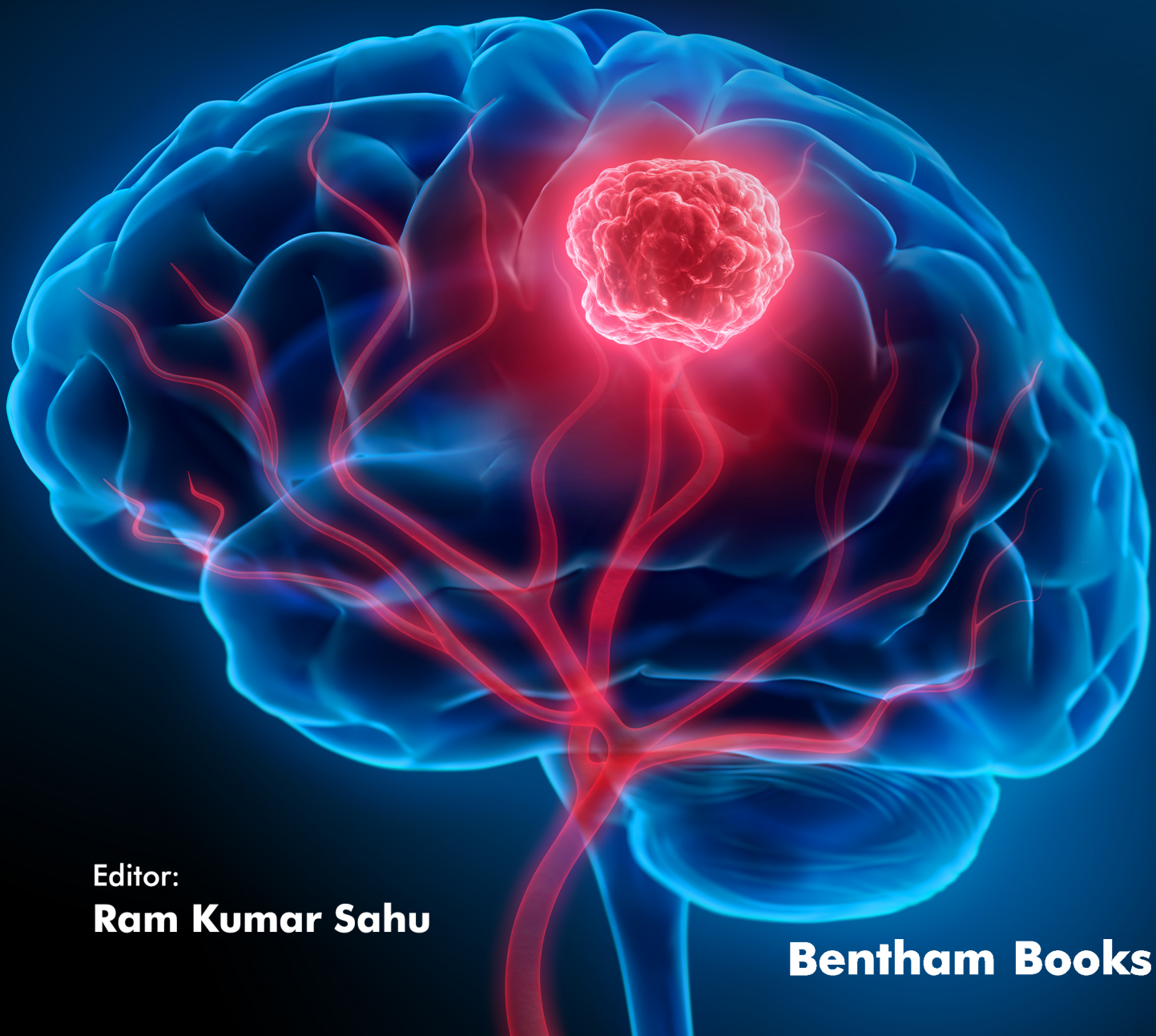
BRAIN TUMOR TARGETING DRUG DELIVERY SYSTEMS:

ADVANCED NANOSCIENCE FOR THERANOSTICS APPLICATIONS



Editor:
Ram Kumar Sahu

Bentham Books

Brain Tumor Targeting Drug Delivery Systems: Advanced Nanoscience for Theranostics Applications

Edited by

Ram Kumar Sahu
Department of Pharmaceutical Sciences
Hemvati Nandan Bahuguna Garhwal University (A Central University)
Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India

Brain Tumor Targeting Drug Delivery Systems:
Advanced Nanoscience for Theranostics Applications

Editor: Ram Kumar Sahu

ISBN (Online): 978-981-5079-72-2

ISBN (Print): 978-981-5079-73-9

ISBN (Paperback): 978-981-5079-74-6

First published in 2023.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

There are still many unmet medical requirements, including brain tumours. Brain tumours can now be treated with considerably less toxicity and better pharmacokinetics and pharmacodynamics because of recent nano-drug delivery technologies. It is still difficult to treat brain tumours due to their rapid growth and poor prognoses, even with surgery, radiation, and chemotherapies. To combat the disease, therapeutic delivery methods that maximise drug accumulation in the tumour location and decrease toxicity in normal brain and peripheral tissue are a potential new strategy. The fact that brain tumours differ in many ways from tumours in other tissues means that drug delivery to brain tumours can take advantage of the constantly changing vascular characteristics and microenvironment. For brain tumour theranostics, nanocarrier-based delivery methods address brain architecture and tumours in addition to the advances and problems in delivering medicines across the blood brain barrier. Theranostics combines diagnostics and therapeutics. A growing number of people are becoming interested in individualised therapy and diagnostics approaches. As well as conserving money, this method also limits the negative effects of a specific goal.

This book contains several sections on nanotechnology, including the most recent developments in the field and practical advice on how to build more effective nanocarriers for medication and gene delivery. There is much helpful information in this book that will help readers to create innovative drug delivery systems for brain tumour therapy that will help to boost nanomedical technology. The key features highlighted in this book are various theranostic-based delivery systems for brain tumour diagnosis and treatment. This book will be of interest to many academicians, scientists, and researchers. It will enable them to understand the possible prospects of nanotechnology for delivering nanocarriers that can better diagnose and cure brain tumours in the future.

Ram Kumar Sahu
Department of Pharmaceutical Sciences
Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus
Tehri Garhwal-249161, Uttarakhand, India

List of Contributors

Amitha Muraleedharan	Shraga Segal Department of Microbiology, Immunology, and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
Ardra Thottarath Prasanthan	Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India
Aseem Setia	Department of Pharmacy, Shri Rawatpura Sarkar University, Raipur, (C.G) - 492015, India
Ayodeji Folorunsho Ajayi	Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria
Devesh Kapoor	Dr. Dayaram Patel Pharmacy College, Bardoli, Surat, Gujarat, India
Deepak Prashar	KC Institute of Pharmaceutical Sciences, Una-177207, H.P., India
Emmanuel Tayo Adebayo	Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria
Grace Fumilayo Adigun	Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria
Geetika Sharma	Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, 484887, India
Jiyauddin Khan	School of Pharmacy, Management and Science University, 40100 Shah Alam, Selangor, Malaysia
Kajal Kumari	Department of Pharmacy, Banasthali Vidyapith, Banasthali, P.O. Rajasthan, India
Krishna Yadav	University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh 492010, India
Manish Philip	Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India
Madhulika Pradhan	Rungta College of Pharmaceutical Sciences and Research, Kohka, Kurud Road, Bhilai, Chhattisgarh, 490024, India
Nikhil Ponnoor Anto	Shraga Segal Department of Microbiology, Immunology, and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
Nirdesh Salim Kumar	Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India
Nidhal Khazaal Maraie	Department of pharmaceutics, college of pharmacy, Al-Farahidi University, Baghdad, Iraq
Narayana Subbiah Hari Narayana Moorthy	Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, 484887, India

Oluwadunsin Iyanuoluwa Adebayo	Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria
Payal Kesharwani	Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India Rameesh Institute of Vocational and Technical Education, Greater Noida, India
Ram Kumar Sahu	Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India
Sivadas Swathi Krishna	Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India
Shiv Kumar Prajapati	Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India
Smita Jain	Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India
Swapnil Sharma	Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India
Swati Dubey	Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, 484887, India
Shalini Singh	Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, 484887, India
Sunita Minz	Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, 484887, India
Tayo Adebayo	Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria
Vidya Viswanad	Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India
Zainab H. Mahdi	Department of pharmaceutics, college of pharmacy, Applied Science Private University, Amman, Jordan
Zahraa Amer Al-Juboori	Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

CHAPTER 1

Anatomy and Physiology of the Brain: Pathophysiology of Brain Tumor

Amitha Muraleedharan[1,*] and **Nikhil Ponnoor Anto**[1]

[1] *Shraga Segal Department of Microbiology, Immunology, and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*

Abstract: The brain is an efficient processor of information. It is the most complex and sensitive organ in the body and is responsible for all functions of the body, including serving as the coordinating center for all sensations, mobility, emotions, and intellect. The magnitude of its myriad function is often realized usually when there is a disruption of the nervous system due to injury, disease, or inherited predispositions. Neuroscience is the field of study that endeavors to make sense of such diverse questions; at the same time, it points the way toward the effective treatment of dysfunctions. The two-way channel of information: findings from the laboratory leading towards stricter criteria for diagnosing brain disorders and more effective methods for treating them and in turn, the clinician's increasingly acute skills of diagnosis and observation that supply the research scientist with more precise data for study in the lab diligently expands the field of neuroscience. Tumors of the brain produce neurological manifestations through several mechanisms. Stronger hypotheses about the mechanism of a disease can point the way toward more effective treatments and new possibilities for a cure. In highly complex disorders of the brain, in which many factors genetic, environmental, epidemiological, even social and psychological—play a part, broadly based hypotheses are exceedingly useful. With the advancements in technology and a better understanding of brain anatomy and physiology, the quest to discover an efficient cure for life-threatening tumors of the brain is underway.

Keywords: Blood brain barrier, Brain, Brain tumor, Glia, Nervous system, Neuron, Synapse.

INTRODUCTION

The nervous system is a very complex structure that can be divided into two major regions: the central nervous system (CNS) which consists of the brain and spinal cord and the peripheral nervous system (PNS) which is an extensive net-

* **Corresponding Author Amitha Muraleedharan:** Shraga Segal Department of Microbiology, Immunology, and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel;
E-mail: prashardeepak99@yahoo.in

Ram Kumar Sahu (Ed.)

work of nerves that consists of (i) Craniospinal nerves having 12 pairs of cranial nerves and 31 pairs of spinal nerves, (ii) Visceral nervous system comprising the sympathetic nervous system and parasympathetic nervous system connecting the CNS to the muscles and sensory structures [1, 2]. The spinal cord is a single structure, whereas the adult brain is divided into four major regions: (i) The cerebral hemispheres, comprised of the cerebral cortex, basal ganglia, white matter, hippocampi, and amygdalae; (ii) The diencephalon, with the thalamus and hypothalamus; (iii) The brain stem, consisting of the medulla, pons, and midbrain; and (iv) The cerebellum. The brain is the central control module of the body and coordinates activities like task-evoked responses, senses, movement, emotions, language, communication, thinking, and memory [3, 4]. In this book chapter, we discuss the anatomy of the brain, its functions, development, and pathology with a special focus on brain carcinogenesis.

THE ANATOMY OF THE HUMAN BRAIN

The brain is protected by the skull (cranium) which is in turn covered by the scalp. The scalp is composed of an outer layer of skin, which is loosely attached to the aponeurosis, a flat, broad tendon layer that anchors the superficial layers of the skin. The periosteum, below the aponeurosis, firmly encases the bones of the skull and provides protection, nutrition to the bone, and the capacity for bone repair. Below the skull are three layers of protective covering called the meninges that surround the brain and the spinal cord. The meningeal layer closest to the bones of the skull called the dura mater (meaning *tough mother*) is thick and tough and includes two layers; the periosteal layer lines the inner dome of the skull followed by the meningeal layer below. The space between the layers allows the passage of veins and arteries that supply blood to the brain. Below the dura mater lies the arachnoid mater (*spider-like mother*) which is comprised of a thin web-like connective tissue called arachnoid trabeculae and is devoid of nerves or blood vessels. The innermost meningeal layer is a delicate membrane called the pia mater (*tender mother*). The pia mater firmly adheres to the convoluted surface of the CNS, lining the inside of the sulci in the cerebral and cerebellar cortices, and is rich in veins and arteries. Between the arachnoid mater and pia mater is the subarachnoid space which is filled with cerebrospinal fluid (CSF)**,** produced by the cells of the choroid plexus—areas in each ventricle of the brain (discussed further below). The CSF serves to deliver nutrients and removes waste from neural tissues and also provides a liquid cushion to the brain and spinal cord (Fig. **1**) [5, 6].

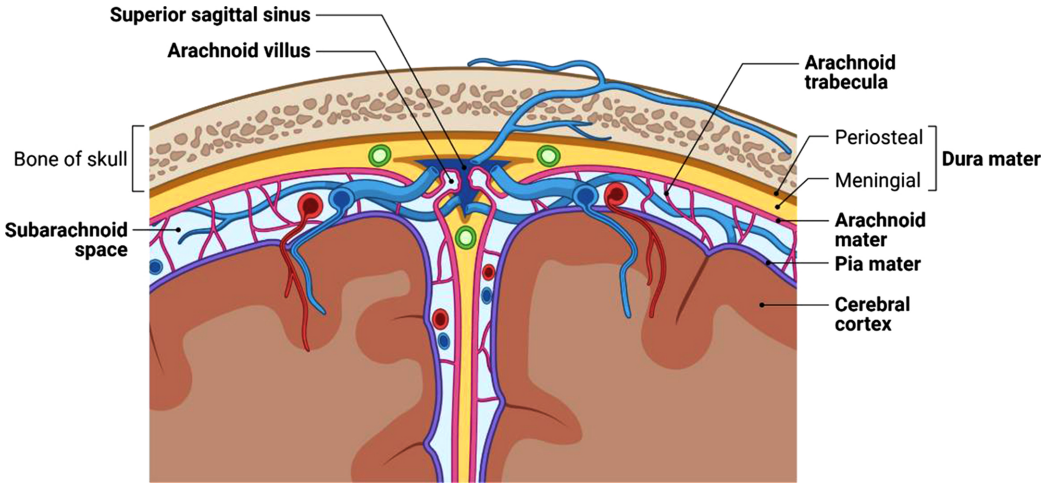


Fig. (1). The layers of the tissue surrounding the human brain including three meningeal membranes: the dura mater, the arachnoid mater, and pia mater.

Cerebrum

The cerebrum, which appears to make up most of the brain mass, consists of two cerebral hemispheres demarked by a large separation called the longitudinal fissure. Each hemisphere has an inner core composed of white matter-the corpus callosum-and and an outer surface-the cerebral cortex- composed of gray matter. The corpus callosum, the largest of the five commissural nerve tracts, provides the major pathway for communication between the two hemispheres. According to the concept known as localization of function, different regions of the cerebral cortex can be associated with particular functions. In the early 1900s, an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex was undertaken by a German neuroscientist named Korbinian Brodmann who divided the cortex into 52 separate regions based on the histology of the cortex. The results from Brodmann's work on the anatomy align very well with the functional differences within the cortex and resulted in a system of classification known as Brodmann's areas, which is still used today to describe the anatomical distinctions within the cortex [7]. Each hemisphere is conventionally divided into four lobes namely the frontal lobe, temporal lobe, occipital lobe, and parietal lobe (Fig. **2**).

- **Frontal lobe:** positioned at the front of the brain, the lobe is associated with executive functions. Containing a majority of dopamine-sensitive neurons, the region is responsible for self-control, planning, reasoning, motivation, and abstract thinking. Broca's area is responsible for the production of language, or

CHAPTER 2

Barriers to Targeted Drug Delivery Strategies in Brain

Payal Kesharwani[1,2], Kajal Kumari[1], Smita Jain[1] and **Swapnil Sharma[1,*]**

[1] *Department of Pharmacy, Banasthali University, P.O. Rajasthan, India*

[2] *Rameesh Institute of Vocational and Technical Education, Greater Noida, India*

Abstract: Brain tumor is considered to be the most detrimental disease found in humans. Amongst the various brain tumors, glioblastoma has emerged as a highly invasive malignant disease that has contributed to significant mortality worldwide. Despite surgical and drug innovations, most of the patients suffering from brain tumours have shown poor prognosis, with a median life span. The presence of the blood-brain barrier (BBB) acts as a protective layer outside the brain for most of the conventional, diagnostic and therapeutic agents, which in turn leads to poor diagnosis and less efficacy in most clinical subjects. In recent years, multifunctional nanotechnology systems have been employed to deliver theranostic agents to the brain, showing promising outcomes in the treatment of various forms of cancer. The present chapter provides comprehensive information on the most recent developments in BBB-crossing nanotechnology, with a slight focus on the thoughtful design of multifunctional nanoplatforms for effective BBB penetration, accurate tumor imaging, and substantial brain tumor inhibition. Besides, various physiological barriers and transportation mechanisms, different drug delivery systems for brain tumors are also highlighted. Furthermore, major advancements in brain tumor theranostics pertaining to employing different nanosystems such as liposomes, polymeric nanoparticles, bio-nano particles, and inorganic-nanoparticles for effective nano-drug delivery for theranostics in brain tumors have also been discussed.

Keywords: Blood-brain barrier, Brain tumour, Nanotechnology, Stimuli-responsive, Theranostic.

INTRODUCTION

The brain is the most sophisticated organ of the human body. Several ailments of the brain, such as encephalitis, neurological disorders, multiple sclerosis, stroke, and tumor, have no effective therapy to date [1]. Brain tumor is one of the most atrocious kinds of cancer among numerous cancer types due to its poor prognosis,

* **Corresponding Author Swapnil Sharma:** Department of Pharmacy, Banasthali University, P.O. Rajasthan, India; E-mail: skspharmacology@gmail.com

Ram Kumar Sahu (Ed.)

aggressive nature, and large number of deaths observed among kids and adults every year. According to the latest survey by WHO, 86,000 people were diagnosed with a brain tumor, and 700,000 people are suffering from the same [2]. There are two classes of brain tumors: primary brain tumor which grows in the brain itself and secondary brain tumor which migrates to the brain from other organs of the body [1]. Among all the available treatments for a brain tumor, Radiotherapy and Chemotherapy are the most often used. However, there are significant flaws associated with chemotherapy which include poor quality of life and limited duration of response. Due to the variety of factors involved in cancer therapy, treating the tumor with an anticancer drug has become quite challenging [3, 4]. The distribution of drugs to the brain tissues is challenging due to the robust protection that exists immediately outside the brain, anatomically known as the blood-brain barrier (BBB), protecting it from shock. It restricts the passage of anticancer drugs hydrophilic in nature and diagnostic agents into the brain and shows its effectiveness. This generates the need for an effective strategy for delivery of drugs to the brain cells [5].

Recently, scientists are focused more on the development of a delivery system that effectively delivers drugs to the tumour cells and benefits the cancer patient. The nanostructured drug delivery system has recently gained attention for transporting drugs to tumour cells and tissues present at the tumour site of the brain and avoiding damage caused to the normal tissue nearby. Altogether they perform two important functions, the first is the therapy to the tumour site and the second is its diagnosis [6]. They can transport therapeutic compounds across the BBB, such as tiny chemicals, proteins, peptides, and genetic material [1]. The new drug delivery system includes a combination of drugs and molecular imagining probes such as metal nanoparticles (NPs), polymer-drug conjugates, polymer micelles, liposomes, and dendrimers [7].

Theranostic application is also used bringing a new opportunity to bridle the hurdles faced in the current treatment/therapy of brain tumors [1]. It requires the usage of molecular imagining tools along with a drug delivery system. The molecular imagining tools include computed tomography (CT), magnetic resonance imaging (MRI), optical and ultrasound (US) imaging, positron emission tomography (PET), and single-photon emission computed tomography (SPECT), which are currently under study with drug delivery system. The theranostic approach uses sensible and specific probes which help to achieve the specific therapeutic application [7]. Despite significant attempts to create diagnostic tools and therapeutic avenues in the field of brain cancer therapy and its diagnosis, researchers and scientists face significant difficulty. This Chapter aids in the comprehension of various barriers and transportation mechanisms for drug delivery to brain tumors. It also focuses on major advancement in brain tumor

theranostic: A description of the creation of different nanosystems such as Liposomes, Polymeric Nanoparticles, Bio-nanoparticles, and Inorganic-nanoparticles for effective nano-drug delivery for theranostic in brain tumors.

BRAIN TUMOUR: CAUSE, SYMPTOMS, CATEGORY, AND LIMITATIONS OF CONVENTIONAL THERAPY

Brain Tumour: Cause and Symptoms

The term “Brain tumor” refers to a group of primary and metastatic neoplasms that affect the central nervous system (CNS) and have a poor prognosis and survival rate [6]. The CNS consists of the brain and spinal column, and it is here that all critical processes such as cognition, speech, and body movement are governed. This implies that as a brain tumor grows, it impairs a person's critical functions. Patients with brain tumors may have nausea, vomiting, cognitive abnormalities, hemiparesis, aphasia, urine incontinence, and headache, depending on the size, location, and pace of invasion of the tumor. At the time of diagnosis, 50% of the patient who are diagnosed with a brain tumor had a headache [8]. Genetic susceptibility could be one of the risk factors for a brain tumor as studies of syndromes, gene-linkage, mutagen sensitivity, and familial agglomeration suggest its genesis of glioma. Although brain tumor caused due to rare inherited mutations accounts for a few cases, they only provide genetic pathways for the identification of glioma [9]. Research studies have provided a piece of very clear evidence for the role of platelet-derived growth factor receptor (PDGFR) over-expression which allows cells to evade apoptosis in the pathophysiology of brain tumors [10]. Human herpesviruses (HHV), notably Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Human herpesviruses 6 (HHVs6), are thought to have an important role in brain tumor pathophysiology, according to recent research. These viruses have been found in most gliomas which facilitate its comodulation and immunomodulation and also promote tumour cell proliferation, invasion, and apoptosis. Although a direct relation between these viruses with a brain tumor is still not cleared [11]. Apart from these factors exposure to large therapeutic, high-dose radiation or impaired DNA repair plays a potential role in the development of brain tumors [12].

Classification of Brain Tumour

Brain tumor has five stages based on their progression rate (Stage-0,1,2,3 and 4). Stage-1 tumours refer to the one which do not spread to the surrounding cells, while at stage-2 and 3, tumor cells spread rapidly to the nearby cells. At stage-4, tumor cells spread throughout the body which is a devastating stage [13]. Brain tumors can be either benign or malignant. Malignant brain tumors are cancerous and originate from the brain which is the most lethal type of tumours whereas

CHAPTER 3

Theranostics Polymeric Nanoparticles for Brain Tumor Diagnosis and Treatment

Sivadas Swathi Krishna[1], Ardra Thottarath Prasanthan[1], Nirdesh Salim Kumar[1], Manish Philip[1] and **Vidya Viswanad[1,*]**

[1] Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala, India

Abstract: Theranostics, a dual strategy, helps in better tumor imaging, the biodistribution of drugs (the ability to direct therapeutic agents to the tumor site), and understanding the progress and effectiveness of therapy. Theranostics is an emerging technology for the diagnosis and management of brain tumors which differ from peripheral tumors in several ways because of their complexity in the genesis of oncogenes. Several factors must be considered for successful brain tumor-targeted drug delivery. Nanotheranostics for brain cancer therapies have been identified now, and polymeric nanoparticles (PNP) are one of the most efficient and promising nanotechnological platforms. They can be utilized as a new imaging method to optimize chemotherapeutic drug delivery into brain tumors while reducing the drug's dissemination and toxicity in healthy people. Smart carriers and theranostic nanoparticles can diagnose, deliver, and track the therapeutic response synchronized. This chapter gives an insight into superparamagnetic, ultrasound-triggered radionuclide bearing, and fluorescent PNPs as potential theranostic approaches for brain tumor management.

Keywords: Brain tumor targeting, Fluorescent nanoparticles, Polymeric nanoparticles, Superparamagnetic nanoparticles, Theranostics.

INTRODUCTION

Transport of the drug into the brain is a significant defiance owing to the strong brain defense mechanism against foreign molecules. This necessitates the creation of more efficient distribution methods. Targeted drug delivery or targeted nanotechnology implementation is an appealing solution when contemplating all anatomic issues of brain tumors, as it can improve brain drug delivery [1]. A targeted drug delivery system (TDDS) is a technique for delivering therapeutic

* **Corresponding Author Vidya Viswanad:** Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS, Health Science Campus, Kochi, Kerala, India;
E-mails: vidyaviswanad@aims.amrita.edu, vidyanitin26@gmail.com

Ram Kumar Sahu (Ed.)

agents selectively and preferentially to the target site while limiting access to non-target sites. It aims at concentrating the medicament at the target tissue and thereby relatively reducing its concentration in other parts of the body; this increases the effectiveness while lowering the toxicity [2].

Nanoparticles have many benefits over traditional formulations, including the ability for drug conjugation, targeting effects, and improving drug pharmacokinetic characteristics. The half-life of the drugs can be extended using nanoplatforms using molecular probes. This provides various advantages. It provides accurate delivery of the anticancer medicament to the target tissues and releases the drugs with the help of detectors by responding to various stimuli Nanoparticles made of polymeric materials stand out as a powerful tool for increasing drug bioavailability and delivering drugs to their target sites. These are colloidal structures made up of natural or synthetic polymers, and the polymers' flexibility makes them theoretically suitable for meeting the needs of each drug-delivery system [3].

Theranostic nanoparticles appear to be a promising system that offers a novel solution to address present brain tumor management and diagnosis drawbacks. Options such as limiting metabolization of medications, providing simultaneous delivery with combined effects of two or more drugs, and enabling regulated and exact release, reducing adverse effects, are offered by theranostics. This technique aids in tackling the intra- and inter-patient heterogeneity of brain tumors, leading to a potential application of personalized medicine [4]. Nowadays, brain targeted drug delivery has received much interest because of its slow release, controllable and targeted protection.

MECHANISMS OF TARGETED DRUG DELIVERY IN BRAIN TUMOR

Due to the intricacy of brain tumors, several factors should be considered for efficient brain tumor-targeted drug delivery, including the barriers, the microenvironment in the tumor, and tumor cells [5]. Some of the factors which affect brain drug delivery include 1. Drug /polymer concentration gradient. 2. The drug's molecular weight. 3. Cell-to-cell sequestration. 4. Protein affinity for efflux transporters 5. Metabolism by tissues other than the liver. 6. Circulation in the brain. 7. Enzymatic stability throughout the body.8. Drug/polymer clearance rate. 9. The state of the disease. 10. Stability of cellular enzymes. 11. The drug's lipophilicity [6]. To address these problems, various active targeting mechanisms for designing a successful medication delivery system to the brain were used. The blood-brain barrier (BBB) targeting mechanism and the Blood-brain tumor barrier (BBTB) targeting mechanism are the two main types of mechanisms mentioned in Fig. (**1**) [5].

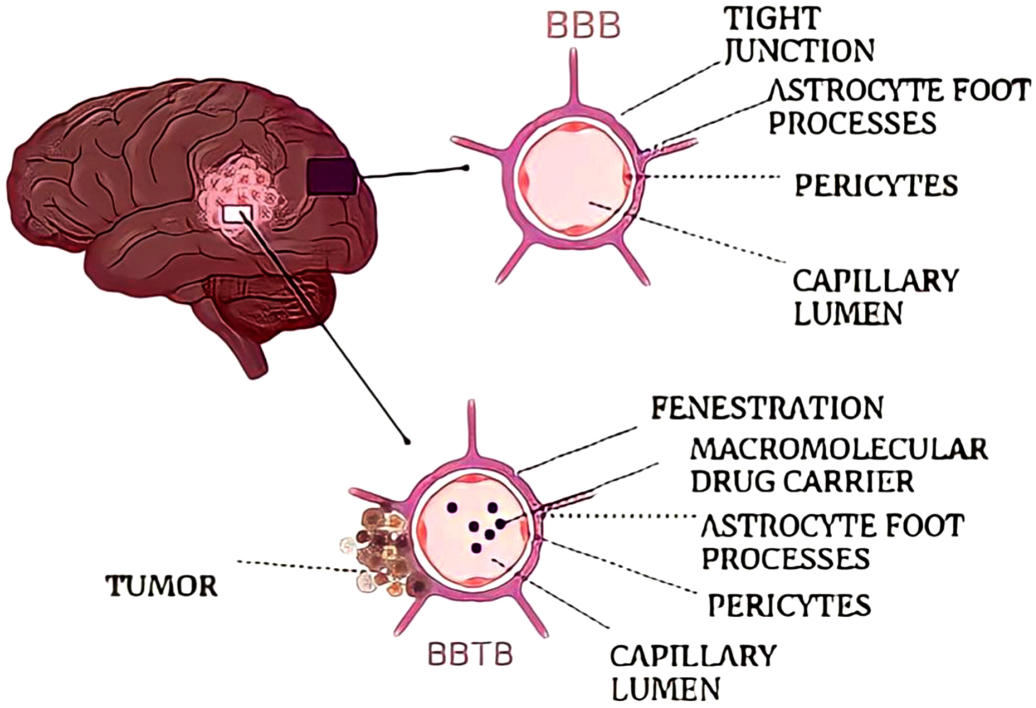


Fig. (1). Argeting mechanisms for brain tumor drug delivery.

The Blood-Brain Barrier Targeting Mechanism

The BBB serves as a physical (tight junctions), metabolic (enzymes), and immunological barrier, limiting drug transport into the brain. The BBB is made up of a variety of cells, including brain capillary endothelial cells (BCECs), pericytes, astrocytes, and neuronal cells, with BCECs being the most abundant. The continuous tight junctions between brain capillary endothelial cells restrict the transport of compounds in a paracellular manner from the blood to the brain and result in exceptionally high trans-endothelial electrical resistance (TEER) between blood and brain, limiting the passive diffusion of compounds. Despite these constraints, the BBB has several overexpressed receptors and carriers that can regulate the movement of various ligands and their drugs. Furthermore, the BBB membrane is negatively charged and has a high affinity for positively charged molecules, which could lead to cell internalization. As a result, these ligands could facilitate NP (nanoparticles) penetration through the BBB through a variety of activities targeting strategies as shown in Fig. (**2**) [7].

CHAPTER 4

Theranostic Liposome for Brain Tumor Diagnosis and Treatment

Payal Kesharwani[1,2], Shiv Kumar Prajapati[3], Devesh Kapoor[4], Smita Jain[1] and **Swapnil Sharma[1,*]**

[1] *Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India*

[2] *Rameesh Institute of Vocational and Technical Education, Greater Noida, India*

[3] *Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India*

[4] *Dr. Dayaram Patel Pharmacy College, Bardoli, Surat, Gujarat, India*

Abstract: The treatment of brain tumours is often a challenging task due to the low permeability of drugs through the blood-brain barrier and their poor penetration into the tumour tissues. Liposomes enhance the delivery of chemotherapeutics to the brain without using any invasive approach. Liposomes are biomimetic nanocarriers that exhibit good biocompatibility, high loading capacity, and the ability to reduce the amount of encapsulated drugs. It is a promising candidate performing a dual function of both drug delivery and diagnosis. This approach helps to locate the tumour tissue with appropriate biodistribution of liposomes. The theranostic liposomes provide a platform for imaging tumour cells for early diagnosis and simultaneously, delivery to the brain enhances the targeting delivery. Fluorescent dyes, magnetic resonance imaging, and nuclear imaging are the few approaches used in the diagnosis of tumour cells. A new approach involving semi-conductor-based quantum dots has emerged as an imaging reagent for brain tissues. The theranostic application of liposomes provides the real-time monitoring of the administered drug, reducing the risk of under-or over-dosing and allowing for more customized therapy regimens. This chapter highlights the techniques for directing liposomes to solid tumours in-depth, potential targets in cancer cells, such as extracellular and intracellular targets, and targets in the tumour microenvironment or vasculature. Additionally, this chapter also concludes recent efforts for improving anticancer drug delivery at the tumour site using surface functionalization techniques, and the different contrast agents which help in diagnosis are discussed.

Keywords: Liposomes, MRI, Nuclear Imaging, Surface Modification, Theranostics.

[*] **Corresponding author Swapnil Sharma:** Department of Pharmacy, Banasthali Vidyapith, Banasthali, P.O. Rajasthan-304022-India; E-mail: skspharmacology@gmail.com

Ram Kumar Sahu (Ed.)

INTRODUCTION

Liposomes structurally can be defined as spherical vesicular moiety with lipid base having 100- 200 nm diameter. Soon after their development in the early 1960s, the potential utility of these vesicles as a carrier system for therapeutically active chemicals was realized [1, 2]. It is composed of a phospholipid which forms a lipid bilayer enclosing the aqueous core. The aqueous core helps in the encapsulation of hydrophilic drugs or small molecules [3]. Liposomes have been studied in recent yearsas carriers of therapeutic drugs, imaging agents, and for the delivery of genes, with a focus on neurological diseases, their therapy, and/or diagnostics [4]. Scientists are more focused on the development of active targeting of liposomes to a specific cell type which can be achieved by conjugation or surface modification with ligands such as monoclonal antibodies, antibody fragments, proteins, peptides, carbohydrates, glycoproteins, aptamers, and small molecules [5]. These substances can be attached to the surface of the liposomes making them targeted to a specified surface receptor [6]. Such strategies are very effective while targeting the brain tumour. The brain is the most complicated part of the body and it is very difficult to deliver the therapeutic entity to the targeted area in the brain due to the presence of BBB [7]. Therefore, it becomes challenging to diagnose and treat the tumour at the primary stage. The conventional treatment of brain tumour includes surgery and chemotherapy or radiotherapy which usually produces side effects on the human body [8]. Liposomes are the emerging strategy that acts as a drug carrier to deliver drug[s] at the targeted site without any systemic toxicity. It allows the active targeting of cell receptors with a surface-attached ligand which delivers a drug to a tumour-associated stromal cells [6].

Theranostic medicines are playing an important role to improvise both diagnosis and therapeutics [9]. The liposomes are also successfully emerged to be utilized in the theranostic nanoplatform encapsulating the contrast agent which successfully helps in MR microangiography of the neurovascular as well as monitoring CED of drugs to brain tumours [10]. Liposomes allow achieving desirable properties in accordance with pharmacokinetics, target specificity, therapy monitoring, and signal amplification in contrast agent MR imaging-based liposomal contrast agents [11]. It increases the specific behavior and efficacy of the anticancer drugs [12]. The theranostic liposomes provide various advantages such as high biosafety, prolonged half-life in the circulatory system, concomitant loading of therapeutic and contrast agents, small size, high surface functionalization, and the ability to perform concomitantly diagnosis/monitoring and therapeutic approaches in real-time [13]. This strategy is very helpful in diagnostics and to obtain therapeutic efficacy in brain tumour. The theranostic nanosystem is developed to such an extent that it provides the encapsulation of magnetic nanoparticles inside

the liposome core and acts as a responsive drug delivery system [13]. There are many key challenges that are faced during the development of surface-modified liposomes when established to scale up production. It becomes very difficult to characterize the ligand-functionalized liposome formulations, as well as the inadequate recapitulation of *in vivo* tumours in the preclinical models currently used to evaluate their performance [6]. This chapter explains the advantage of using liposomes for brain tumour imaging along with various contrast agents used in diagnosis. It also depicts in detail various strategies used for targeting tumour in brain cancer. Techniques such as dual-targeted liposomes, gene therapy-based targeting liposome, proteins as targets, small molecules as targets, are discussed.

MECHANISM OF LIPOSOMES TARGETING BBB AND BBTB

The human brain is a very complex organ of the body that governs and coordinates several important functions at the same time and makes a balance [14]. Successful drug delivery to a brain tumour is restricted because of the barrier possessed by the brain to reach the targeted area after systemic circulation [15]. Tight junctions, transporters, receptors, enzymes, and the ATP-dependent 170-kDa efflux pump P-glycoprotein all contribute to the BBB's physical barrier, which is made up of vascular endothelial cells [16]. The BBB restricts the passage of compounds with amolecular weight of more than 500 Da, as well as some of the small molecules (Fig. **1**) [17]. ATP-binding P-gp also serves as an efflux pump for xenobiotics, and their high expression prevents substrates from passing across the BBB. Because the bulk of chemotherapeutics are hydrophobic and have a greater molecular size, they are unable to cross the BBB on their own [18]. Chemotherapeutics are also substrates for multidrug-resistant drug efflux pumps, which are found in tumour vascular cells as well as the BBB [19]. Liposomes have the unique property to incorporate hydrophilic, lipophilic, and hydrophobic therapeutic agents because of their unique physicochemical characteristics [20]. Furthermore, cationic lipids enable the adsorption of polyanions, like DNA and RNA [21]. They also exhibit high biocompatibility and biodegradability, as well as minimal toxicity, drug-targeted delivery, and controlled drug release in order to enhance blood circulation and supply to the brain [22]. Included macromolecules such as polymers, polysaccharides, peptides, antibodies, or aptamers can further modify the liposome surface [23].

Drug-loaded liposomes must easily penetrate the highly electrostatic BBB for more effective therapeutic effects. The surface charge of the liposomes is one of the criteria for improved brain permeability (positive, negative, and neutral) [3]. Cationic liposomes are mostly used due to their effectiveness in carrying a drug molecule and genes. The most convenient reason for this conclusion is the electrostatic interaction between the cationic liposomes and the negatively

CHAPTER 5

Theranostics Dendrimer for Brain Tumor Diagnosis and Treatment

Aseem Setia[1], Ram Kumar Sahu[2,*], Ayodeji Folorunsho Ajayi[3] and **Emmanuel Tayo Adebayo[3]**

[1] *Department of Pharmacy, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh - 492015, India*

[2] *Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India*

[3] *Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria*

Abstract: Brain tumors have become one of the deadliest types of cancer. Tragically, the blood-brain barrier (BBB), an astringent regulatory, well-coordinated, and effectual obstacle, prevents most substances from passing through it. As a result, breaking through this hurdle is amongst the most difficult challenges in devising effective CNS therapies. In the USA, approximately seven lakh people have a principal brain malignancy, with an ample eighty-five thousand predicted to be afflicted by 2021. Capillaries are essential for delivering oxygen and nutrients to all body tissue and vital organs. The capillaries that vascularize the CNS have a special feature known as the blood-brain barrier, which enables such vessels to firmly enforce the transfer of ions, substances, and cells in-between the blood-brain barrier. This accurate estimation of CNS homeostasis leads to proper neuronal function while also protecting neural tissue from toxic substances and microorganisms, and changes in such mechanical strength are a major aspect of the pathology and transformation of various neurological diseases. Theranostic strategies were also postulated and deemed enticing in recent times. Due to the smaller size, better topical functionalization, and capability to integrate various processing elements in one system, nanotechnology is beneficial for this system. For cancer therapy, the structure of nanotherapeutic systems focusing on diagnostic and therapeutic applications is increasing tremendously. This dual system is extremely useful for personalized medicine-based clinical applications because it seeks to analyze the position of malignancy, the biodistribution of nanosized systems, along with an advanced and efficacious therapy. Proteins, molecular markers, and genes are some of the theranostic strategies that could be used to amplify the surface of the nanotheranostics particle and make benefit of the features of the micro-environment utilising stimulus-based triggers. The current chapter focused on the theranostic approach of dendrimer for brain tumor treatment. It also enlightened about various diagnostic techniques for brain tumors with a special emphasis on nanotherapeutics.

[*] **Corresponding author Ram Kumar Sahu:** Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India E-mail: ramsahu79@gmail.com

Ram Kumar Sahu (Ed.)

Keywords: Blood-Brain Barrier, Brain tumor, Dendrimers, Theranostics.

INTRODUCTION

Brain diseases are the most challenging issues in healthcare because, as the global population ages, the percentage of patients with brain diseases will increase, resulting in high social repercussions due to severe morbidity and mortality [1]. Furthermore, glioma accounts for 80 percent of all melanoma and has a sudden onset and intensified belligerence [2]. Among most individuals with cerebral tumor cells, the contemporaneous treatment scheduling with radiation, surgery along with chemotherapy was found very risky, with minimum (in months) survival time [3]. Regardless of the potential bioactive agents obtained through medical updates, adequate remedies remain an unlocked therapeutic requirement because systemic administration agents are frequently ineffective due to a conventional biological obstacle: BBB (barrier between the blood and brain). A brain cancer is a malignant tissue overgrowth in the CNS region that could impede normal brain function. The cell types associated with brain tumors, as well as the tumor's location in the brain, can be identified. Gliomas are cancer cells of the brain caused by glial cells. The three subtypes of cells that produce astrocytoma, oligodendroglioma, and ependymal cells are astrocytoma, oligodendroglioma, and ependymal cells [4]. The WHO categorizes Glioma into 4 categories *i.e* grade I-IV. Grade I or II called as low grade tumours are being treated and managed by surgery and monitoring. Cancer with a greater extent of malignant glioma *viz.* III or IV grade might be harder to cure, and radiotherapy and chemotherapy are examples of alternative treatments. Targeted therapy, on the other hand, may be mandatory. Glioblastoma multi forme (GBM) is a cancerous one which is complicated to be diagnosed because of surgical resistance and invasiveness. Moreover, the poor prognosis and resistance to chemo and radiotherapy across the CNS provides limited options of therapies [5]. In US, approximately 7 lakh patients are diagnosed with primary brain tumor with an increase of around 85, 000 by the year 2021. Nearly 70% of all brain tumors are benign, with the remaining 30% being malignant. Females account for approximately 58% of all brain tumors. Males account for approximately 42% of all brain tumors [6]. The lack of particular methods for delivering therapeutic agents through the central nervous system (CNS) barriers makes the treatment of brain tumors complicated. The current practice is surgical resection, which is accompanied by multiple-therapy (chemo-radio-immuno therapy). Advantages of present therapy, on the other hand, are negligible for the patient. The term “theranostics” is a mixture of the terms identification and treatment, and it refers to techniques that have combined diagnostic along with therapeutic application (Fig. **1**). Presently interest in personalized treatment and diagnostic techniques is

increasing day by day. This is a time saving approach along with the money while also limiting the negative consequences of a particular objective [7]. NPS are nanoparticles that have been used in combination with medicines and diagnostic probes, metallic nanoparticles, liposomes, polymeric combinations, dendrimers, micelles *etc*. Due to the numerous limitations of bioactive compounds, developing an optimal delivery platform for treating cancer is exceptionally hard for formulation scientists as well as clinicians in the current scenario. Furthermore, traditional chemotherapeutic agents' poor biodistribution and undesirable pharmacokinetics lead to poor treatment outcomes and serious complications affecting healthy organs. To address these constraints, efficient and useful vectors are urgently required for better targeting, efficient transit (without degradation), and optimized release of drug and at most with least toxicity [8].

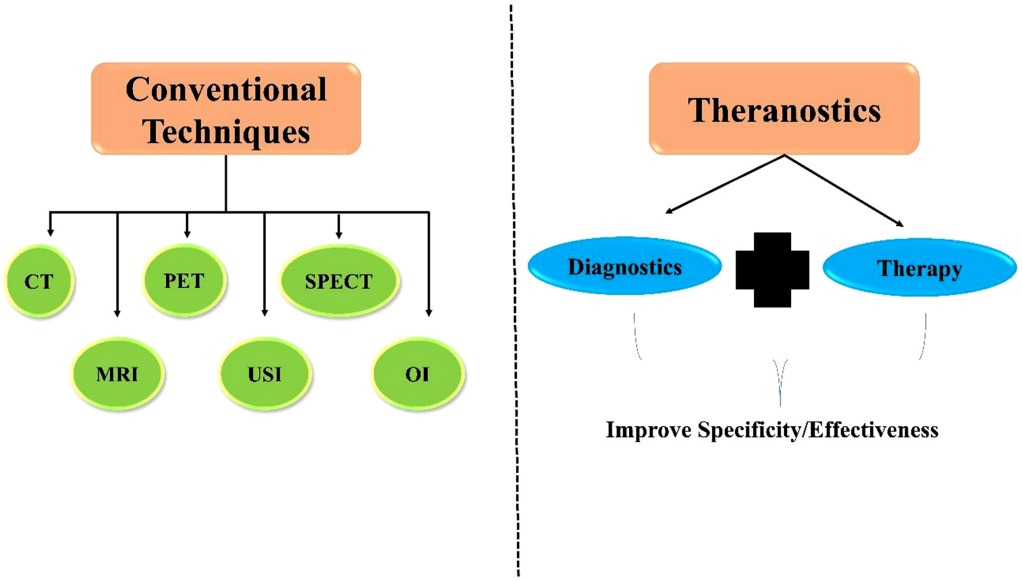


Fig. (1). Concept of conventional and theranostics technique

PHYSIOLOGY AND PHARMACOLOGY OF BLOOD-BRAIN BARRIER

BBB (Blood Brain Barrier) is an expression used to designate the special features of the CNS microvasculature. CNS consists of non-fenestrated vessels, with numerous properties that allow them to firmly enforce the drive of materials, ions, and cells between the systemic circulation and CNS [9]. Such a severely limited hurdle prompts BBB endothelial cells to closely restrict CNS homeostasis, which is required for absolute neuron functioning. Although it protects the CNS from pathogens, toxins, injuries, and diseases [10]. Various neuroactive solutes such as glutamate, epinephrine, glycine, *etc*. protect the brain. BBB, BCSFB, and the

CHAPTER 6

Theranostics Nanoemulsion for Brain Tumor Diagnosis and Treatment

Deepak Prashar[1,*], Ram Kumar Sahu[2], Jiyauddin Khan[3], Oluwadunsin Iyanuoluwa Adebayo[4] and **Grace Fumilayo Adigun[4]**

[1] *KC Institute of Pharmaceutical Sciences, Una-177207, H.P., India*

[2] *Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India*

[3] *School of Pharmacy, Management and Science University, 40100 Shah Alam, Selangor, Malaysia*

[4] *Reproductive Physiology and Bioinformatics Research Unit, Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria*

Abstract: Cancer or malignancy is the most widely occurring ailment in the recent scenario. Brain tumor is considered to be one of the most fatal among all types of tumors. The brain-related tumors are numerous and need to be treated and diagnosed in different ways. The diagnosis of brain tumor is done by various methods like MRI, CT scan and neurological testing. In the recent past, a number of nanoemulsion formulations have been formulated and developed to treat and diagnose brain cancer. The present work presents the present status of anti-cancer drugs, the parameters related to their working and the advancement in technology.

Keywords: Brain tumor, Diagnosis, Malignancy, Nanoemulsion, Treatments.

INTRODUCTION

Brain tumor is one of the critical aliments that have been associated with the medical field for the last many years. In the mid 1950-60's, this disease is considered to be the fatal disease with the least chance of survival. But with the advancement of technologies, the chances of survival and the rate of treatment have increased a lot. Still, the disease remains one of the most lethal as far as developing countries are concerned. A number of drugs are being incorporated

[*] **Corresponding author Deepak Prashar:** KC Institute of Pharmaceutical Sciences, Una-177207, H.P., India; E-mail:prashardeepak99@yahoo.in

Ram Kumar Sahu (Ed.)

into the treatment of brain tumors (Table **1**) approved drugs (by the National Cancer Institute) and their combinations are highlighted.

Table 1. FDA Approved Drugs for Cancer Treatment [1]

S. No.	Drug Name	Brand Name	FDA Approval Status	Therapeutic Uses
1.	Everolimus	Afinitor Afinitor Disperz Zortress	Yes	• Breast carcinoma • Pancreatic Carcinoma • Gastrointestinal cancer • Pulmonary cancer • Renal cell carcinoma Astrocytoma
2.	Bevacizumab	Avastin Mvasi Zirabev	Yes	• Cervical cancer • Colorectal cancer • Glioblastoma (a type of brain cancer) • Hepatocellular carcinoma (a type of liver cancer) • Nonsquamous non small cell pulmonary carcinoma • Ovarian carcinoma • Oviduct carcinoma • Peritoneal carcinoma (primary) •Kidney cancer
3.	Carmustine	BiCNU	Yes	• Brain tumor • Hodgkin lymphoma • Non Hodgkin lymphoma • Multiple myeloma
4.	Carmustine	Gliadel Wafer	Yes	• Glioblastoma multiforme •Malignantglioma
5.	Naxitamab-gqgk	Danyelza	Yes	• Neuroblastoma
6.	Lomustine	Gleostine	Yes	• Brain tumors • Hodgkin lymphoma
7.	Temozolomide	Temodar	Yes	• Anaplastic astrocytoma • Glioblastoma multiforme (GBM)
8.	PCV combination	P = Procarbazine Hydrochloride C = Lomustine (CCNU) V = Vincristine sulphate	Yes	• Brain tumors

Nanoemulsions are drug carriers which are colloidal particles system of sub micron size. They are been widely employed in the delivery of drugs for the treatment of ailments. The size range in which they are available is from 10-1000nm. Structure wise, these are the solid spherical particles with negative

charge supported by amorphous and lipophilic surfaces. Nanoemulsions are the mini-emulsions that are basically the oil/water or water /oil dispersion. They are stabilized by an interfacial film of surfactant molecules having a droplet size range 20- 600nm. This small size of nanoemulsion provides it the transparent nature. Practically, three types of the nanoemulsion can be formulated (Fig. **1**).

1. o/w nanoemulsion (dispersed phase oil and continuous phase water/aqueous)

a. Oil in water nano-emulsion (Neutral)
b. Oil in water nano-emulsion (Cationic)
c. Oil in water nano-emulsion (Anionic)

2. w/o nanoemulsion (dispersed phase is water and continuous phase is oil)

3. Bi-continuous Nanoemulsion

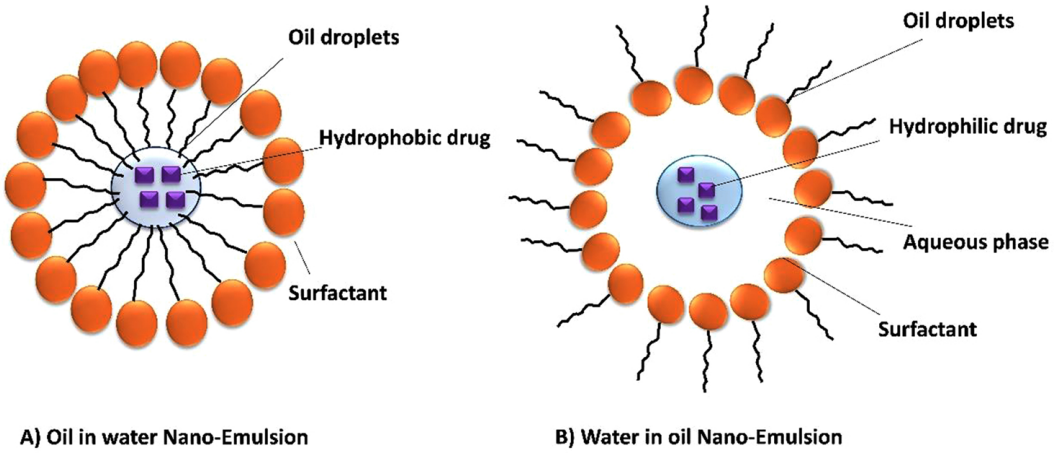


Fig. (1). (A) Oil In Water Nano-Emulsion (B) Water In Oil Nano-Emulsion

BASICS OF NANOEMULSION

Nanoemulsion is being utilized in numerous fields as the drug delivery carrier. The fields in which nanoemulsion is required include parenteral delivery, oral delivery, ocular delivery, transdermal delivery, and topical delivery of the drugs. Moreover, these nanoemulsions have also shown their applicability in biotechnology and targeted drug delivery. The merits of the nanoemulsion are quite large in number too. In site-specific drug delivery, a large quantity of hydrophobic drugs can be dissolved, protecting the drug from degradation with longer stability, serving as a good substitute for liposomes to enhance bioavailability. They also have the ability to make multiple formulations having a

CHAPTER 7

Theranostics Micelles for Brain Tumor Diagnosis and Treatment

Nidhal Khazaal Maraie[1,*], Zainab H. Mahdi[2] and **Zahraa Amer Al-Juboori[3]**

[1] *Department of Pharmaceutics, College of Pharmacy, Al-Farahidi University, Baghdad, Iraq*

[2] *Department of Pharmaceutics, College of Pharmacy, Applied Science Private University, Amman, Jordan*

[3] *Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq*

Abstract: Brain cancer is considered one of the most vicious and devastating tumors owing to its poor prognosis and high mortality rate. Common strategies for treatment include surgery, radiation, and chemotherapy. Unfortunately, these are limited due to their invasive nature and the inherent difficulties of brain surgery, given there is a high possibility of tumor relapse. Further, radiation and chemotherapy have a non-selective harmful effect on normal tissues, accompanied by limited drug delivery due to the presence of various barriers, including the blood-brain barrier. For this reason, the theranostic approach was developed by incorporating one or more therapeutic and diagnostic agents in a single nanocarrier moiety which could be modulated at its surface with certain proteins, legend, surface markers, or a stimuli-responsive agent that is capable of selectively targeting the tumor site after passing through the blood-brain barrier. This new field will permit the early and precise detection of cancer tissue, facilitate the process of drug delivery and assist in monitoring treatment outcomes. Micelles are considered one of the most commonly used nanocarriers due to their high stability and loading capacity, along with efficient release controlling properties. This chapter will present brief information about brain anatomy and cancer, and will discuss the main strategies implemented in the diagnosis and treatment of brain cancers. Furthermore, it will introduce the theranostic micelle approach by highlighting micelles types and preparation techniques, as well as explain the different barriers and approaches to targeting.

Keywords: Active targeting, Blood-brain barrier, Blood-brain tumor barrier, Brain cancer, Brain tumor stem cells, Chemotherapy, Computed tomography, Focused ultrasound, Gene therapy, Magnetic resonance imaging, Optical imaging, Paracellular, Passive targeting, Photodynamic therapy, Photothermal therapy, Polymeric micelles, Stimuli-responsive targeting, Theranostic, Transcellular, Tumor microenvironment.

[*] **Corresponding author Nidhal Khazaal Maraie:** Department of Pharmaceutics, College of Pharmacy, Al-Farahidi University, Baghdad, Iraq, E-mails: dr_nidhal_khazaal@yahoo.com, , drnidhalkhazaal@uoalfarahidi.edu.iq.

Ram Kumar Sahu (Ed.)

INTRODUCTION

The brain is a unique organ isolated in a chamber distant from other organs, yet it controls every other organ in the human body. However, like any other organ, it is susceptible to different diseases. Brain tumors are considered the most vicious and dreadful type of tumor, ranging from benign to malignant, often ending up being metastatic [1]. Central nervous system tumors account for 2-5% of all tumors, as brain involvement is 80% while 20% for the spinal cord. The majority of brain tumors are primary, although 20-40% can develop metastasis. These tumors cause 2% of deaths from the total percentage of deaths resulting from all cancers, and they account for 20% of all cancers in children [2].

Brain tumors include gliomas, meningiomas, and pituitary tumors. The most common brain tumors are malignant gliomas, which are divided into oligodendrogliomas, astrocytomas, ependymomas, and oligoastrocytomas. The benign form of this tumor is characterized by slow growth, and it can be removed easily by surgery with or without the aid of radiotherapy [3]. However, the malignant form is characterized by rapid growth and lower survival rate, while medulloblastoma and ependymoblastoma are considered lethal forms of this tumor [4].

According to the World Health Organization, a grade from I -IV is given to brain tumors based on the severity of cancer according to their various catastrophic outcomes. Grades I and II are designated to tumors with a good prognosis, while by contrast, the higher grades III and IV are designated to malignant tumors with severe complications [5].

Based on population studies, primary CNS tumors affect more than 60,000 people per year in the USA; one-third of these cases are estimated to develop into a malignant type [6]. The mortality rate of brain tumors is estimated at 3 per 100,000 worldwide. 11 new cases are diagnosed on daily basis in the UK, while only two are expected to survive. The global prevalence of brain tumors among males and females is 3.6 and 2.5 per 100,000, respectively, and this rate has been increasing over the years [7]. Despite the low incidence of primary brain tumors compared with other types, this type gives rise to an inconsistent level of morbidity and mortality. In addition, it interferes with the patient's ability to move and speak, which requires more attention and clinical interventions [8].

The rate of prevalence of brain tumors in developing countries is ambiguous due to a lack of advanced diagnosis techniques. Such undiagnosed cases are associated with a lower level of reporting in these countries [9].

The risk factors associated with the development of brain tumors are not fully clear, however, according to different researchers, the sum of all the possible factors associated with primary tumors are listed in Table **1**, and by contrast, glial and meningeal neoplasms definitely arose due to ionizing radiation [10]. Generally, the most agreed-upon risk factors that are associated with brain tumors are genetic causes; several genetic syndromes have been reported to correlate with primary brain tumor development. Moreover, viral infection is a potential risk factor, although the correlation is unclear. However, several viral families have been reported to be associated with brain cancer development, such as polyomaviruses and herpesviruses [11].

Table 1. Risk factors associated with brain tumors [11]

Potential Risk Factors
Radiation: Ionizing
Head trauma
Allergies
Diet and vitamins N-nitroso compounds Fat intake Aspartame ingestion Tobacco Alcohol
Chemicals Hair dyes and sprays Traffic-related air pollution
Infection Simian Virus 40 Human Cytomegalovirus Polyomaviruses (e.g. JC and BK) Toxoplasma infection Varicella-zoster – protective role
Genetics Neurofibromatosis type 1 Neurofibromatosis type 2
Occupational Exposure Electrical workers and electromagnetic fields Agriculture workers are exposed to pesticides, herbicides, and fungicides Other industries (vinyl chloride, petrochemical, and rubber industries

CHAPTER 8

Theranostics Inorganic Nano-particles for Brain Tumor Diagnosis and Treatment

Krishna Yadav[1], Swati Dubey[2], Shalini Singh[2], Geetika Sharma[2], Madhulika Pradhan[3], Narayana Subbiah Hari Narayana Moorthy[2] and **Sunita Minz[2,*]**

[1] *University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh 492010, India*

[2] *Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India*

[3] *Rungta College of Pharmaceutical Sciences and Research, Kohka, Kurud Road, Bhilai, Chhattisgarh, India*

Abstract: Brain tumors pose a major threat to human health due to difficult treatment, rapid progression, and poor prognosis, resulting in a terrible fatality rate that has remained high over the years. As arteries have limited drug permeability into brain tumor tissue, the success rate of chemotherapy remains low. Considering the anatomic concerns of brain tumors and the interaction between the blood-brain barrier (BBB) and nano-particles (NPs), nanotechnology is deemed an attractive approach as it has the potential to increase brain drug distribution. Theranostic strategies have also been proposed in recent years and they are seen promising. NPs are considered ideal due to their size, ease of surface modification and, adaptability to integrating several functional components in one system. In lieu of this, the design of nano-particles with therapeutic and diagnostic uses has increased tremendously, particularly in cancer treatment. This two-pronged technique aids in understanding tumor tissue location, treatment progress, nanoparticle's bio-distribution and, its efficacy as it is particularly valuable for personalized medicine-based treatments. In this chapter, we will focus on the properties of the blood-brain barrier and the blood-brain tumor barrier (BBTB), two important hurdles in brain-tumor targeted delivery, and the targeting strategies that aim at different stages of brain tumor growth and development as well as their recent advances in brain tumor-targeted novel nano-drug delivery systems.

Keywords: Blood-brain barrier, Brain targeting, Brain tumor, Inorganic nano-particles.

[*] **Corresponding author Sunita Minz:** Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India; E-mail id-sunita.minz@igntu.ac.in

Ram Kumar Sahu (Ed.)

INTRODUCTION

Cancer is often regarded as one of the major causes of death worldwide. It is estimated that more than 10 million instances of cancer are discovered each year, with this figure projected to increase approximately to 28.4 million by 2040. As a result, it is critical to obtain early diagnosis and treatment of this fatal illness. The options for cancer treatment include surgery, radiation and chemotherapy which the latter is the most commonly utilized treatment modality in both early and advanced-stage malignancies [1]. Chemotherapeutic drugs, on the other hand, have disadvantages such as low stability, difficulty to penetrate the cell membrane, non-specific distribution, and vulnerability to drug resistance [2].

As a result, new methods to improve the care of patients with malignant brain tumors are required, including early detection, monitoring therapy response as well as more effective medicines. In terms of therapeutics, medication delivery to the brain is a significant problem due to its strong resistance to foreign molecules' entrance. Many compounds were reported effective for brain diseases yet they had failed therapeutic trials due to their inability to pass the blood-brain barrier [3]. This necessitates the development of more effective drug transport methods. Nanostructured delivery systems have gained the attention of researchers in both treatment and diagnosis, claiming two uses simultaneously due to their ability to transport a variety of therapeutic substances including drugs, proteins, peptides and, nucleic acids [4].

In this context, theranostic nano-particles (NPs) would promote systems that offer opportunities for a controlled and specific release of the drug by overcoming the limitations of current brain tumor treatment/diagnosis options at the clinic, protecting the drug from metabolism and simultaneously transporting two or more drugs to exert a synergist effect [5].

In creating theranostic nano-particles, a thorough understanding of the treatment and detection process is required. This expertise comprises a grasp of many aspects such as chemical compatibility, synthesis parameters with special regard to the chemicals used, toxicity concerns, biocompatibility and biodegradability of formulation ingredients, pharmacokinetics, and dynamic parameters. An ideal theranostic nanoparticle should possess several characteristics such as a selective and fast gathering of NPs in cancerous cells, effective administration of the optimal dosage of medication, minimal harm to nearby non-cancerous cells, rapid removal from the body or metabolism into non-toxic metabolites [6].

Nanoscale compounds that are utilized in cancer therapy can be classified as organic and inorganic. Polymeric NPs, liposomes, dendrimers, and solid-lipid NPs are some examples of organic materials. Inorganic NPs on the other hand, are

either metal-based, semiconductor-based or magnetic material-based nano-particles. Inorganic NPs provide a greater potential as drug carriers than organic NPs due to high quantum yields, simple surface modification, controlled drug release, safety concern, enhanced bioavailability, high loading capacity, extended lifespan, high stability against light, and wide surface area [7, 8]. Of late, most research on inorganic NPs has focused on cancer detection, diagnosis, and treatment. Inorganic NPs have received quite an attention due to their exclusive physicochemical (material and size-dependent) characteristics, which organic NPs do not possess. In general, inorganic NPs are constituted of a core and a shell region, where the former is composed of inorganic materials such as gold, iron oxide or, silica while the latter consists of organic polymers such as proteins or complex sugars. Furthermore, the shell region would protect the inner core from undesirable physicochemical interactions. Gold NPs, quantum Dots, mesoporous silica NPs, superparamagnetic iron-oxide NPs, and hybrid nanocarriers are the most frequently utilized inorganic NPs for therapy and diagnosis of cancer as they possess high stability, ease of fabrication, surface modification, inertness, and magnetic properties. Therefore, they are considered as the most appropriate modality for imaging, and removal of cancerous cells. Moreover, inorganic NPs also possess higher quantum yield, longer lifespan and better photostability than organic NPs [9, 10].

This chapter focuses on the various methods of brain targeting, uptake and processing of NPs in the brain, and the role and applications of inorganic nano-particles as theranostic systems for cancer therapy.

BARRIERS TO TARGETED DRUG DELIVERY STRATEGIES IN BLOOD BRAIN BARRIER

Brain tumors pose a significant threat to human health due to their rapid growth, poor prognosis, and difficult treatment which would result in persisting terrible mortality rate. Due to poor drug permeability from the vessels into brain tumor tissue, chemotherapy has made limited progress to date. The effectiveness of a brain tumor-targeted nano-drug delivery system is evaluated based on the accuracy of the drug delivery to the exact foci. Moreover, a reduction in the accumulated drugs in the peripheral tissue and normal brain has been observed in recent decades [11]. There are certain barriers that prevent various targeted drug delivery systems from reaching to the brain (Fig. **1**).

Blood-Brain Barrier Targeting Methods and Related Mechanisms

Neurological disorders such as infections, psychiatric disorders, pain, cancers, neurodegenerative diseases, *etc.* are the most common causes of mortality, morbidity, and disability, affecting people around the world and the numbers are

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

L

M

N

O

P

R

S

T

U

V

X

RAM KUMAR SAHU

Dr Ram Kumar Sahu is an Associate Professor at the Department of Pharmaceutical Sciences, Hemvati Nandan Bahuguna Garhwal University (A Central University), Chauras Campus, Tehri Garhwal-249161, Uttarakhand, India. He had more than 17 years of teaching and research experience. He delivered guest lectures in various Universities of Malaysia, Thailand, Philippines and Indonesia. Dr. Sahu's research work highlights on Isolation and characterization of active constituents, novel drug delivery system, formulation and standardization of herbal drugs, screening and evaluation of various Pharmacological activities of samples. He has made innovative, outstanding, and original contributions both in education and research in the area of natural products. He is a recipient of different awards from International and National organizations. He received six International and five National awards. Under his supervision & Co-supervision twenty-six PG scholars and four PhD scholars were awarded. He is the author of over 100 scientific publications in the field of Pharmaceutical Science and has authored 08 books and 12 chapters for pharmacy books. Dr. Sahu is an invited speaker and panelist in various Abroad and Indian conferences. He has organized various National and International Conferences. He is on the editorial boards and reviewer of various national and international peer review journals. He has visited Singapore, Taiwan, Malaysia (Five times), Thailand (Twice times), Egypt, and Indonesia for presentations.