List of Patents and Publications

Detail of patents:

S.no.	Patent Title	Name of Applicant	Patent no.	Award Date	Agency/ country	Status
1.	Polymeric Nano-Formulation For Delivery Of Temozolomide And Method Of Preparing The Same	Deepak Chitkara, Prabhjeet Singh, Deepak Kumar Sahel, Reena Jatyan, Anupama Mittal	Appl. No. IN202311047526	Filed on. 14th July 2023	India	Pending

Detail of publications:

S. no.	Author(s)	Title	Name of Journal	Volume and Page	Year	Impact Factor
1.	Reena Jatyan, Deepak Kumar Sahel, **Prabhjeet Singh**, Rajeev Sakhuja, Anupama Mittal, and Deepak Chitkara	Temozolomide-fatty acid conjugates for glioblastoma multiforme: In vitro and in vivo evaluation	Journal of Controlled Release	359, 161-174	2023	10.8
2.	Reena Jatyan, **Prabhjeet Singh**, Deepak Kumar Sahel, Y. G. Karthik, Anupama Mittal, and Deepak Chitkara	Polymeric and small molecule-conjugates of temozolomide as improved therapeutic agents for glioblastoma multiforme	Journal of Controlled Release	350, 494-513	2022	10.8
3.	Saurabh Sharma, Sudeep Pukale, Deepak Kumar Sahel, **Prabhjeet Singh**, Anupama Mittal, and Deepak Chitkara.	Folate targeted hybrid lipo-polymeric nanoplexes containing docetaxel and miRNA-34a for breast cancer treatment	Materials Science and Engineering: C	128, 112305	2021	8.45
4.	Imran Ansari, **Prabhjeet Singh**, Anupama Mittal, Ram I. Mahato, and Deepak Chitkara.	2,2-Bis(hydroxymethyl) propionic acid based cyclic carbonate monomers and their (co)polymers as advanced materials for biomedical applications	Biomaterials	275, 120953	2021	14
5.	**Prabhjeet Singh**, Aditi Singh, Shruti Shah, Jalpa Vataliya, Anupama Mittal, and Deepak Chitkara.	RNA Interference Nanotherapeutics for Treatment of Glioblastoma Multiforme	Molecular Pharmaceutics	17, 11, 4040–4066	2020	5.36
6.	Abdul Rahaman Shaik, **Prabhjeet Singh**, Chandini Shaik, Sunil Kohli, Divya Vohora & Serge Livio Ferrari	Metformin: Is It the Well Wisher of Bone Beyond Glycemic Control in Diabetes Mellitus?	Calcified Tissue International	108, 693–707	2021	4.2

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Review

RNA Interference Nanotherapeutics for Treatment of Glioblastoma Multiforme

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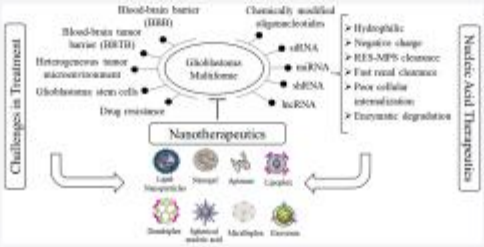
ABSTRACT: Nucleic acid therapeutics for RNA interference (RNAi) are gaining attention in the treatment and management of several kinds of the so-called "undruggable" tumors via targeting specific molecular pathways or oncogenes. Synthetic ribonucleic acid (RNAs) oligonucleotides like siRNA, miRNA, shRNA, and lncRNA have shown potential as novel therapeutics. However, the delivery of such oligonucleotides is significantly hampered by their physiochemical (such as hydrophilicity, negative charge, and instability) and biopharmaceutical features (*in vivo* serum stability, fast renal clearance, interaction with extracellular proteins, and hindrance in cellular internalization) that markedly reduce their biological activity. Recently, several nanocarriers have evolved as suitable non-viral vectors for oligonucleotide delivery, which are known to either complex or conjugate with these oligonucleotides efficiently and also overcome the extracellular and intracellular barriers, thereby allowing access to the tumoral micro-environment for the better and desired outcome in glioblastoma multiforme (GBM). This Review focuses on the up-to-date advancements in the field of RNAi nanotherapeutics utilized for GBM treatment.



KEYWORDS: *glioblastoma multiforme, nucleic acid therapeutics, molecular pathways, nanocarriers, siRNA, miRNA*

1. INTRODUCTION

Cancer is considered a deadly and debilitating disease, primarily characterized by abnormal cell growth with an ability to invade adjoining tissues, organs, and other parts of the body. According to the WHO Globocan report, around 18.1 million new cases of cancer were estimated in 2018, and 9.6 million cancer patients died. Also, as per 5-year global cancer prevalence data, a total of 43.8 million people have cancer, of which 17.38 million are Asian,[1,2] highlighting the unmet medical attention required for cancer management and treatment. Among neurological cancers, glioblastoma multiforme (GBM) is a common brain malignancy with a significant increase in incidences per year. According to the CBTRUS statistical report, the average incidence rate of GBM is 3.22 per 100 000 people, and profoundly higher in patients with hereditary tumor syndromes like turcot and li-fraumeni syndrome.[3,4] GBM is a heterogeneous type of malignancy, usually known as astrocytoma, that arises from neoplastic glial cells and is considered to be one of the most lethal forms of brain cancer.[5] Unlike other tumors, GBM invades the affected organ but does not undergo metastasis. It is usually located in the frontal, temporal-parietal, and occipital lobes of the brain, with higher incidence rates in frontal and multiple lobes with overlapping tumors, as well as very rarely seen/observed in the spinal cord.[3]

The current treatment for GBM includes tumor resection, with concomitant radiation therapy and chemotherapy. Despite intensive treatment, the average survival of GBM-affected patients remains around 50−65 weeks.[6] The reason behind the cases of tumor relapse is not clearly known; however, it could be attributed to physiological barriers, the effect of drug action on tumor cells, the development of resistance, etc. During the treatment phase, access of most drugs to the target site is altered because of physiological barriers, including a blood−brain barrier (BBB) and blood−brain tumor barrier (BBTB), which the drugs must cross after the systemic administration.[7] BBB is characterized by monolayered, tightly packed epithelial cells that prevent the entry of foreign or non-permissive substances, whereas BBTB constitutes the existing and newly formed components that are mainly responsible for the delivery of nutrients and oxygen delivery to the glioma cells.[8] Temozolomide (TMZ), an alkylating agent, is currently the primary chemotherapeutic

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Polymeric and small molecule-conjugates of temozolomide as improved therapeutic agents for glioblastoma multiforme

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ABSTRACT

Temozolomide (TMZ), an imidazotetrazine, is a second-generation DNA alkylating agent used as a first-line treatment of glioblastoma multiforme (GBM). It was approved by FDA in 2005 and declared a blockbuster drug in 2008. Although TMZ has shown 100% oral bioavailability and crosses the blood-brain barrier effectively, however it suffers from limitations such as a short half-life (~1.8 h), rapid metabolism, and lesser accumulation in the brain (~10–20%). Additionally, development of chemoresistance has been associated with its use. Since it is a potential chemotherapeutic agent with an unmet medical need, advanced delivery strategies have been explored to overcome the associated limitations of TMZ. Nanocarriers including liposomes, solid lipid nanoparticles (SLNs), nanostructure lipid carriers (NLCs), and polymeric nanoparticles have demonstrated their ability to improve its circulation time, stability, tissue-specific accumulation, sustained release, and cellular uptake. Because of the appreciable water solubility of TMZ (~5 mg/mL), the physical loading of TMZ in these nanocarriers is always challenging. Alternatively, the conjugation approach, wherein TMZ has been conjugated to polymers or small molecules, has been explored with improved outcomes *in vitro* and *in vivo*. This review emphasized the practical evidence of the conjugation strategy to improve the therapeutic potential of TMZ in the treatment of glioblastoma multiforme.

1. Introduction

Glioblastoma (GBM) is the most prevalent and deadly primary malignant brain tumor in adults, accounting for 16% of all brain and central nervous system tumors [1]. Regardless of sophisticated diagnostic methods and finest multimodal treatment, constituting surgical resection, radiotherapy, and concurrent temozolomide chemotherapy, the major number of patients experiences nominal progression-free survival and tumor relapse. This could be attributed mainly to tumor heterogeneity, its infiltrative pattern, and location, thereby rendering it more lethal. A small molecule, temozolomide (TMZ), has demonstrated a promising effect in treating malignant gliomas and other hard-to-treat malignancies in conjugation to radiotherapy. It is a second-generation imidazotetrazine DNA alkylating prodrug, stable at acidic conditions that converts to the active alkylating agent under physiological conditions liberating 5-aminoimidazole-4-carboxamide (AIC) and a highly reactive methyl diazonium carbocation. This carbocation is responsible for the addition of the electrophilic methyl group to the susceptible nucleophilic DNA sites within the tumor cells resulting in DNA double-strand breaks, cell cycle halt, and subsequent cell death [2].

In a randomized phase III clinical study, administration of TMZ displayed the median overall survival time around 14.9–16.6 months, with progression-free survival (PFS) ranging from 5.5 to 6.7 months and a 2-year overall survival rate up to 34.2% [3], with at best 5-year survival rate up to 9.8% in newly diagnosed glioblastoma [2,4]. Furthermore, patients with MGMT methylation were found to be positively associated with improved overall survival (up to 21.4 months) and PFS (up to 8.7 months) [3]. Clinical evaluation of TMZ in GBM patients demonstrated linear wide tissue distribution pharmacokinetics with almost 100% bioavailability after oral administration to adults and children. However, the treatment with TMZ also showed multiple adverse effects. For instance, patients administered with TMZ exhibit positive effects against GBM and refractory anaplastic astrocytoma in adults, but TMZ is also known to induce negative effects towards

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