (MDR) towards drugs of chemotherapy is a major challenge for effectively treating cancer.<sup>4,5</sup> Cancer is one of the diseases that are prevailing and most impactful presently.<sup>6,7</sup>

The aim of this essay is to modulate MDR by the use of nanoparticle via co-delivery.<sup>8</sup> In this research essay, specific theoretical understanding will be established regarding the key concepts relevant to this research issue.<sup>9</sup> A brief discussion on specific topics will be presented that include Mdr-1 and survivin-targeting, Docetaxel and siRNA, Paclitaxel and curcumin, Doxorubicin and paclitaxel and Doxorubicin and PSC 833 and a brief summary will be provided to conclude the essay.

### MDR-1 and Survivin-Targeting

MDR is the biggest challenge faced in successfully completing chemotherapy for the treatment of cancer.<sup>10,11</sup> There is a complicated mechanism involved with several factors affecting the same such as proteins functioning, ABC transporters and extrude drugs and toxins.<sup>12</sup> Survivin is a new member of the family of apoptosis inhibitors.<sup>13</sup> The functional role is possible in the case of apoptosis control and cell division. This is up-regulated in case of human cancers that make it a new potential target for the treatment of cancer.<sup>14</sup> For the purpose of overcoming MDR, some compounds of the small molecule were utilized in the form of functional inhibitors like promethazine, cyclosporine A, and verapamil. However, their unknown pharmacokinetic interaction with toxicities and chemotherapeutics restricted their utilization in clinics. Additional reports were made that the encapsulation of chemotherapeutic agents within nanoparticles could end up evading the pumps of drug efflux. This further ended up increasing the concentration of the intracellular drug.

This rarely showed the effects of anti-tumor. In addition, such increased level of concentration did not lead towards the proportionately increasing death of cell on blocking the apoptosis pathway. It was recently investigated and discovered that MDR can enable partial reversal as the gene coding expression is silenced. Their experiments on *in vivo* anti-tumor only ended up exhibiting the capability to reduce the growth of tumor but without decreasing the volume of the tumor.

### Docetaxel and siRNA

The combination of several therapeutic approaches with various mechanisms can be a feasible option for effectively treating cancers with combined or synergistic impacts.<sup>15</sup> Small interference of RNA was a strong technique with a feasible therapeutic option to silence genes targeted in a number of diseases.<sup>16</sup> A number of different therapeutics based on siRNA have established for treatment of diseases effectively.<sup>17</sup> However, there cannot be an easy crossing of cell membranes in siRNA due to the involvement of negative charge and there is a delay in downstream effects.<sup>18</sup> This is in comparison with the conventional therapeutics based on protein or small molecule. In addition, for being successful in clinically applying siRNA, there is a requirement to be effective in delivering vehicles. This is crucial for overcoming several barriers in the cell. In addition, anti-cancer drug effect of the small molecule is fast in comparison with siRNA. This is specific in the process of intracellular uptake. Simultaneously, nanocarriers will be targeting the drugs while lowering the side effect.<sup>19,20</sup> Therefore, the set of newly emerging therapy based on siRNA with traditional procedures of chemotherapy can be considered advantageous. Until yet, a number of promising systems for the purposes of co-delivery are established on the basis of silica, liposomal and polymeric based cationic NPs. When compared, non-viral vectors based on polymer have major benefits in comparison with cationic lipids. These advantages are specific to physiological stability, large scale production, convenience, and safety. There has been an investigation of several natural and synthetic cationic polymers as carriers of siRNA or gene. These include chitosan, polylysine, and polyethyleneimine.

### Paclitaxel and Curcumin

Curcumin is a polyphenol, also termed as diferuloylmethane. Its extraction is done from *Curcuma longa*, which is a perennial herb.<sup>21,22</sup> This has been researched extensively considering its level of therapeutic efficacy for a number of disorders that include other inflammatory diseases such as cancer and Alzheimer's. On extensively researching curcumin, a number of its significant functions are revealed.<sup>23</sup> It comes in interaction with a number of proteins inhibiting the performance of several kinases and controlling the activated factors of transcription. These have specific involvement in survival and proliferation of the cell. Irrespective of the effectiveness delivered by curcumin, it has limited use in the clinic because of its property of hydrophobicity and low level of *in vivo* bioavailability.<sup>24</sup> However, due to the attribution of several therapeutic activities with curcumin, a solution to these issues is being searched persistently. Delivery systems of nano-sized drugs are identified as crucial for overcoming these limitations. In addition, the establishment of MDR is among the crucial factors that fail several conventional chemotherapies. Three main

mechanisms are involved in which resistance to the drug is acquired by the cancer cells. These are: decreasing the intake of the drug with water solubility, intracellular modifications impacting the performance of cytotoxic drugs like shifted cycle of the cell, and increased efflux of hydrophobic drugs dependent on energy.

### Doxorubicin and Paclitaxel

Chemotherapy is not considered a good option because of its undesirable negative implications on the health.<sup>25</sup> This is supported by a low level of bioavailability along with the development and emergence of drug resistance. Several reports have stated that resistance to multiple drugs will be significantly limiting the penetration in tumor tissues by anti-cancer drugs.<sup>26</sup> This leads towards poorly concentrated anti-cancer drugs inside the tumor which further fails the procedure of chemotherapy.<sup>27</sup> For the purpose of overcoming these limitations, a number of drug delivery systems with effective advancement are designed by the use of various biocompatible nano-materials. A pharmaceutical strategy that is most promising is the system of polymeric nanomicelle that has been applied in a number of trials. Polymeric micelles are known for exhibiting various benefits in comparison with other delivery systems of the drug like eased production, longer circulation, and ability of targeting. In addition, specific protection will be provided to entrapped drugs of anti-cancer from inactivation in the media of biology. This is because of the specific structure of core-shell across the system of the polymeric micelle. In collective terms, it has been discovered that polymeric micelles are the excellent system of nano-drug delivery for chemotherapy. Even though polymeric micelles are known for significantly affecting the establishment of anti-cancer delivery systems loaded with nano drugs, there is a scope of improvement in a certain aspect. This is because 40 per cent of tumors in humans have the ability to develop resistance against agents of chemotherapy.

### Doxorubicin and PSC 833 (Valspodar)

Chemotherapy can be identified as the mainstream approach for treating metastasized and localized cancers.<sup>28,29</sup> However, the establishment of resistance from multiple drugs by cancer cells along with side effects of systemic toxic take place due to the unspecific localization of such drugs to areas without tumor is major challenges.<sup>30</sup> There can be the occurrence of MDR by transporters of the drug efflux which are active in effluxing out drug. This results in reducing the accumulation of intracellular drugs and decreasing the level of therapeutic efficacy. The role played by P-gp within MDR has resulted in efforts for modulating the activity of P-gp.<sup>31</sup> Several compounds known for possessing the inhibitory activities of P-gp are synthesized specifically for addressing this problem. Inhibitors of the first generation are compounds active pharmacologically which provided evidence of inhibiting P-gp even though being researched for different purposes.<sup>32</sup> However, significant nephrotoxic and immunosuppressive effects, cardiac toxicities, poor specificity and low potencies for transporters of drug efflux end up limiting their clinical application.

### SUMMARY

There is a requirement of an efficient carrier for delivering therapeutic RNA of small interference to the site of a target as a number of natural challenges have to be dealt with.<sup>33,34</sup>

Poly is a specific biodegradable polymer that consists of base-sensitive or acid ester bonds and amino segments. This enables PAEs for condensing the molecules of nucleic acids at physiological pH while releasing them across

cytoplasm at acidic lysosomal or endosomal environment. Even though several reports are made to employ PAEs as vehicles of RNA, the efficiency of RNAi may not be as high as per the expectation set.

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