17 Maximizing Local Access to Therapeutic Deliveries in Glioblastoma. Part I: Targeted Cytotoxic Therapy

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Abstract: Glioblastoma (GBM), a primary brain tumor, remains an unmet medical need. One of the major obstacles to GBM treatment is the adequate properties of drugs. Complex pathobiology of GBM, including local invasion and intratumoral heterogeneity, represent major challenges to generating effective therapies. We discuss here the design of targeted cytotoxic drugs with an increased access to tumors and pathophysiologically important tumor compartments. Our research and others' have shown that interleukin 13 receptor alpha 2 (IL-13RA2), EphA2, and EphA3 receptors are overexpressed in most patients with GBM, but not in normal brain, and also in spontaneous canine high-grade gliomas like GBM, an excellent translational model of GBM. These receptors and also the EphB2 receptor are overexpressed and are functional in several GBM compartments involved

in tumor progression and/or resistance to therapies. We pursue the novel idea of targeting all four receptors with one targeted cytotoxic compound (QUAD-CTX). We are constructing a molecularly targeted anti-GBM drug that (i) may not require patient prescreening, (ii) will attack most tumor compartments known to be pathobiologically important, and (iii) performs these functions in one pharmaceutical entity, so it will be suitable for monotherapy. We thus wish to take advantage of a unique opportunity to produce an off-the-shelf, highly specific, molecularly targeted drug candidate suitable to treat perhaps even all patients with GBM. We envision that this "molecular resection" will translate into clear-cut durable responses in patients suffering from this dreadful disease.

Key words: Convection-enhanced delivery; Glioblastoma; IL-13RA2; Receptors; Targeted cytotoxins

Introduction

Effective therapy of glioblastoma (GBM) remains an elusive goal. Despite nearly 80 years of effort, only 1 month per decade has been added to the mean survival rate of GBM patients, and the 2-year survival rate remains below 25% with practically no cures (1). Recently, several highly anticipated efficacy trials including antiangiogenic therapies all failed in patients with GBM (2–5). Similarly, inhibiting a vital signaling pathway in a single compartment of GBM, namely, glioma stem-like cells (GSCs), conferred no clinical benefit (6, 7). Many small-molecule inhibitors have not progressed beyond early-phase trials based on little objective benefit (8, 9). On the other hand, immunotherapy trials showed promising results, including dendritic cell vaccination against IL-13RA2 (10), among other targets, and peptide vaccination against EGFRvIII (11). Although the vaccination against EGFRvIII in recently finished efficacy trial reproduced results from Phase I and II, the control group unexpectedly showed an increase in overall survival by 40% from previously observed (12). This is reminiscent of a similar happening when an IL-13-based cytotoxin was used in Phase III PRECISE trial (13, 14). Of interest, a medical device called Optune (Novocure) generating electric fields demonstrated clinical efficacy (15, 16). In short, GBM remains refractory to standard and experimental treatments. Predictions about translational potential of virtually all therapeutic approaches have not been realized thus far.

High mortality in GBM is often attributed to its complex pathobiology, including high cellularity, neovascularization, hypoxia/necrosis, immune cell infiltration, and local invasion (17). Moreover, GSCs may play an important role in GBM progression/recurrence and resistance to therapies like chemotherapy or radiation (18, 19). Recently, four genomic subtypes of GBM were delineated: proneural, neural, mesenchymal, and classical (20, 21), supportive of the complex pathobiological nature of GBM. Common treatment approaches involve surgery (22), radiation therapy (23), and various chemotherapeutic regimens (24, 25).

Other major obstacles to GBM treatment is the presence of barriers like blood–brain barrier (BBB) and blood–brain tumor barrier (BBTB), limiting or outrightly preventing any diffusion of drugs into tumors when given systemically (Figure 1). We believe that we can improve treatment of GBM by addressing crucial issues in
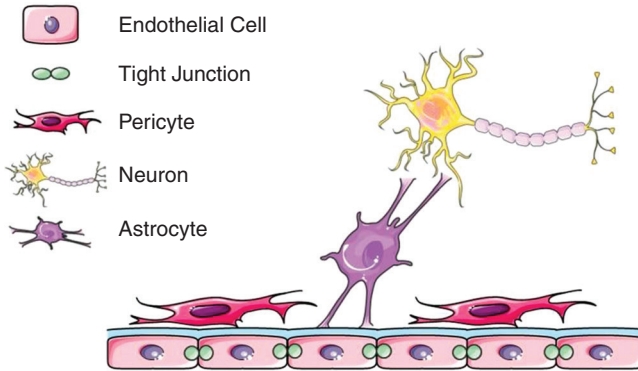
Figure 1 Schematic drawing of the blood-brain barrier. The blood–brain barrier is comprised of neurovascular units. Endothelial cells are connected by tight junctions and share a basement lamina with pericytes. Astrocytic end-feet are also at the basement lamina interface and these cells interact with neurons (This figure was developed using Servier Medical Art (http://www.servier.com/Powerpointimage-bank) under a Creative Commons attribution 3.0 Unported License). (Adapted from Pharmaceutics 2015;7(3):175–187.)

drug design and their delivery by maximizing drugs access to tumors and their targets. This can be achieved by generating anti-GBM drugs that attack concomitantly multiple GBM compartments that are responsible for tumor progression and resistance to the existing therapies and experimental therapies. For example, we can aim at four molecular targets like IL-13RA2, EphA2, EphA3, and EphB2 receptors that are specifically overexpressed on GBM tumor cells.

Targeted Cytotoxic Therapy of GBM

GBM is the most common primary brain tumor in adults, and the median survival is only ~14.5 months (1, 26). We discovered that interleukin 13 receptor alpha 2 (IL-13RA2) and EphA2 receptor are overexpressed in most patients with GBM, but not in normal brain (27–31), and also in spontaneous canine GBM, an excellent translational model of GBM (32–35). Expression of IL-13RA2 and EphA2 is partially overlapping; hence, the combined overexpression is ~90% in patients with GBM (31). IL-13RA2 and EphA2 are targets for multiple therapeutic approaches currently in the clinic or under preclinical evaluation (36–52). The first generation of an IL-13-based cytotoxin produced in our laboratory, which nonspecifically targeted IL-13RA2, demonstrated clinical efficacy in patients with recurrent GBM (13, 53–55). We developed a protocol for a Phase I clinical trial in dogs with gliomas (see also chapter 21, page 405) and began the trial using a cocktail of cytotoxins targeting IL-13RA2 (using a variant of IL-13 as a specific targeting ligand) and EphA2 receptor (based on ephrin A1, a ligand for the EphA2 receptor). The drugs are given locoregionally through convection-enhanced delivery (CED) using anti-reflux catheters (Figure 2 in Chapter 21). We have already seen significant antitumor responses in this dose-finding trial.
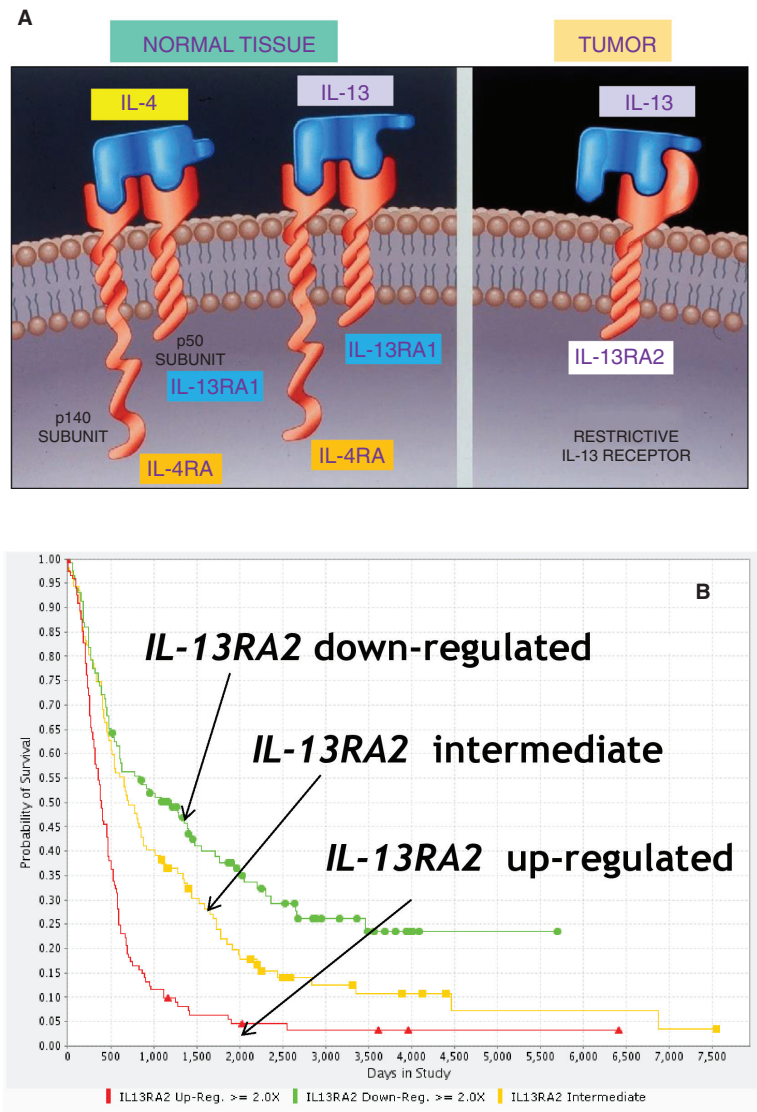
Figure 2 IL-13RA2 and EphA2 in cancer. (**A**) Schemata of normal tissue, IL-13RA1/IL-4A, and tumor-associated receptor, IL-13RA2 for IL-13 (adapted from Sci Med 1998;5:36–42). (**B**) Kaplan–Meier survival plots with differential *IL-13RA2* gene expression. REMBRANDT database of human gliomas was used for calculations (https://caintegrator.nci.nih.gov/rembrandt/). All differences were statistically significant. (**C**, **D**) Schemata of Eph receptors and their ligands, ephrinAs, respectively. (**E**) Kaplan–Meier survival plots with differential *EphA2* gene expression. REMBRANDT database of human gliomas was used for calculations as in *B*. All differences were statistically significant.
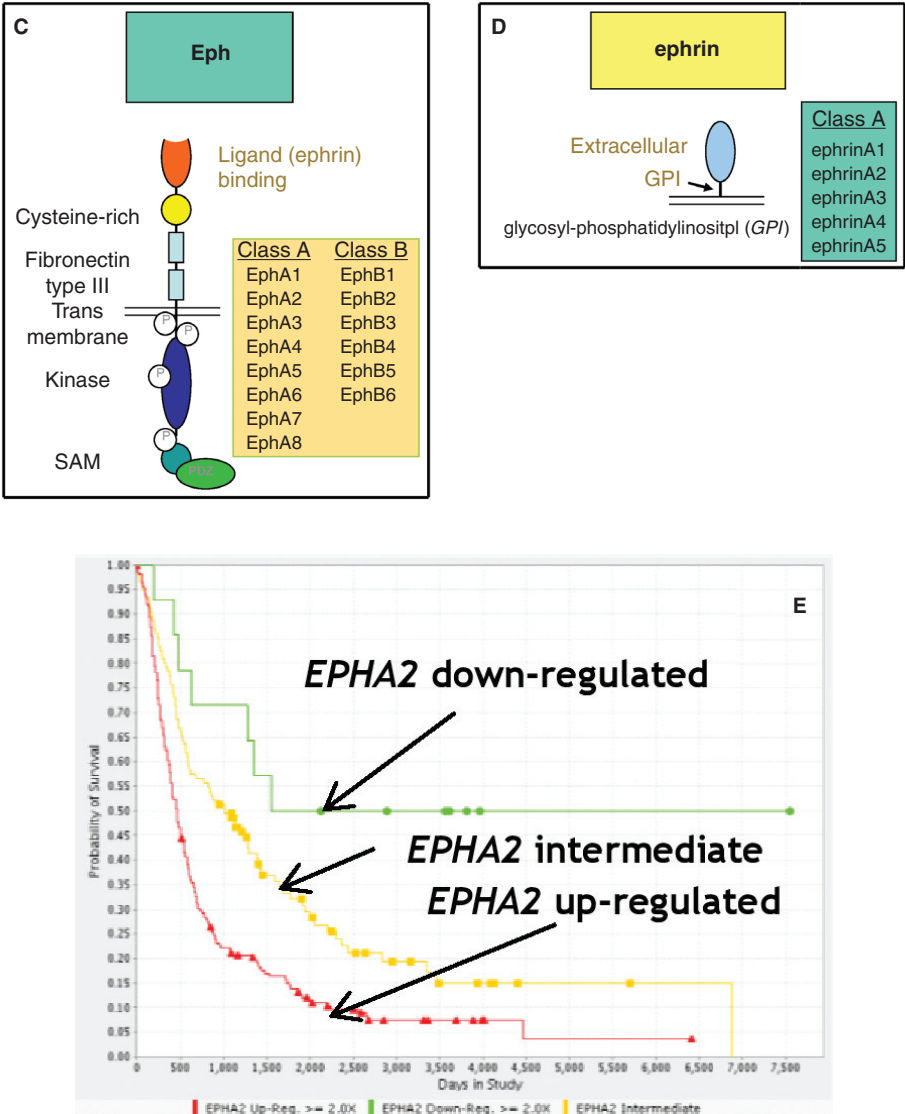
Figure 2 (Continued). **IL-13RA2 and EphA2 in cancer.** (**A**) Schemata of normal tissue, IL-13RA1/IL-4A, and tumor-associated receptor, IL-13RA2 for IL-13 (adapted from Sci Med 1998;5:36–42). (**B**) Kaplan–Meier survival plots with differential *IL-13RA2* gene expression. REMBRANDT database of human gliomas was used for calculations (https://caintegrator.nci.nih.gov/rembrandt/). All differences were statistically significant. (**C**, **D**) Schemata of Eph receptors and their ligands, ephrinAs, respectively. (**E**) Kaplan–Meier survival plots with differential *EphA2* gene expression. REMBRANDT database of human gliomas was used for calculations as in *B*. All differences were statistically significant.

Our research and others' have shown that IL-13RA2, EphA2, and also EphA3 (Figure 2) are widely present in various compartments of GBM tumors. For example, all three receptors are expressed in tumor cells of the core of GBM tumors. Importantly, IL-13RA2, EphA2, and EphA3 are present on tumor-infiltrating cells, while EphA2 is also overexpressed in tumor neovasculature (56, 57). Interestingly, IL-13RA2, EphA2, and EphA3 were associated with, and play crucial roles in, the pathobiology of GSCs. IL-13RA2 is abundant in cells isolated as GSCs from GBM (58–60) and contributes to their cell stem properties (61). EphA2 and EphA3 drive self-renewal and tumorigenicity of GSCs (62–64). Finally, the EphA3 receptor can be readily detected in GBM-infiltrating cells of monocytic origin, tumor-associated macrophages (TAM) (Figure 3). Thus, collectively, IL-13RA2, EphA2, and EphA3 are expressed in several GBM compartments documented to be involved in tumor progression and/or resistance to therapies (18, 19). Of importance, ephrin-A5 (eA5) binds EphA2 and EpA3 receptors and also the EphB2 (17, 65, 66) receptor, all present in abundance in
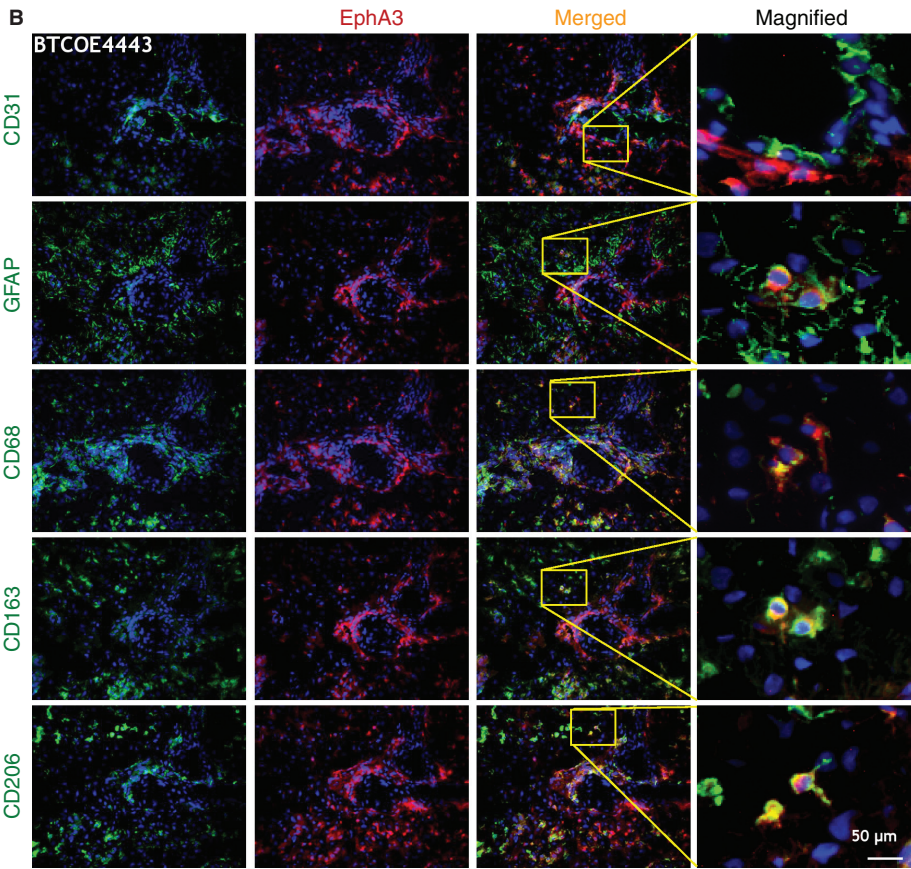

Figure 3 EphA3 receptor in GBM. Immunofluorescent staining of EphA3 (red) and CD31, GFAP, CD68, CD163 and CD206 (green) on consecutive sections of the same GBM specimen. Nuclei were stained with DAPI (blue). (Adapted from Oncotarget 2016;7(37):59860–59876.)

GBM tumors, but not in normal brain. Here, we discuss the novel idea of targeting all four receptors with one pharmaceutical compound. We are exploiting the favorable properties of our previously generated IL-13 variants and those of engineered eA5, to construct a human IgG$_1$ scaffold-based single pharmaceutical compound. The multivalent compound will bind IL-13RA2, EphA2, EphA3, and EphB2 and deliver a catalyst(s) to GBM tumors, specifically killing tumor cells and abnormal cells of the tumor environment. Such an approach offers a unique opportunity to gain an increased access to tumor compartments of high resistance, or poor availability, to current treatment modalities.

ATTRACTIVE MOLECULAR TARGETS IN GBM

We discovered the first receptor target overexpressed in most GBM patients, but not in normal brain: IL-13RA2 (29). IL-13RA2 is a monomeric receptor to which only IL-13 binds, unlike its normal tissue counterpart, IL-13RA1/IL-4A, which binds IL-13 and IL-4 (5) (Figure 2A). *IL-13RA2* is (i) associated with GBM patients' survival, (ii) expressed preferentially in a GBM mesenchymal subtype, and (iii) its gene, based on TCGA data, is overexpressed in 58% of patients (58; Figure 2B) and in the protein in up to 75% of GBM cases (35). IL-13RA2 was readily detected in cells isolated as GSC (59, 60) and appears to contribute to GBM cell stemness. For example, GBM cells selected for lack of IL-13RA2 have a significantly lower stem cell–like forming and tumorigenic potential (61). This observation provides strong rationale for treatments eliminating IL-13RA2 positive cells. IL-13RA2 may influence intracellular signaling (67) and may be a signaling molecule (68).

Our continuous efforts to find pharmaceutically tractable molecular targets led to discovery of the EphA2 receptor in GBM (31, 69–71). EphA2 belongs to the largest protein tyrosine kinase receptor family in eukaryotes (72–75) (Figure 2C); these receptors are bound by natural ligands called ephrins (Figure 2D). EphA2 is over-expressed in ~ 60% of patients with GBM (31, 76), but jointly with IL-13RA2 it is over-expressed in ~90% of all GBM, while absent in normal brain (31). Expression of *EphA2* and EphA2 correlates with glioma patients' survival (75) (see also Figure 2E) (77, 78). IL-13RA2 and EphA2 exist in a significant proportion of locally infiltrating GBM cells, and EphA2 is overexpressed on abnormal endothelium of tumor-associated vessels (52, 79). EphA2 activation by its preferred ligand, ephrin-A1 (eA1), induces prominent, dose-dependent inhibitory effects on anchorage-independent growth and invasiveness of GBM cells (79, 80). The EphA2/eA1 system function in GBM is complex; the receptor is oncogenic when ligand unactivated, but tumor suppressing when activated by eA1 (68, 69). EphA2 is also important for the self-renewing and tumorigenic potential of GSCs (62, 63). Thus, IL-13RA2 and EphA2 are attractive molecular targets for urgently needed targeted combinatorial therapy (31, 80, 81).

Most recently, we found that another receptor of the EphA subfamily, the EphA3 receptor, is overexpressed in GBM (Figure 3). The gene for *EphA3* was highly upregulated in G48a GBM cell tumorspheres (56) and even more so in nonpassaged GBM cells. Others found the EphA3 receptor is important for the self-renewing potential and tumorigenicity of GSCs (64). Interestingly, the distribution of EphA2 and EphA3 receptors only partially overlaps. For example, EphA3 receptors are found in cells of monocytic origin infiltrating GBM (82) like TAMs (Figure 3). The difference in

these receptors' distribution also agrees with the existence of multiple phenotypic types of GSCs (83). EphA3 often co-localized with a GSC marker Nestin *in situ*, in accordance with a recent report (64). EphA3 did not co-localize with the endothelial cell marker CD31 (Figure 3). Microglia/macrophages variably infiltrate gliomas and contribute to the total tumor mass (82). Three markers of monocyte/macrophage lineage (CD68, CD163, and CD206) co-stained with EphA3 on a subpopulation of cells within the tumor and surrounding the tumor neovasculature (64). This novel finding widens the spectrum of GBM compartments that can be exploited as targets in molecular anti-GBM therapies using Eph receptors.

PROMISING TREATMENT BYPASSING THE BBB

We and others have continued to optimize CED as a minimally invasive approach (33–35, 84–97). This way of drugs delivery is discussed in Part II of the chapter (page 347). A critical therapeutic advantage in using cytotoxins *via* CED is that they cause death of targeted cells (70). Even though the GBM tumor environment is highly immunosuppressive (98, 99) and patients with GBM are immunosuppressed (100, 101), a large number of killed tumor cells provides a "danger signal" and evokes effective antitumor immune responses. Our published (41) and unpublished observations suggested, and another study demonstrated directly (102), the existence of effective immune responses in preclinical studies with cytotoxic proteins. Importantly, the "*in situ* vaccine" effect of a treatment causing cell death is also the principal mechanism of antitumor action when using oncolytic viruses delivered directly to tumors using CED (6, 103). In this approach, the virus is delivered only to a portion of GBM tumors through a single catheter, but cell death at the site and near the virus injection appears sufficient to produce readily measurable immune responses in patients and subsequent antitumor effects (6, 103). Therefore, if one cannot distribute cytotoxins perfectly throughout the whole tumor and its vicinity in all patients at all times, the death of most cells in tumors during each treatment will result in an antitumor vaccination effect meaning new influx of immune cells responsible for the whole mechanism of response. This principle is tested in other cancers like melanoma; the viral gene therapy drug, Imlygic, has been approved by the FDA (104). Conceivably, the addition of immune checkpoint inhibitors should result in potentiation of such responses (105, 106).

INCREASING DRUGS ACCESS TO TUMOR COMPARTMENTS AND OPTIMIZING CED FOR EFFECTIVE GBM TREATMENT

The clinical results obtained with the first generation of IL-13-based cytotoxin, huIL-13-PE38QQR, which is a fusion protein between a wild type IL-13 and a modified pseudomonas exotoxin A (PE) represent promising translational starting point to improve treatment of patients with GBM. Early-phase trials with huIL-13-PE38QQR showed up to 56 weeks of median survival and a number of long-lasting responses (107). Importantly, the efficacy trial extended the lives of patients with recurrent GBM by almost 50%, but the control arm had extended from previously observed survivals and the favorable difference did not achieve statistical significance (13). The ways to improve the CED are described in further detail in chapter 18 (page 359) and chapter 21 (Page 405).

TARGETING EPH RECEPTORS SIMULTANEOUSLY

As pointed out above, IL-13RA2, EphA2, EphA3, and EphB2 are overexpressed, functionally important, and linked to survival in patients with GBM. They are all pharmaceutically targetable as demonstrated in preclinical and clinical studies. These receptors are distributed among several tumor compartments important for progression of GBM. Debinski's group has long been advocating attacking GBM with a combinatorial approach (31, 80, 81). Given that only two modified ligands may be needed to generate a drug delivery system targeting all four receptors, we have a completely new opportunity for combinatorial therapy and highly increased drug access in a complex disease of dismal prognosis, with just one pharmaceutical agent.

eA5 can bind and induce internalization of the Eph receptors A2, A3, and EphB2. Hence, we produced a dimeric form of eA5 in a fusion with an Fc fragment of human IgG$_1$, eA5-Fc (Figure 4A) (56). We also made an eA5-Fc-PE38QQR cytotoxin chemical conjugate (Figure 4A). eA5-Fc-PE38QQR killed U-251 MG, U-373 MG, and G48a GBM cells very efficiently and specifically (Figure 4B). The IC$_{50}$ of eA5-Fc-PE38QQR was in the range of 10^{-11} M. To confirm the specificity of the cytotoxin in targeting EphA2 and EphA3, the three GBM cell lines were pretreated with either eA1-Fc or eA5-Fc at 10 µg/mL for 1 h. As expected, the cytotoxin was less active on the three cell lines tested when pretreated with eA1-Fc, which binds only the EphA2 receptor, and completely lost its activity when cells were pretreated with eA5-Fc, which binds EphA2, EphA3, and EphB2 (Figure 4B). Even though the readings in colorimetric cell viability assay were not reaching 100% kill, the live/dead assay (Life Technologies) demonstrated that vast majority of GBM cells were dead at
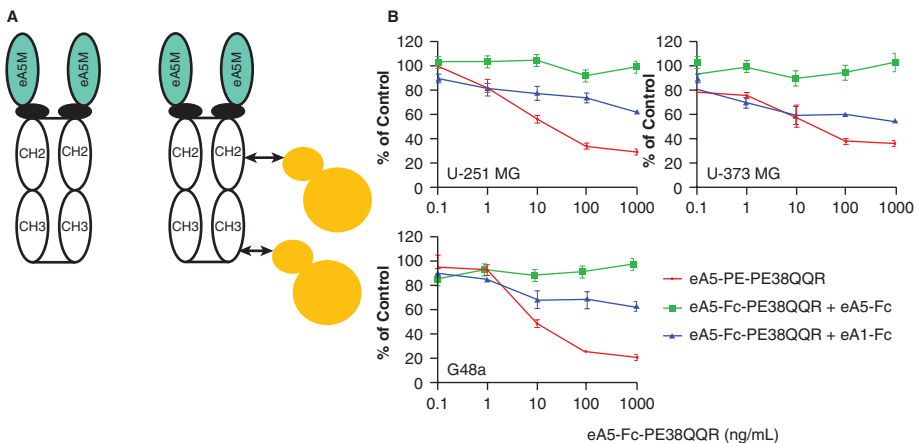

Figure 4 **EA5-Fc-PE38QQR kills GBM tumor cells, specifically targeting both EphA3 and EphA2 receptors. (A)** The structure of an eA5-Fc and eA5-Fc chemically conjugated to PE38QQR (right). Opposite arrows represent chemical conjugation. Closed small ovals represent hinge regions; thin straight lines represent disulfide bonds. Orange circles are the domains of PE: smaller = D2 and larger = Domain III. **(B)** Cell viability assay on GBM cell lines treated with eA5-Fc-PE38QQR for 48 h or pretreated with either eA1-Fc or eA5-Fc. (Adapted from Oncotarget 2016;7(37):59860–59876.)

10 ng/ml of conjugate concentration and almost all were dead at 100 ng/ml of conjugate (56).

TARGETING EPH RECEPTORS AND IL-13RA2 SIMULTANEOUSLY

eA5-Fc interacts with EphA2, EphA3, and EphB2 receptors. To further widen the reach of a targeting agent, we are incorporating mutated IL-13 (IL-13M), which has dramatically altered reactivity toward the normal tissue receptor, IL-13RA1/IL-4RA, but not toward the tumor-associated receptor, IL-13RA2 (41, 108–111) into the eA5-Fc construct (Figures 2A and 5A). The very first construct retained an ability to bind to the EphA2 receptor and IL-13RA2. Next, we will produce a chemical conjugate between eA5M-Fc-IL-13M and PE38QQR to demonstrate feasibility of the QUAD-CTX approach in a direct way similarly to eA5-Fc-PE38QQR. We will also make conjugates of eA5-Fc-IL-13M with chemotherapeutics like WP936 (112). This will eliminate several potential problems related to possible systemic delivery of toxin-based therapeutics.

QUAD-CTX BASED ON SCFV RECEPTOR TARGETING

We are generating another type of QUAD-CTX drug candidate in which we will use single-chain (sc) Fv fragments of antibodies (scFv) directed individually against the three Eph receptors: A2, A3, and B2. It will be also based on a human IgG$_1$ scaffold similarly to eA5M-Fc-IL-13M. We have already made the first step in generating a quadrivalent scFv(EphA2)-scFv(EphA3)-scFv(EphB2)-Fc-IL-13M. We have produced a bivalent scFv(EphA2)-Fc-IL-13M (Figure 6A). We will stepwise introduce scFvs for EphA3 and EphB2 receptors (Figure 6B) with various placement configuration and test for the exhibition of expected binding properties. Once it is made, the quadrivalent ligand will be conjugated to either modified toxins or a chemotherapeutic like WP936 (Figure 6C).
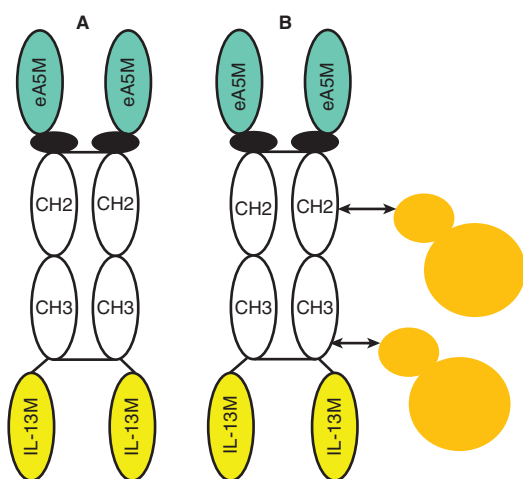

Figure 5 **Design of a QUAD-CTX.** (**A**) Schemata of eA5M-Fc-IL-13M in which the moieties of eA5M and IL-13M are targeting ligands. (**B**) Schemata of eA5M-Fc-IL-13M conjugated to PE38QQR. Closed small ovals represent hinge regions. Opposite arrows represent chemical conjugation. Closed small blue ovals represent chemotherapeutic. Filled triangles represent chemotherapeutic. Orange circles are the domains of PE: smaller = D2, and larger = Domain III.
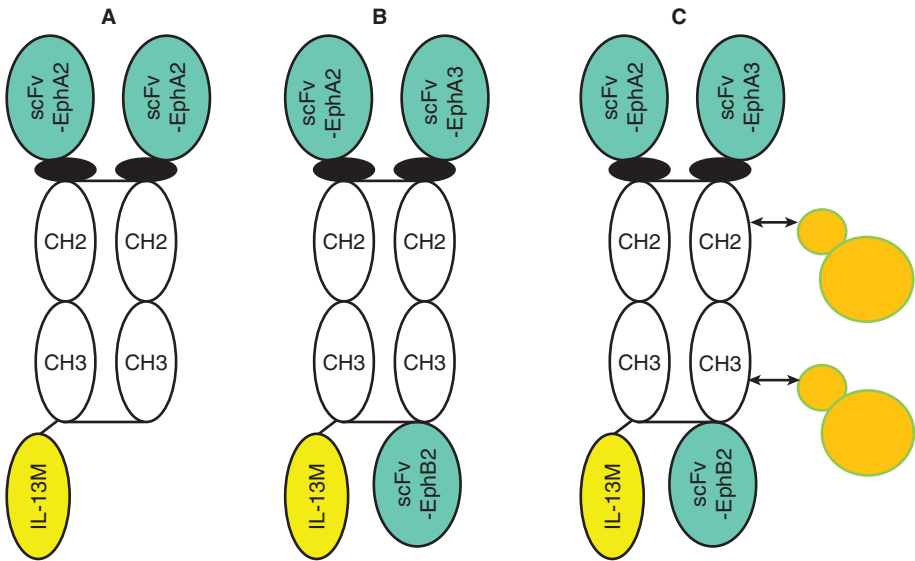
Figure 6 **Construction of a QUAD-CTX based on scFvs.** (**A**) Bivalent scFv(EphA2)-Fc-IL-13M construct. (**B**) Schemata of a quadrivalent scFv(EphA2)-scFv(EphA3)-scFv(EphB2)-Fc-IL-13M construct. (**C**) Schemata of a quadrivalent scFv(EphA2)-scFv(EphA3)-scFv(EphB2)-Fc-IL-13M chemical conjugate with toxic load. Closed small ovals represent hinge regions; thin straight lines represent disulfide bonds. Opposite arrows represent chemical conjugation. Closed small blue ovals represent either toxins or chemotherapeutic.

Conclusion

We have discussed our idea to target the three molecular targets that we identified in GBM: IL-13RA2, EphA2, and EphA3, and yet another receptor, EphB2 that are specifically overexpressed on GBM tumor cells as well. We are developing a cytotoxic drug of highly unique properties that can recognize four receptors, QUAD-CTX. Also, because virtually all GBM patients have these receptors in abundance, prescreening patients for this treatment may not be necessary. Thus, our new design will increase drug access to hard-to-target GBM compartments believed to be responsible for dismal prognosis of the disease. Thus, despite significant obstacles in drug delivery to GBM and the high complexity and heterogeneity of GBM, an off-the-shelf drug used as monotherapy can represent an effective combinatorial therapy approach using both passive and active immunotherapy.

Conflict of Interest: Dr. Waldemar Debinski is an inventor on the patent applications filed or patents issued on the subject of this chapter. He is also a Scientific Advisor to Targepeutics, Inc. and holds equity in the company.

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