selective association with cancer cells for the treatment and diagnosis of brain tumors.[129]

Yang and David formulated magnetic iron oxide nanoparticles (MIONs) coated with a molecule that is noncovalently associated with a brain-targeting molecule. The coated MIONs comprise an anti-tumor agent linked to a cell-penetrating peptide.[130] MIONs are oriented at the site of the brain tumor with an external magnetic field.[130] In a patent by Dixit *et al*.[131]gold nanoparticles conjugated with peptides against both EGFR and TfR and loaded with the photosensitizer phthalocyanine 4 have been designed and characterized. Laser was then applied to activate the photosensitizer, causing subsequent cell death.[131]

On the other hand, nonthermal techniques to reversibly open BBB have been studied. One of these techniques is using ultrasound in the presence of microbubbles (MB).[132,133] MB work by resonating in an ultrasound beam, rapidly contracting and expanding in response to the pressure changes of the sound wave.[134] Inertial cavitation and destruction of microbubbles are capable of producing strong mechanical stress to enhance the permeability of the surrounding tissues and further increase the extravasation of drugs into the cytoplasm or interstitial cells.[135] Chen *et al*.[136] studied MB-carrying TGFβ1 inhibitor combined with ultrasound sonication to induce BBB/BTB disruption and enhance drug delivery. Pulsed-mode ultrasound exposure therapy was recently shown to enhance the antitumor effect of an EGFR-targeting chemotherapeutic drug facilitating antiglioma treatment.[137]

NUCLEIC ACID TECHNOLOGIES

MicroRNA

MicroRNAs (miRNAs) are endogenous RNAs composed of about 22 nucleotides. The miRNAs can play important regulatory roles in animals and plants by targeting mRNAs for cleavage or translational repression.[138,139] Currently, about 2% of known human genes encode microRNAs.[140] A growing body of evidence shows that miRNAs are one of the key players in cell differentiation and growth, mobility, and apoptosis.[141-143] Most microRNAs in animals are thought to function by inhibition of effective mRNA translation of target genes through imperfect base pairing with the 3-untranslated region of target mRNAs.[138,140]

MiRNAs are appealing therapeutic targets and potential biomarkers of GBMs.[141-143] Chan *et al*.[144] were the first to investigate the functional properties of a single miRNA in GBM cell lines. They discovered that high expression of miR-21 is a common feature of GBM.[144] In GBM, 15 types of miRNAs are the most studied (miR-7, miR-10b, miR-15b, miR-17, miR-21, miR-23a, miR-25, miR-124, miR-128a, miR-128b, miR-132, miR-137, miR-195, miR-221 and miR-222).[145] In a patent by Park *et al*.[146] hypoxia-induced angiogenesis-associated diseases including cancers was suggested to be treated by miRNA-125.

Aptamers

Aptamers are nonbiological oligonucleotides that can bind to protein targets.[147] Aptamers can be used for therapeutic purposes in the same way as monoclonal antibodies.[147] However, unlike traditional methods for producing monoclonal antibodies, no organisms are required for the *in vitro* selection of oligonucleotides.[147] For this reason, aptamers avoid the immunogenicity of antibodies while maintaining all their properties.[147] However, there still remain largely unknown pharmacokinetic properties which make them harder to develop than any given therapeutic antibody.[147]

Aptamers, consisting of a single-stranded nucleic acid having 100 nucleotides or less that specifically bind to tumor-initiating cancer cells, were developed and described by Rich *et al*.[148] The aptamer specifically binds to tumor-initiating cells of GBM.[148] Aptamers were the targeting agent of choice for a patent by Bloembergen *et al*.[149] where they used an aptamer-biopolymer-active agent conjugate system for the treatment of cancer.

CONCLUSIONS AND FUTURE DIRECTIONS

The development cycle of new therapeutic drug entities for brain and CNS costs from $500 million to $1.5 billion to get to market. Such huge expense could be directly attributed to drugs failing late in clinical trials or during the post-market follow-up (Phase IV).[150] In spite of the advances in drug discovery technologies and high-throughput screening techniques, the development cycle of new therapeutic entities is still costly and lengthy. It is challenging to ensure efficacy and safety throughout the four phases of clinical trials.[151,152]

To overcome these problems and alleviate some of the costs associated with new drug entity letdown, pharmaceutical formulators spend effort modifying and reinventing therapeutic and diagnostic agents, giving them new characteristics with enhanced safety and efficacy profiles. The use of novel nano-sized drug delivery systems (nanoDDS) is a major approach in such reinvention process. The nanoDDS can provide methods for targeting and releasing large quantities of therapeutic agents in exact, well-defined organs or tissues. Furthermore, they can easily be tailored, decorated, and modified via various agents such as stimuli-sensitive moieties, targeting agents, pharmacokinetics-modifying mediators, diagnostic agents, cell-penetrating peptides, protective PEGylation layer, or antibodies. Such modifying moieties can provide novel functions and better efficacy or safety profiles to current therapeutic agents. Furthermore, most nanoDDSs provide both hydrophobic and hydrophilic environments, facilitating better drug solubility and enhanced physicochemical characteristics.[153]

Despite their advantages, nanoDDS suffer from many problems such as stability issues, formulation scale-up difficulties, and short shelf life. Developing novel complexes and sophisticated systems that could never reach the market due to high cost, inability of scaling-up the system, or instability of the final formulation is a major problem. Major process and formulation development concerns exist with respect to the scale-up process of complex nanoparticulate carriers. To overcome

these problems, pharmaceutical formulators started to divert their effort from nanoDDS to simple bioconjugate techniques to directly attach old problematic active pharmaceutical agents such as stimuli-sensitive moieties, targeting agents, pharmacokinetics-modifying mediators, diagnostic agents, cell-penetrating peptides, protective PEGylation layer, or antibodies. Active pharmaceutical ingredients can be directly conjugated to antibodies against specific cell-type markers to create a hybrid smart molecule that is able to direct the active molecule to the disease tissue specifically. Consequently, many patents currently focus on simple bioconjugate structuresthat are easily synthesized with high yield, reduced cost, and high stability of the final formulation. This could provide a practical direction for the development of novel management tools and therapeutics for brain cancer for researchers worldwide, paving the road to affordable, scalable, stable, efficient, and safe management strategies.

All such techniques and technologies were illustrated in the recent patents analyses discussing brain drug delivery during 2010 to 2015. Despite such efforts, the development of brain drug delivery carrier system is still costly and troublesome in its transformation from bench to bedside. Such systems require huge effort in their *in vivo*, *in vitro* testing and clinical trials. Most of the research funding in academia for brain delivery research comes from investing companies. Most of the companies investing in this field are small startups such as to-BBB and BiOasis Therapeutics. If such industrial startups fail to develop a promising moiety or carrier for brain drug delivery, their existence is usually jeopardized.[154,155] An integrated ”bench-to-clinic” approach, realized through a structural collaboration between industry and academia, would strongly promote the development of brain tumor-targeted nanomedicines towards effective and safe clinical application.[156]

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