Gemcitabine-carbon nitride dots as nanocarrier to target specifically pediatric glioma tumors

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Commmentary

The article discusses a study to target-specific gemcitabine delivery to pediatric glioblastoma tumors across the blood-brain barrier (BBB) using carbon nitride dots (CNDs) as a nanocarrier. CNDs can be identified as a third-generation novel nano dot material after semiconductor metal quantum dots and carbon dots. Similar to its predecessor carbon dots, CNDs have excellent stability, water dispersibility and non-toxic properties in comparison to the metal quantum dots. The approach of fusing N into CDs to overcome the inherent limitation of low photoluminescence quantum yields led to the way for CNDs [1]. Its unique graphene-like heteroatom structure of C3N4 gained increased interest with variety of applications such as metal detection, catalysis and solar energy for over a decade [2, 3]. Recently, the CNDs were introduced into the biomedical world by focusing on bioimaging applications due to its high photoluminescence quantum yields achieved, however much less known in other aspects. Furthermore, by using different methods and materials CNDs can be tuned with different characteristics and defective surfaces comprised with abundance of functional groups to facilitate various applications [4-6]. There are not many studies conducted so far that focus on the use of CNDs as therapeutic or delivering agent apart from a bioimaging tool. In this study, CNDs are used as a nanocarrier for the delivery of a therapeutic agent to a specific target site [7, 8].

The CNDs have been synthesized using a microwave synthesis approach with urea and citric acid as precursors which are abundantly accessible and low in cost. The importance is that the synthesis does not require any harsh materials or advanced instruments/conditions thus, easily achievable, low cost and environmentally friendly.4 Microwave approaches for nanomaterial synthesis has been trending recently, due to the ease of use, less time consuming and capability to reach high thermal conditions over other traditional methods. For biomedical applications, it is immensely important that the materials are non-toxic and biocompatible [9]. Therefore, purification plays a major role in laboratory synthesized materials for reliability purposes. The study in interest has focused significantly on this aspect, that several purification techniques has been enrolled such as centrifugation, filtration and dialysis in relevance to the compound molecular weights.

The study focused on target delivering the discussed drug platform to high-grade pediatric glioblastoma brain tumors. Brain tumors identified one of the most dangerous cancers today, remain with a very low survival rate beyond 5-years. These can be categorized into two types; primary where the tumor arises in the brain and secondary where the tumor metastasizes into brain from elsewhere of the body. Regardless of the origin, brain tumors are hard to control and eradicate due to the unachievable locations and sensitive organ environments. In children, high-grade gliomas originating at brain glial cells, have been reported to be highly aggressive although the reported number of cases are low compared to the adult counter parts. Moreover, the available prognosis data are low and treatments are mostly dependent on the data obtained from similar studies of adult gliomas [10]. But this approach is questionable, given the results of several recent studies showing outcomes that pediatric glioma biological and genomic data differ from the adult versions[11]. Further, many current treatments are based on the successful therapeutic regimens on adult studies thus, use non-targeting highly strong therapeutic drugs such as doxorubicin, temozolomide and vemurafenib [12]. These are known to be strong anti-cancer agents and cause severe adverse side effects on long term use such as cardiotoxicities and other major biological toxicities [13, 14]. Thus, when administered on still developing organs of the pediatric patients, these can cause life threatening or long-term side effects irrelevant to cancer survival. Several studies have reported on such cases where the patients are unable to recover to a normal life years after cancer survival due to the organ damage caused by treatment regimens at pediatric level [15]. Thus, it is of utmost importance to develop anti-cancer treatments which can be self-targeting to the cancer site and thus, cause minimal damage to other organs and tissues. It is in this regard, that nanoparticle drug delivery systems gained popularity in recent years [16]. But not many carbon-based nanoparticle systems have shown promising results or approved for treatments. Therefore, the discussed study focused on the capability of CNDs to deliver the anti-cancer agents to the tumor cells without affecting the non-cancerous cells thus, lowering the possible adverse side effects.

Two drug delivery systems have been compared, with and without a targeting protein ligand, namely transferrin (Tf). The anti-cancer agent GM is used which has been previously proven to demonstrate potent anti-glioma effects on preclinical studies. However, the adult clinical trials have been largely disappointing as well as few pediatric studies which showed no increase on overall survival rate [17]. Nevertheless, GM is an attractive potent cancer cell death inducer by blocking the DNA polymerase activity. Several different types of brain tumor cells have been studied for viability in vitro [18, 19]. The CN-GM conjugate has shown effective targeting anti-cancer activity on high-grade pediatric glioma (SJGBM2) over non-cancerous cells whereas the single agent GM showed no specificity in targeting. It is discussed to be due to the CNDs capability to disguise as glutamine and use glutamine transporter that the specific targeting ability arise. The results are very attractive in which the conjugate is capable to cause

death of almost all the SJGBM2 cells in comparison to no harm visible to non-cancer cells. But the conjugate seems to lose its capability at lower concentrations. Thus, the use of Tf has come in to play as a targeting ligand due to the high abundance of Tf receptors on cancer cell membranes which is needed for its metabolic demands. The results have shown an immensely attractive improvement of the drug quantity administered[20]. The CN-GM-Tf conjugate had been capable of achieving a 100-fold lower concentration preserving the same efficacy and selectivity as of CN-GM preciously. Thus, CNDs conjugates show capability to selectively administer therapeutics to target pediatric gliomas with minimal influence on non-cancerous cells at in vitro studies. However, it is of utmost importance to further elaborate these studies in vivo to understand the capability of CNDs platforms to be use in clinical treatments. The study has moved further into bioimaging owing to photoluminescence emission of CNDs to confirm the selective targeting and entry of the CNDs and its conjugates into SJGBM2 cells. Several imaging studies have been conducted and the statistical investigations showed that the conjugates enter the tumor cells significantly compared to the non-cancerous cells which only show an insignificant amount of obtained luminescence due to possible passive diffusion of small quantities into the cells. Thus, in conclusive the CNDs mostly seem to use the glutamine transporters that are abundant in specifically SJGBM2 cells, by mimicking its structure using the functional groups present such as amine, amide and carboxylic. In comparison, the non-cancerous cells are low in these means thus, the entry amounts are insignificant or very low.

In treatments for diseases in the central nerves system (CNS), another unavoidable hurdle is discussed in the study, BBB. The BBB acts as a biological barrier that hinders the entry of many unwanted toxic materials, thus avoiding possible harmful effects brought to CNS. This barrier has become an obstacle to many brain related treatments since almost 99% of therapeutics are not capable of penetrating. Only certain nutrition supplies and relevant pay-load carriers are capable of crossing thus, the developed materials possibly should be able to imitate or carry such compounds to be able to enter the brain [21]. The study reports two approaches of overcoming BBB, 1) by CNDs self-penetrating capability and 2) by loading Tf as a Trojan horse on the nanosystem to target abundant Tf receptors on the endothelial cells. A zebrafish model has been used for this investigation due to its genetic homology to humans among other facts of ease of handling and translucent body. The investigations have proven that the CNDs alone are capable of penetrating BBB through bioimaging using confocal microscopy. Further studies have conducted to confirm that in conjugating, the conjugates do not lose this capability and it shows that CN-GM is also capable of penetrating the BBB. Moreover, due to high Tf receptor presence in the BBB due to the high iron demand in the brain, the payload on Tf ligand carriers inevitably crosses the BBB in spite of their self-inability [22]. This can aid in further increasing the amount of drug entering the brain. Further investigations need to be carried out on the quantifications of the drug amounts entering the brain because it is important to achieve the pharmacologically effective concentrations in the target tumor site for effective treatments [23].

In summary, the study in discuss have constructed a conjugate system using a possible new glioma therapeutic with CNDs as a nanocarrier platform which shows self-capability to overcome two importance hurdles in pediatric glioma treatments, which are penetrating the BBB and targeting the cancerous cells with low adverse side effects. Thus, further investigations of this promising new platform into in vivo and other preclinical studies will enhance the capability to understand its capacity as a clinical treatment candidate.

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