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Precision Nanomedicine for Glioblastoma: Engineering Nanoparticles to Overcome the Blood–Brain Barrier, Tumour Heterogeneity and Therapeutic Resistance

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ABSTRACT:
Glioblastoma GBM) is the most aggressive primary malignant brain tumor, with poor clinical outcomes despite maximal surgical resection, radiotherapy, and temozolomide chemotherapy. The limited effectiveness of current therapies is largely associated with the restrictive blood–brain barrier (BBB) and blood–tumor barrier (BTB), extensive intratumoral heterogeneity, glioma stem cell populations, and multiple mechanisms of therapeutic resistance. Nanomedicine offers a promising strategy to address these interconnected challenges through rationally engineered nanoparticles capable of improving brain delivery and therapeutic specificity. This review discusses current approaches for overcoming the BBB/BTB, including receptor-mediated transcytosis, focused ultrasound, convection-enhanced delivery, and intranasal administration. Major nanocarrier platforms, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, metallic nanoparticles, mesoporous silica nanoparticles, and extracellular vesicles, are examined for their therapeutic and theranostic potential. Particular emphasis is placed on multifunctional systems designed to target molecularly heterogeneous GBM populations and overcome resistance mechanisms involving MGMT-mediated DNA repair, drug efflux, PI3K/AKT signaling, and immunosuppressive tumor microenvironments. Emerging strategies integrating biomarker-guided targeting, co-delivery systems, theranostics, artificial intelligence, machine learning, patient-derived organoids, and humanized BBB models may enable personalized nanomedicine. However, challenges involving biological translation, protein corona formation, manufacturing, regulatory requirements, and clinical accessibility remain. Integrated and patient-specific nanoparticle design may provide a future pathway toward more effective precision treatment of GBM.

KEYWORDS: Glioblastoma; Precision Nanomedicine; Blood–Brain Barrier; Targeted Nanoparticles; Therapeutic Resistance.

I.INTRODUCTION

The most common and fatal adult primary malignant brain tumour glioblastoma (GBM) has a median overall survival time of only 12-15 months despite maximal multimodal therapy. It remains the standard of care to undergo maximal safe debulking followed by radiation and temozolomide chemotherapy concurrently and this strategy has changed relatively little in the last twenty years offering little added survival benefit before nearly inevitable recurrence driven by infiltrating tumour margins and subsequent drug resistance[1]. The lack of effective therapeutics for GBM can be attributed not to the absence of novel drugs, but the repeated failure to overcome a problem inherent in the way drugs are delivered-the so-called drug delivery problem. It is threefold. First tight junctional complexes and active efflux pump the blood-brain barrier (BBB) and blood-tumour barrier (BTB) actively exclude most drug molecules from crossing either paracellularly or transcellularly, respectively. Second, and to a high degree, the biological landscape of both within and between GBM patients comprises various subtypes with heterogeneous molecular mechanisms of pathogenesis and resistant subclones within a single tumour along with a glioma stem cell (GSC) niche for which specific single targeted approaches remain ineffective. Lastly, drug resistance against cytotoxic and specific cellular therapies operates via mechanisms which include various DNA repair pathways, drug efflux systems and immunosuppressive tumour microenvironments[2]. Standard drug delivery mechanisms however, were developed considering pharmacokinetics only ignoring entry barriers into the central nervous system and tumour complexity leaving these three points unchecked in a drug

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candidate until nanotechnology provided the potential for addressing them. Rational design of nanoparticles (e.g., controlling particle size and surface chemistry with relevant ligands for functionalization) can mediate receptor mediated transcytosis, thereby navigating the BBB/BTB, carrying targeted multivalent drug delivery systems specifically towards resistant subpopulations and mechanisms of resistance with precision[3]. In turn, the integration of these strategies with stimuli-responsive systems, targeted diagnosis and diagnostics and machine learning have started to lead to a form of "precision nanomedicine" rather than empirical formulation of nanocarriers. No specific mechanism of nanoparticle design is adequate for a successful nanocarrier in all three facets an agent that perfectly navigates the barrier but fails to deliver across resistant cell clones or target against the clonally diverse resistant infiltrative margins will ultimately fail. In this review, current approaches to nanocarrier design against the three faceted problems posed by BBB/BTB penetrance intratumor heterogeneity and drug resistance the progress and obstacles to clinical translation and future perspectives in nanoparticle development against GBM are surveyed[4].

II.THE BLOOD–BRAIN AND BLOOD TUMOR BARRIERS

The BBB is composed of BMECs also bearing pericytes, astrocytes, and the basal membrane (neurovascular unit) they are surrounded by tight junction complexes made of claudin-5 occluding and junctional adhesion molecules all anchored intracellularly by the zonula occludes family of proteins that so effectively seal cells together by limiting paracellular diffusion and by minimal pinocytic vesicle formation that the bulk of drugs is directed to transact transcellular transport, additionally, efflux transporter that is principally P-glycoprotein (P-gp/ABCB1), BCRP (ABCG2) and a range of MRPs pump chemicals such as metabolites of temozolomide or doxorubicin back to the bloodstream and efflux activity typically increase after chemotherapy treatment[5]. Selective influx transporters and receptors, such as GLUT1, LAT1, insulin receptor, transferrin receptor, LRP1, remain the dominant means for larger or hydrophilic compounds to cross the barrier, and also serve as potential entry targets into nanoparticles i.e., there is basically no other physiological entry point to the CNS for either macromolecular or nanoparticles Carriers, why so much of this field's engineering work has revolved around a small set of targets. BTB within the tumour doesn't appear to be nearly as "leaky" a structure as the early literature about Nanomedicine suggests. The BTB of GBM is most compromised within the highly vascularized core of the tumour where it has invaded the brain most aggressively, whereas it is more intact near the infiltrative margin-i.e., the critical region containing cells most often identified in recurrence after resection, a region that most passive nanoparticles should have trouble reaching. This heterogeneity differs from patient-to-patient, lesion-to-lesion, or even intra-lesion, and has parallels to what can be clinically observed as contrast-enhancing vs. non-enhancing regions on MRI this difference is systemically under represented by preclinical xenograft model systems which typically develop more homogeneous barriers than is present in human GBM, overestimating delivery in translatable ways[6]. Nanoparticles designed to preferentially deliver to well-vascularized barriers within the tumour's heavily infiltrated centre may be completely ineffective at reaching invasive disease in the infiltrative margin due to near non-existent concentrations. Similarly, there is nearly no therapeutic impact when nanoparticles can't get to tumours' infiltrative margin where they cause their infiltration; this effect limits the utility of classic EPP in GBM where BTB permeability is reduced and far more heterogenous than it is in peripheral tumours, there is little lymphatic drainage in the brain (though the glymphatic system exists and serves this role to a degree) higher intratumoral pressure can impede convective transport and there has proven to be a poor correlation between EPP-predicted tumour accretion and clinical effectiveness in both preclinical and clinical GBM studies[7]. While passive, EPR-triggered accumulation has led to drugs being successfully incorporated within liposomes that are now approved as drugs to treat solid tumours in other parts of the body it cannot deliver effective concentration to GBM due to the aforementioned limitations and it represents an oft-underestimated reason why many nanoparticle platforms have had disappointing success in the clinic, thus prompting the current push to devise truly active/targeting-mediated or device assisted strategies[8].

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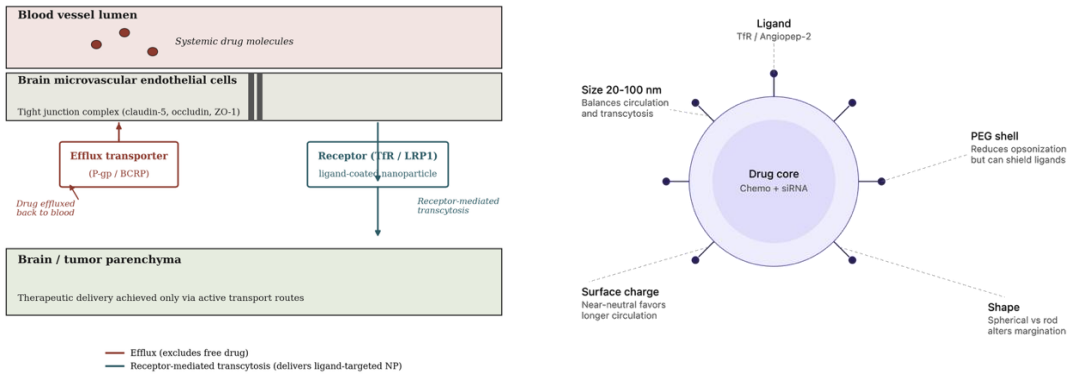

Figure 1 shows the blood-brain barrier's cellular architecture — the neurovascular unit, tight junctions, and the two competing transport routes (efflux pumps vs. receptor-mediated transcytosis)

III.FOR BARRIER ENGINEERING NANOPARTICLES PENETRATION

The best-characterized active method is receptor-mediated transcytosis (RMT), essentially an endogenous BBB influx mechanism co-opted. Receptors like the highly expressed on brain endothelium transferrin receptor can be targeted with antibodies or peptides to mediate uptake and nanoparticle transcytosis; however, strong receptor-ligand affinity leads to retention on the luminal membrane (the "affinity ceiling") and lysosomal degradation instead of release on the brain side. Angiopep-2, a 19 amino-acid peptide that has been shown to bind to LRP1 and is currently a frequent conjugation choice for polymeric and liposomal carriers (and for targeting insulin receptor or LAT1 receptors by alternate ligands) also engages endogenous pathways (ligand binding can block cellular processes like receptor internalization). Ligand density must be tightly controlled too high a density can cause receptor multimerization and early lysosomal uptake too sparse and the targeting ligand doesn't work. Bypassing biology altogether requires physical/device means[9]. Using MRI-guided Focused Ultrasound (FUS) along with i.e. microbubble injection causes transient opening of junctions by cavitation yielding a several fold increase in brain concentration now in Phase I/II GBM, and it is readily tenable and reversible although it needs specialized hardware and can causes off-target physical/thermal damage. Local concentration by positive pressure convection enhanced delivery (CED) through brain parenchyma bypassing entirely BBB and with no nanoparticle shape restriction, though invasive, has highly variable delivery patterns due to backflow. Modest and variable depth drug delivery to brain parenchyma through neuronal or trigeminal pathways is achievable intranasally[10]. Overall, physical and device approaches complement and are important alternatives to ligand targeting especially for targeting the tissue surrounding the surgical resection margin where recurrence typically originates, especially when the highest possible local concentrations must be achieved. Intrinsic physicochemical properties govern BBB penetration beyond the targeting approach itself, with the 20–100 nm particle size range and near-neutral surface charge giving the best balance of circulation time and permeability to paracellular transport or matrix diffusion. Particle charge increases binding capacity and uptake via adsorptive transcytosis, though cationic surfaces hasten clearing and raise toxicity concerns long circulation times of neutrally charged materials are achievable with slower uptake rates. The "PEG dilemma" refers to sterically impeding ligand activity for increased circulation from PEGylated coatings. particle shape behaviour differs significantly from spheres and is relatively uncharted. Overall, these different intrinsic and active, device-dependent aspects of nanoparticle design must be controlled simultaneously[11].

IV.NANOCARRIER PLATFORMS

Lipid-based and polymeric nanocarriers represent the most mature systems, having the advantages of decades of formulation experience, manufacture on a large scale and prior successful regulatory submissions for CNS therapies in non-CNS disease areas. Multi-segmented spherical lipid-bilayer vehicles, namely liposomes, are most advanced in terms of PEGylation/ligand functionalization, and are arguably the most clinically advanced

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Angiopep-2-functionalized nano delivery system yet applied to CNS clinical trials namely Angiopep-2 conjugated paclitaxel (ANG1005); their drug-release properties are easily modulated by varying the cholesterol/lipid ratio. Solid lipids nanoparticles (SLNs), known to be structurally stable, are drawing a lot of attention for nucleic acid therapy (e.g. Anti-resistance gene siRNA) thanks to the easy formulation into Nanoparticles. Polymeric nanoparticles synthesized from biodegraded polymeric materials like PLGA or PCL could be manufactured to breakdown at desired intervals, owing to their specific physical and chemical structure, thus being a viable strategy in terms of placing nanoparticles into a post resection cavity, but in terms of CNS applications their rate of diffusion can be manipulated on the basis of polymer molecule weight as well as their constituent units[12]. Dendrimers have the multivalent surface, allowing to combine drug, diagnostic imaging and targeting in one nano vehicle package, however costs and clinical manufacture limitations of the nanoparticles, has placed it at a relatively later stage of development as compared to other systems described before. Although described systems constitute bulk of reported clinical nano delivery, there are several other emerging inorganic, composite as well as biological nano systems capable of incorporating increased numbers of theragnostic approaches into one targeted therapeutic nanostructure; to mention gold nanoparticles which are also sensitive to radiation (radio sensitization) owing to their unique physical characteristics, and are being investigated for enhancing CT imaging, superparamagnetic iron oxides particles that could be utilized for MRI guided targeted imaging and thermal ablation of tumours, as well as porous silica nanoparticles that afford significant surface area for the loading of great amount of therapeutic drug as well as precisely modulated drug release. Biological carriers such as exosomes have a high capability to penetrate the blood brain barrier and reach cells naturally, they consist of naturally occurring biological vesicles thus offering patient safety through lacking exogenous components that would otherwise raise immune response. Beyond just targeting of specific locations or cells within the CNS, controlling the rate of drug delivery represents a second-generation need for CNS nanomedicine. There are various smart nanocarriers being developed that can differentiate between normal brain tissue and tumour site based on unique physiochemical properties present within either compartment (e.g., pH; redox status or enzymes[13] PH-sensitive nanoparticle drugs would be designed to only degrade in a mildly acidic milieu prevalent in the tumour extracellular space; a reduced environment within the tumour cell could lead to cleaving of the linkage holding the nanoparticle, and enzyme-sensitive systems may utilize tumour-specific proteinases such as Matrix Metalloproteinases. Another parameter, the hypoxic core within gliomas (especially GBM), might also be an area to explore to target delivery of therapeutics into these specific environments. Use of external stimuli such as infrared radiation, magnetic fields, or ultrasound can target systems designed to be triggered thermally. One overriding challenge for nearly all of the above systems, in addition to achieving effective penetration into and delivery within the target CNS compartment, is the sustained exposure and minimal dissipation within that particular region of the body[14].

V.CONFRONTING TUMOR HETEROGENEITY

GBM has become understood as a molecularly heterogeneous disease, characterized not as a single disease but a constellation comprising transcriptional subtypes including perineural (PDGFRA amplification, IDH mutation), classical (EGFR amplification), and mesenchymal (NF1 loss, inflammation/hypoxia)-as well as widespread intratumoral clonal heterogeneity. It has become clear through single cell sequencing that subtypes are not static but differ throughout a given tumour, and that in fact there are no 'fixed' cellular subtypes; the signature of a diagnostic biopsy will not necessarily represent the tumour in response to therapy, and because each tumour has an evolving clonal branching architecture targeted nanotherapeutics are likely to be selected against with any one targeting drug[15]. Additionally, differences in vascularity and immune infiltration at different sites within the same tumour result in vastly different delivery to a single target, for example EGFR; an added difficulty. Furthermore, glioma stem cells (GSCs), defined functionally by self-renewal and exaggerated susceptibility for resistance to therapy and recurrence are maintained within specialized niches (such as their peri vascular niche

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where Notch and nitric oxide paracrine signalling supports stemness and resistance to therapy, or their hypoxic/peri necrotic niche where HIF-1/HIF-2 programs support stemness and radio resistance, among others). Here their GSC biology relies not only on niche factors, but also upon exaggerated expression of efflux transporters (like ABC pumps) and resistance to DNA damage through efficient repair mechanisms, directly connecting their biology to therapy resistance; while nanoparticle entry is encouraged in their niche, an abundant GSCs that is already quiescent is largely ineffective against cell cycle-dependent therapies such as DNA damaging chemotherapies, thereby prompting the creation of targeting agents in addition to such cytotoxic therapies that will be presented the cells surface, targeting not just markers like CD133 but also markers such as CD44 or in combination therapies that could simultaneously push the cell into differentiating therapies an attempt to get the resistant, self-renewing stem-like state momentarily to enter that fragile differentiated state where its survival may be compromised[16]. As a result of the subtype heterogeneity of GBM, evolutionary forces, GSC biology, and the diverse biological landscapes of tumours, the use of nanomedicine with single targets will not lead to significant control over cancer and instead combinations approaches such as the co-administration of dual-functionalized targeted nanomedicine (e.g. Particles dual targeting for both EGFR andIL-13R2), multiple combinations of single-targeted nano carriers for formulation flexibility (though often with greater regulatory complexity), and multiple drugs encapsulated into individual nanoparticles for functional targeting beyond purely receptor binding (such as chemotherapy with resistance-modulating siRNA, or a combination targeting payload alongside differentiating therapy agents) would offer greater potential, and ultimately personalization where combinations could be determined based upon individual patient tumours[17].

VI.OVERCOMING THERAPEUTIC RESISTANCE

Glioblastoma (GBM) resistance occurs through numerous and often co-occurring mechanisms that the smartest nanoparticle countermeasures have to consider simultaneously. O6-methylguanine-DNA methyltransferase (MGMT) is able to directly reverse temozolomide-induced DNA adducts prior to the mismatch repair-mediated cell death cascade and its promoter status is now a recognized prognostic marker of temozolomide treatment response in patients thus MGMT inhibitors and/or MGMT-silencing nucleic acids encapsulated in nanoparticle delivery system might overcome this resistance[18]. Alternatively, increased base excision repair, homologous recombination and non-homologous end-joining also account for treatment-induced damage while both P-gp and BCRP-mediated efflux mechanisms are found on vascular and tumour cell membranes and abrogated pro-apoptotic signal transduction (loss of PTEN, activation ofPI3K/AKT signalling) and increase autophagy impede cytotoxic effect-suggesting the limiting advantage of strategies focusing on amelioration of one resistant mechanism[19]. The direct nanoparticle co-delivery of cytotoxic compounds and resistant-modifying nucleic acids or small molecules into a single carrier, such as the co-delivery of temozolomide and MGMT-silencing siRNA/shRNA or other chemotherapy drugs combined with P-gp and BCRP-silencing siRNAs, is emerging as a particularly promising approach since co-delivery ensures that the potentiating agents encounter their targets either prior to or concurrent with the cytotoxic agent upon release inside the tumour cell; small-molecule chemosensitizers such as PARP-inhibitors (exploiting synthetic lethality for tumour cells deficient in repair processes) and PI3K/AKT inhibitors have also been encapsulated individually or together to produce synergy rather than summation although release kinetics-matching remains an engineering challenge in translation and clinical outcomes fail to keep pace with pre-clinical successes; the immunosuppressive tumour microenvironment mediated by M2-polarized macrophages, regulatory T-cells and PD-L1 expression contributes significantly to resistance and renders existing anti-tumour immunity futile[20]. Therapeutic doses of anti-PD-1/PD-L1 immune-checkpoint blockade delivered via nanoparticles overcome poor brain penetrability and localizing the immune effect so as to potently suppress immuno-suppressing myeloid activity and Favor a T-cell-competent tumour microenvironment; the high-atomic-number nano-objects, such as those made out of gold and hafnium oxide, are highly effective radiosensitizers which increase the dose delivered to the tumour when coupled with radiotherapy and it can also induce robust anti-tumour immunity and thus boost it when it becomes integrated with nanomedicine, by eliciting the release of tumour antigens and damage-associated molecular patterns;

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focused ultrasound, on the other hand, is demonstrating effectiveness in targeting delivery of notoriously impermeable nanoparticle-delivered anti-PD-1/PD-L1 drugs to tumour targets, thus revealing its role in coupling barrier-penetrating delivery strategies (as previously described in Section 3) to targeted resistance-overcoming nanomedicine, which, presumably, will define the development of second-generation combinatorial nano-strategies for the treatment of GBM[21].

VII.TOWARD PRECISION AND PERSONALIZATION

Instead of empirically designing nanoparticles, biomarker-directed design focuses on molecules rationally chosen to be enriched in GBM with regard to normal brain. EGFR is produced by an in-frame deletion causing constitutively active receptor signal; majority of GBMs express this, as does normal brain and EGFR thus represents an effective, low-off target antibody or peptide target, although the clonality of target distribution will pose a challenge for consistent targeting[22]. Overexpression of IL-13R2 throughout the majority of GBM tumor cells with higher regional homogeneity, along with differential overexpression of PDGFRA intraneural GBM demonstrates a means to rationally select ligand as a function of molecular subtypes. Theragnostic nanoparticle platforms, which have an integrated therapeutic and imaging function, not only reduce one's reliance on tracking nanoparticle biodistribution through indirect methods by allowing non-invasive observation of BBB penetration, accumulation, and delivery in-vivo[23]. Iron oxide particles can be MRI tracked throughout biodistribution while gold particles provide CT-trackable boost in dose delivery of radiotherapy; intraoperative tumor margin localization may be guided by fluorophore or near infrared-emitting particles (few devices also integrate with biosensors for local pH and/or biomarkers, however product development for integrated imaging therapy and biosensing is hindered by unprecedented regulatory challenges), and this strategy also reduces the trial and error method[24]. With AI and machine learning the nanoparticle discovery and design process is accelerating. By using models derived from already screened nanoparticles to predict penetration based upon combination of parameters like PEGylation and additional physical properties or predicting receptor-ligand interaction potentials via molecular docking screens[25]. In the interim patients' tumor cells can be used in orthotopic patient-derived xenografts (PDXs) and organoid models which offer enhanced representation of heterogeneous human tumor cell population and their relevant BBB/BTB barriers than traditional 2D cell cultures and further improve validation of promising nanoparticle drug candidates for ultimately, personalize patient-specific nanoparticle design in complement with these models[26]. Combination of a predictive computer model of ligand candidates coupled with patient-specific organoid models seems like one of the best ways moving forward allowing the candidate drugs to be effectively screened against the patients' own tumor biology[27].

VIII.TRANSLATIONAL LANDSCAPE

Preclinical Models and Translation Therapeutics Preclinical models are inadequate representations of the human BBB and BTB, and no single method is sufficient for comprehensive screening or evaluation of nanomedicines for GBM[28]. Immortalized cell lines provide speed and throughput, but the loss of relevant tumor and BBB/BTB features following long-term culture can limit their utility for translation. Subcutaneous xenografts are convenient and quantifiable, but they neglect BBB complexity and role in lesion containment[29]. Conventional CNS tumor xenografts improve representation of the tumor environment, but artificial disruption of the BBB significantly biases nanoparticle uptake measures. Genetically engineered, spontaneously developing orthotopic tumor models are robust and representative of the complex tumor environment and immune cell response, but developing them can be challenging, costly, and time-intensive[30]. Variability in methods for evaluating nano-penetrance and measuring nanoparticle load can make comparison across laboratories difficult. Clinical Platforms andTranslation Lipid- and liposome-based systems are among the most developed formulations, and Angiopep-2-conjugated paclitaxel represents a heavily researched platform for CNS indications[31]. Lipid-based delivery of conventional cytotoxic drugs has shown similar safety to standard of care, but outcomes remain lower for either regimen, and translation is difficult because of how animal models can potentially overestimate delivery via an inadequate BTB. Phase I safety and pharmacokinetic studies have been undertaken for

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some nanomedicine platforms, while early clinical trials for ultrasound-guided BBB opening have shown feasibility[32]. Larger, more extensive Phase II/III trials will be necessary to determine clinical benefit. Consideration of BBB/BTB integrity, regional brain penetration, and nanoparticle distribution is required for accurate pharmacokinetics. Evaluation of nanoparticle-associated neuroinflammation, retention, clearance, and device-related adverse events must follow appropriate standards[33].

IX.CRITICAL BARRIERS TO CLINICAL TRANSLATION

Challenges in Clinical Translation Many challenges remain to be met in order to translate various nanoparticle delivery vehicles from the preclinical to the clinical setting[34]. One major challenge arises from the species gap in BBB physiology. Rodent cerebral capillaries tend to be less resistant to nanoparticles and macromolecules than those of humans, and a difference in total brain size may mean that equal rates of nanoparticle transcytosis result in vastly lower concentrations at the target depth in the human brain[35]. Orthotopic brain tumours may have different and less mature blood-tumour barriers (BTB) than the experimental xenografts in rodents; and differences in receptor expression and binding affinity (transferrin receptor (TfR), low-density lipoprotein receptor 1, for example) could also be barriers to translation. BBB-on-chip models with human-derived endothelial cells, astrocytes and pericytes are currently under development to better understand human BBB transport, although these systems have yet to become scalable, high-throughput, widely used models for disease testing[36]. One final challenge is the bio-nano interface. Once injected, nanoparticles are quickly coated by circulating plasma proteins, which form a protein corona on the nanoparticle surface and can prevent receptor binding of the carrier's targeting ligands[37]. Repeated injections of some PEGylated nanoparticles can also cause anti-PEG antibody formation and nanoparticle clearance[38]. Surfaces made from zwitterionic materials and bio-mimetic cell membranes may be alternatives to PEG. In addition, manufacture, regulation and accessibility issues are formidable[39]. Batches could vary in size and formulation stability during GMP synthesis, the clinical translation pathway is not yet well defined and standards for commercialisation lag behind those for standard drugs, and delivery systems such as focused ultrasound or convection-enhanced delivery could make accessibility challenging[40]. As with all nanotechnology, overcoming these biological, technological, manufacturing, regulatory and accessibility hurdles will be crucial for success[41].

X.FUTURE PERSPECTIVES

Nanomedicine is now transitioning from the development of single-mechanism formulas towards integrated, multi-functional nanomedicine platforms-incorporating not just barriers but also heterogeneity and resistance in the same Nanomedicine platform designs[42]. Such a dream scenario would likely require more advanced use of AI-and ML-driven nanomedicine design; from simple permeability predicting and ligand designing to the real integration of design through discovery to the clinic and its integration with modeling BBB transcytosis, tumor sub-type targeting and patient-derived organoid validation[43]. Secondly, nanoparticle delivery can expand upon genetic and cellular therapies; using them not just to administer CRISPR components, or mRNA-encoded therapies but also in supporting CAR-T and other cell-engineered T-cell approaches with CNS-targeted, non-viral gene-editing and immune-engineering delivered-payload which, unlike either small-molecule or biologics delivery system, cannot achieve at all[44]. On atheranostic, Nanomedicines are supposed to make a transition in a fashion of dynamic and live monitored treating of the recurring diseases, where the repeated administered dosage, after real-time image tracing the Nanomedicine distribution and tumor response, gets its component and the targeting aspect to-be dynamically tuned instead of pre-designing only one Nanomedicine formula to treat the patient-an attempt away from a fixed decision to a responsive therapy based treatment-when it meets a patient[45]. Efforts to narrow the persistent gap of bench-to-bedside need parallel development in humanized preclinical animal models, Nanomedicine-biology interactions well studied, the regulations on the multi-component system and continuously invested manufacturing process which is robust and reproducible in GMP[46]. The synergy of Nanomedicine design, computational modeling and molecular diagnostic offers the hope and the true direction to clinic with a hard-to-break yet penetrable blood–brain barrier disease at last-two decades' duration if the translational discipline can keep up[47].

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XI.CONCLUSION

Glial blastoma multiforme was the site of initial design focus of early, strictly BBB-focused precision nanomedicine, to the unified engineering problems of BBB transit, tumor heterogeneity and treatment resistance, which today is the prevailing paradigm. As has been documented throughout this review, delivery through the BBB-whether receptor-mediated transcytosis or physical disruption, or by optimizing physical/chemical properties to ease traversal through the BBB- is just one of many preconditions but is not sufficient, in isolation, for penetration across a disparate range of tumours and molecular sub-population as well as glioma stem cell niches and the treatment resistance which is mediated by DNA repair systems, efflux mechanisms, and the suppressed immunity found in the gliomas. It is at this intersection of issues which has spurred the latest and most promising emerging technologies-nanoparticles engineered with multiple targeting ligands or multiple therapies to penetrate into many varied tumours populations yet with combination-loadings of resistances-overcoming or eliminating factors which normally account for patient failure. These platforms are designed at this integration and also aetherometric: that gives us real-time read-out of both passage of nanoparticles to the tumor cells, and also that tumours response; and immunotherapy based on nanomedicines that in tandem achieve improved penetration to the brain with strategies that attack and to remove the tumor microenvironments immunodepression. A large translational gap still exist today- the variability of the BBB across species continues to yield a high preclinical hype which translate to failures in clinics, and we still do not have consistent control over the bio-nano interface, especially over the protein corona effect and immunity clearing/attack over the nanoparticle in circulation, on top of it manufacturing, access, and health cares are substantial roadblocks for translating successful strategies. In despite of all these obstacles, progress in simulation of scales through biology, patient derived models' system and rational combinations therapy is outlining a relatively clearer way for treatment for such a challenging tumor that for over a decade offers limited treatment success. Continued progress requires collaborative efforts not only by materials scientists, cancer biology specialists, and clinical neuro-oncologist but a more translatable, well-chosen research models will guarantee this engineered therapeutic success that it would come out of pre-clinical laboratories to the bedsides.

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