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Review

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Peptide nucleic acid-based targeting of microRNAs: possible therapeutic applications for glioblastoma

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Abstract

A large and incremental number of non-coding RNAs, including microRNAs (miRNAs) have been recently demonstrated to play a very important role in human pathologies, including cancer. Therefore, microRNAs have been proposed as therapeutic targets and molecules exhibiting anti-miRNA activity or mimicking functional miRNAs have been developed. Among biomolecules proposed in anti-miRNA therapy, peptide nucleic acids (PNAs) are appealing, in consideration of their stability and efficacy in recognizing RNA targets. PNAs against tumor associated miRNAs have proven to be efficient in inducing anti-tumor effects both *in vitro* and *in vivo*. For instance, PNAs targeting miR-155-5p are able to induce apoptosis in glioma cell lines and to enhance the sensitivity to temozolomide (TMZ) in TMZ resistant glioma cells. *In vivo*, PNAs anti-miR-21 were found to exhibit anti-tumor effects associated with improved survival when administered to animals with intracranial gliomas.

Keywords: Peptide nucleic acids, glioma, microRNAs, miRNA targeting, delivery, apoptosis, temozolomide

MICRORNAS IN ONCOLOGY

MicroRNAs (miRNAs) are a family of evolutionary conserved small (19 to 25 nucleotides in length) non-coding RNAs playing important roles in the post-transcriptional control of gene expression. This control is operated at the level of mRNA translation and is based on the miRNA-dependent recognition of 3'UTR, CDS and 5'UTR mRNA sequences. This molecular recognition leads to a reduction of protein synthesis[1-4]. Single or multiple mRNAs can be targeted by a single miRNA, while a single mRNA can be recognized and

functionally controlled by several miRNAs (eventually differentially expressed in cells of different histotype); following these considerations, it is calculated that more than 60% of human mRNAs can be considered molecular targets of miRNAs[5,6]. It has been reported in different studies and reviews that the miRNA/mRNA interaction occurs at the level of the RNA-induced silencing complex (RISC), a ribonucleoprotein which incorporates one strand of a single-stranded RNA (in our case a microRNA), acting as a template to recognize complementary mRNA transcripts[1-4]. This molecular interaction is associated to (1) repression of translation or (2) mRNA degradation, depending on the level of miRNA complementarity with nucleotide sequences of the target mRNA[3,4]. Since their discovery and first characterization, the number of human microRNAs identified and deposited in the miRBase database (miRBase v.22, www.mirbase.org) is much more than 2600[7-9] and the research studies on microRNAs have confirmed the very high complexity of the networks constituted by miRNAs and RNA targets[7].

Changes of microRNA expression have been demonstrated to be associated with different human pathologies, and guided alterations of specific miRNAs have been suggested as novel approaches to develop innovative therapeutic protocols[10-13]. Several reports conclusively demonstrated that microRNAs are deeply involved in tumor onset and progression, behaving as tumor promoting miRNAs (oncomiRNA and metastamiRNAs) as well as tumor suppressor miRNAs[14-19]. In general, a miRNA able to promote cancer targets mRNA coding for tumor-suppressor proteins, while microRNAs exhibiting tumor-suppression properties usually target mRNAs coding oncoproteins[15].

Targeting oncomiRNAs and mimicking tumor-suppressor miRNAs: overcoming drug resistance

With respect to targeting oncogenic RNAs and mimicking tumor-suppressor miRNAs in translational medicine, it should be underlined that these non-coding RNAs are suitable targets for therapeutic interventions, as summarized in Figure 1[10-13]. The use of modified miRNA mimetics, either synthetic or produced by plasmid or lentiviral vectors, might lead to potentiation of miRNA functions (miRNA replacement therapy)[20-24]. In this case the miRNA replacement molecules (mimicking the miRNA functions to be up-regulated) are transfected to target cells [Figure 1A, step "a"] where interact with the mRNA to be modulated [Figure 1A, step "b"]. This interaction leads to down-regulation of this mRNA and associated suppression of protein production [Figure 1A, step "c", dotted arrows]. According to this procedure, it is possible to mimic the activity of tumor-suppressor miRNAs (down-regulated in tumors) to achieve down-regulation of miRNA-regulated oncogenes[23,24].

On the contrary, forced down-regulation of miRNA biological functions can be obtained using a large variety of well-characterized miRNA-inhibitor oligomers (such as in the case of direct miRNA antisense therapy based on RNA, DNA, LNA and other DNA analogues)[25-31], miRNA sponges[32-38], mowers[39] or through miRNA masking strategy that interferes with miRNA function by masking the miRNA binding site of target mRNA through hybridization with complementary molecules[40-42] [see Table 1]. In this case the miRNA inhibitors ["a", "b" and "c" of Figure 1B, suppressing the miRNA functions to be down-regulated] are transfected to target cells where they interact with the microRNA target [Figure 1B, step "d"]. This interaction prevents the target miRNA (for instance an oncomiRNA in protocols designed to develop anti-tumor therapy) to bind the specific 3'UTR sequence of the regulated mRNA, causing up-regulation of this mRNA and the associated increase of protein production [Figure 1B, step "e"]. According to this procedure, it is possible to inhibit the activity of oncomiRNAs (up-regulated in tumors) to achieve up-regulation of miRNA-regulated tumor suppressor genes.

Interestingly, in the case of the development of anti-cancer protocols, targeting miRNAs in drug-resistant tumor cell lines has been associated with partial or total reversion of the drug-resistance phenotype, as reported in different studies[43-48].

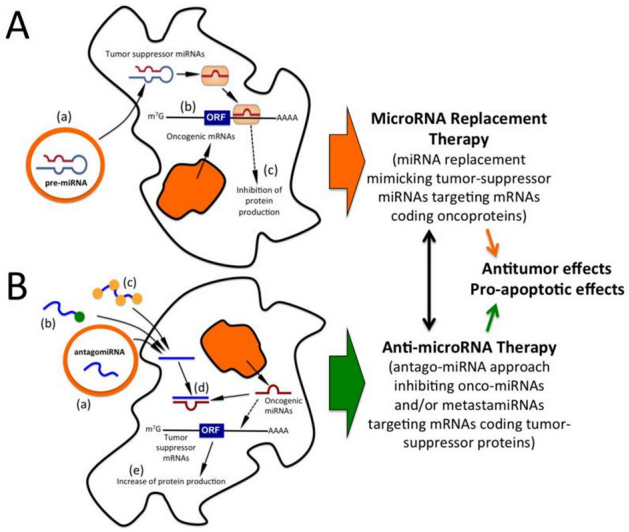

Figure 1. Scheme summarizing the miRNA replacement (A) and anti-miRNA (B) approaches to modify miRNA-regulated gene expression. In panel A the miRNA replacement molecule is transfected to target cells (a) where interact with the mRNA to be modulated (b) causing inhibition of protein production (c, dotted arrow). In panel B the miRNA inhibitors (a-c) are transfected to target cells (d) where they interact with the microRNA target preventing its binding to the specific 3'UTR sequence (dotted arrow) of the regulated mRNA (d). This causes up-regulation of this mRNA with increased protein production (e). Three examples of antagomiRNA molecules are shown: microparticle delivered antagomiRNAs (a), peptide-delivered molecules (b, peptide in green), or chemically-modified molecules (chemical modifications in yellows) to increase biological functions (for instance resistance to enzymatic degradation or delivery efficiency to target cells)

Table 1. Experimental strategies for inhibition of microRNA functions

Strategy	Bioactive molecules	Mechanism(s) of action	Biological effects	References
Use of microRNA inhibiting molecules	RNA, DNA, LNA and other DNA analogues, PNAs and PNA analogues	Sequence-specific hybridization to miRNA targets	Up-regulation of the expression of miRNA-regulated mRNAs	Weiler *et al.*[25], 2006; Lu *et al.*[26], 2009; Lennox *et al.*[27], 2011; Obad *et al.*[28], 2011; Elmén *et al.*[29], 2008; Stenvang *et al.*[30], 2008; Staedel *et al.*[31], 2015
Use of miRNA sponges	Circular RNAs (circRNAs) and long-non-coding RNAs (lncRNAs)	Inhibition of miRNAs by circRNA-miRNA or lncRNA-miRNA interactions	Up-regulation of the expression of mRNAs regulated by sponged miRNAs	Ebert *et al.*[32], 2007; Ebert *et al.*[33], 2010; Kluiver *et al.*[34], 2012; Kluiver *et al.*[35], 2012; de Melo *et al.*[37], 2015; Tay *et al.*[38], 2015
Use of mowers	Synthetic devices containing multiple bulged miRNA binding sites and named them "miRNA-mowers"	"Mowing down" miRNA expression (just like a lawn mower)	Up-regulation of the expression of mRNAs regulated by the "mowed down" miRNAs	Liu *et al.*[39], 2012
MirNA masking	DNA, LNA, PNAs and analogues	Binding to mRNA and interference with the binding of miRNA to its target site	Up-regulation of the expression of "masked" mRNAs by inhibition of miRNA binding	Wang *et al.*[40], 2011; Bak *et al.*[41], 2013; Murakami *et al.*[42], 2014

PEPTIDE-NUCLEIC ACIDS

Peptide Nucleic Acids (PNAs) are DNA analogues described for the first time by Nielsen *et al.*[49], in which the sugar-phosphate backbone has been replaced by N-(2-aminoethyl)glycine units[50-53] [see Figure 2 for the chemical general structure]. PNAs are very interesting molecules for sequence-specific alteration of gene expression, since are capable of forming Watson-Crick double helices after efficient sequence-specific hybridization with complementary DNA and RNA[54]. Furthermore, they are able to generate triple helix with double-stranded DNA and to perform strand invasion[55]. In virtue of these biological activities, PNAs have

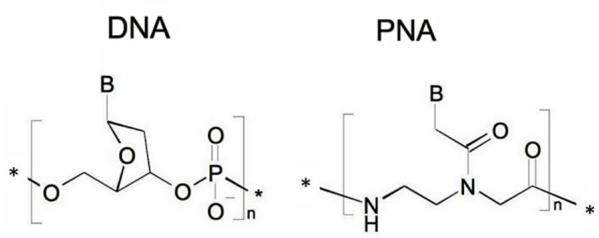

Figure 2. Scheme outlining the differences between DNA (left) and PNA (right) monomers

been demonstrated to be very efficient tools for pharmacologically-mediated alteration of gene expression, both *in vitro* and *in vivo*[56,57].

Summarizing, PNAs and PNA-based analogues were employed as antisense molecules targeting mRNAs, triple-helix forming molecules targeting eukaryotic gene promoters, artificial promoters, decoy molecules targeting transcription factors[54-56]. Relevant in the context of the present review article, PNAs have been demonstrated to be able of altering miRNA functions, both *in vitro* and *in vivo*[58-62]. This has been recently reviewed by Manicardi *et al*[63].

While well-controlled studies are needed to compare the *in vivo* activity of PNAs to those of LNA, RNA and other molecules exhibiting anti-sense potential, several *in vivo* studies on PNAs have been already reported to sustain the usefulness of these molecules and their derivatives.

Gupta *et al.*[64] tried to target miR-210 with an antisense γ-peptide nucleic acids (γPNAs), exhibiting superior RNA-binding affinity, improved solubility, and favorable biocompatibility. The rationale for this approach is that miR-210 is overexpressed in hypoxic cancer cells and is a key player for the adaptation of tumor cells to hypoxia. For cellular delivery, they encapsulated the γPNAs in poly(lactic-co-glycolic acid) (PLGA) nanoparticles. The results obtained show that γPNAs targeting miR-210 cause significant delay in growth of a human tumor xenograft in mice compared to conventional PNAs. Furthermore, histopathological analyses show considerable necrosis, fibrosis, and reduced cell proliferation in γPNA-treated tumors compared to controls[64]. In another paper, Cheng *et al.*[11] efficiently inhibited the function of oncomiRNA miR-155 in a tumor mouse model after the design and realization of a peptide-(anti-miRNA)PNA construct able to target the tumor microenvironment and to transport the anti-miRNA PNA across the cellular plasma membranes under the acidic conditions which characterize solid tumors. A final example is that published by Yan *et al.*[65], demonstrating that PNA-mediated targeting of miR-21 causes inhibition of growth and migration of breast cancer MCF-7 and MDA-MB-231 cells *in vitro*, and tumor growth *in vivo* when nude mice were employed.

GLIOBLASTOMA

Glioblastoma multiforme (GBM), a grade IV glioma, is a lethal malignant tumor accounting for 42% of the central nervous system tumors, the median survival being 12-15 months[66-71]. The current standard therapeutic management of GBM is based on neurosurgery followed by chemoradiotherapy by fractionated external-beam radiotherapy and systemic chemotherapeutic treatment with temozolomide (TMZ) and other agents, including repurposed drugs (such as metformin, disulfiram, rapamycin and derivatives, chloroquine, ionidamine)[71]. There are only very limited possibilities for the treatment of subsequent recurrences, generally with minimal clinical efficacy[69]. Among novel therapeutic strategies for GBM, of interest are inhibitors of aberrantly activated cell signaling pathways, including those regulated by growth factors and their receptors, such as epidermal growth factor family and their receptors[72], platelet-derived growth factors and their receptors[73]. In addition, innovative targets for GBM experimental therapy might

be insulin-like growth factors, fibroblast growth factor and their receptors[74,75]. Excellent review articles describing current therapeutic approaches and novel trends in GBM management are available[69,76-82].

In conclusion, since no curative treatment is available and the most used first-line drug, temozolomide (TMZ), is only able to cause an increase of the life expectancy[69], new drugs are urgently needed for the implementation of therapeutic protocols for anti-glioma treatments. Moreover, a high proportion of gliomas become with time TMZ-resistant. Therefore, a deep interest does exist for combined treatments on TMZ-resistant glioma cells in order to induce therapeutic relevant response, including, but not limited to, apoptosis[81,82].

MICRORNAS IN GLIOMAS: VARIABILITY AMONG THE PATIENTS HAMPERS THE IDENTIFICATION OF POSSIBLE THERAPEUTIC TARGETS FOR PERSONALIZED TREATMENTS

Several studies available from the recent literature clearly support the involvement of microRNAs in gliomas[83-93], outlining a large number of miRNAs demonstrated to be dysregulated in these tumors. Of course, these studies might indicate miRNA targets to be proposed for the development of protocols for therapeutic intervention in glioma, including strategies useful to tackle the issue of drug resistance[94-96]. Comprehensive analysis of microRNA expression profile in malignant glioma tissues has been reported by Piwecka *et al.*[97], Banelli *et al.*[98], Ciafrè *et al.*[99]. The analysis of microRNAs is also associated with tumor onset and progression. For instance a miRNA signature was found associated with glioblastoma tumor tissues. Up-regulated miRNAs were miR-221, miR-222, miR-22, miR-296-3p, miR-195, miR-155, miR-152, miR-132, miR-146b-5p, miR-149, miR-129-3p, miR-34a, miR-671-5p, miR-10a. Down-regulated miRNAs were let-7b, miR-767-5p, miR-505, miR-301b, miR-181a, miR-20a, miR-19a, miR-19b, miR-106a[97-99]. In any case, a large consensus does exist on the fact that tumor tissues are highly heterogeneous with respect to molecular and genetic features, supporting the concept that GBM represents a heterogeneous type of neoplasm when the microRNA patterns are considered[100,101].

However, due to global high-throughput profiling it is possible to select miRNAs that are at high risk of being deregulated in the majority of patients. Thus, there is a considerable hope for utilizing miRNAs as targets in prospects of glioma therapy. A partial list of validated miRNAs dysregulated in gliomas (with their proposed mRNA targets) is reported in Supplementary Table S1.

Among the possible microRNA targets involved in glioma, miR-155-5p appears to be of relevant interest for the following reasons: (1) miR-155-5p may play an important role in the transformation of normal neural stem cell toward glioma stem cells[102]; (2) the elevated expression level of miR-155-5p promotes the proliferation and invasion of glioblastoma cells through suppressing GABA receptors[103], FOXO3a[104] and MXI1[105]; (3) an oligonucleotide targeting miR-155-5p was shown to sensitize glioma cells to taxol-induced apoptotic death[106]; and (4) miR-155-5p overexpression is considered as a major molecular feature of glioblastoma, which can discriminate this malignancy from a similar intracranial tumor, oligodendroglioma[107]. Therefore, miR-155-5p alone or together with other miRNAs is a predictive biomarker for glioma prognosis[107,108]. On the other hand, glioma-targeting therapy based on miR-155-5p anti-oligonucleotides is believed to be efficient to inhibit the progression of glioma[109].

However, several recent studies have pointed out that the translation of the analysis of the expression and content of miR-155-5p and other miRNAs in gliomas into therapeutic strategy is hampered by the high variability of microRNAs among patients[92,100,101]. For instance, in analyzing 31 tumor specimens against paired normal tissue, Yan *et al.*[92] found a significant upregulation of miR-155 in tumor tissues. This study was based on the analysis of surgically dissected glioma specimens and their surrounding brain tissues. In spite of the increased miR-155 expression, a large proportion of tumor samples exhibited a nearly normal

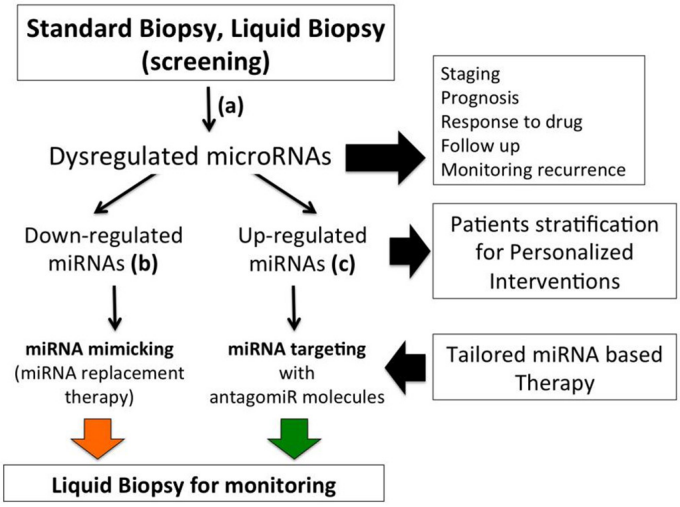

Figure 3. Scheme outlining the strategy to identify dysregulated microRNAs (a) in tumor patients and design possible therapeutic approaches based on anti-miRNA therapy and miRNA-replacement. The activity of down-regulated miRNA might be replaced with the use of miRNA mimicking molecules (b); the activity of up-regulated miRNAs might be counteracted with antagomiRNA molecules (c). A partial list of dysregulated miRNAs in gliomas is depicted in Supplementary Table S1

level of miR-155, supporting the concept that characterization of the GBM patients is required before the activation of a miRNA-155 targeting approach. Therefore, the analysis of the miRNA pattern appears to be a required step in the road of personalized therapy on precision medicine based on miRNA therapeutics.

Figure 3 indicates an overall strategy for determining miRNA targets in cancer patients, on the road of personalized therapy in precision oncology. The first step (step "a") is the characterization of the miRNA profile in tumor tissues, performed with either surgery-based biopsy or liquid biopsy. The characterization of dysregulated miRNAs (down-regulated, "b" and up-regulated, "c") will be helpful for staging, prognosis of the neoplasia as well as for determining the response of the patients to drugs. In addition, the analysis of dysregulated miRNAs might allow stratifying patients with respect to expression of specific miRNAs, with the final objective to propose a therapeutic intervention (either based on anti-miRNA or miRNA-replacement approach, as outlined in Figure 1). Liquid biopsy will be the best choice to monitor the outcome of this tailored therapeutic approach[110].

PEPTIDE NUCLEIC ACID-MEDIATED TARGETING OF MICRORNAS IN GBM CELL LINES

The studies focusing on the possible use of PNAs targeting microRNAs are few. The first report was published by Brognara *et al.*[62], who found that a PNA targeting miR-221 (R8-PNA-a221), bearing an oligoarginine peptide (R8) enabling efficient uptake by glioma cells[58,59,62], strongly inhibited miR-221-3p in U251, U373 and T98G glioma cells. This inhibition of miR-221-3p activity was associated with increased expression of the miR-221 target p27Kip1, analyzed by RT-qPCR and by Western blotting[62,66]. In a second study, Bertucci *et al.*[111] reported the efficient combined delivery of temozolomide and the same anti-miR221 PNA using mesoporous silica nanoparticles[111]. More recently, high levels of apoptosis on glioma cell lines were obtained following co-treatment with two PNAs, one targeting miR-221-3p, the other targeting miR-222-3p. In addition, Seo *et al.*[113] showed the use of a PNA targeting miR-21 as *in vivo* inhibitor of glioma U87 cells.

A further example is a PNA against miR-155-5p. The possibility of obtaining clinically-relevant effects following targeting miR-155-5p with PNA-based molecules is shown in Figure 4 and elsewhere reported in the study by Milani *et al.*[109], describing the synthesis and validation of a PNA targeting miR-155-5p on the temozolomide-resistant T98G glioma cell line[66].

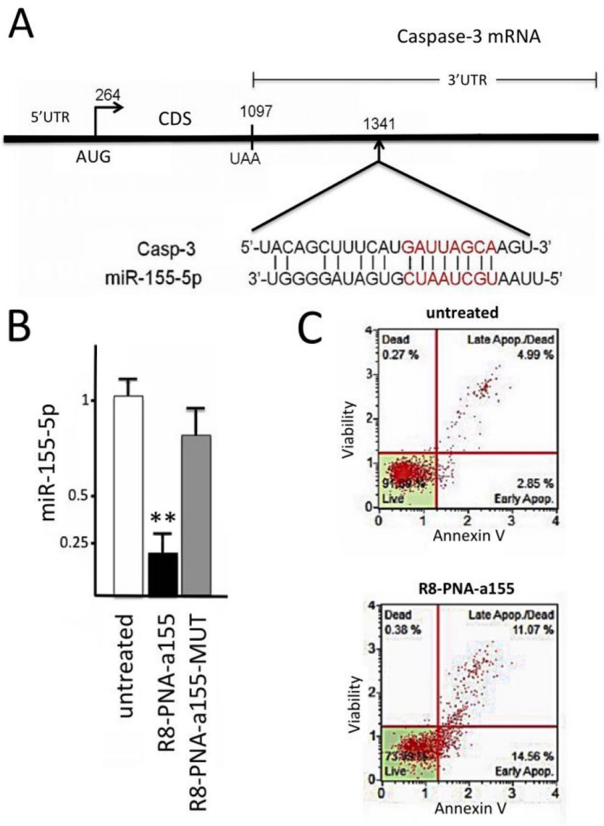

Figure 4. A. Location of a miR-155-5p binding site within the 3'UTR sequence of Caspase-3 mRNA. B. Effects of cell treatment with 4 μM R8-PNA-a155 and R8-PNA-a155-MUT for 48 h on the miR-155-5p hybridization signal. C. Increase of T98G apoptotic cells after treatment for 48 h with 4 μM R8-PNA-a155. Modified from Milani *et al.*[109]

For efficient delivery, the PNA was conjugated with an octoarginine tail (R8-PNA-a155). Apoptosis was analyzed, and the effect of this PNA was associated with a reversion of drug-resistance phenotype. The specificity of the PNA effects at the cellular level was analyzed by RT-qPCR [see Figure 4B], suggesting that the effects of R8-PNA-a155 are specific. The studies on apoptosis [Figure 4C] confirmed that the R8-PNA-a155 demonstrated the pro-apoptotic effects, inducing apoptosis of TMZ-treated T98G cells.

FINAL REMARKS ON MIRNA THERAPEUTICS BASED ON PNA MOLECULES: FROM THE PAST TO FUTURE THERAPEUTIC APPLICATIONS

The data available on the recent literature support the concept that the anti-miRNA strategy [see Figure 1] could lead to therapeutic relevant inhibition of miRNA dependent effects and that PNA-based anti-miRNA molecules are very promising reagents to regulate tumor cell growth. Further research on PNA analogues to increase efficiency of delivery, stability and control of intracellular distribution for specific targets, i.e., mature miRNA, pre-miRNA or pri-miRNA, are further steps for the selection of best candidate drugs. Finally, the studies on miRNA targeting strongly indicate that multiple miRNA targeting, might lead to significant improvement in the efficacy of the treatment. This last conclusion supports also the concept of designing multifunctional PNA-containing systems enabling to perform targeting of different mRNA sequences.

Considering PNAs as anti-miRNA reagents, it should be underlined that one of the most important challenges in PNAs technology is their delivery to cells[114,115], in particular their low uptake by eukaryotic cells. In order to solve this drawback, several approaches have been considered. One of the several approaches

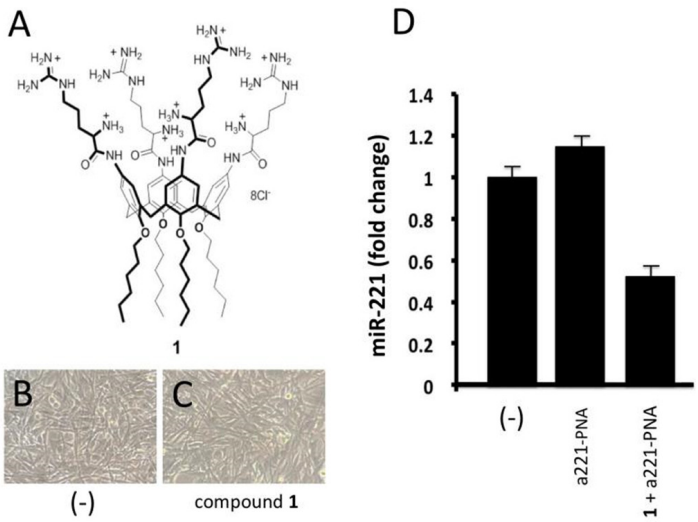

Figure 5. A: Structure of the macrocyclic multivalent tetraargininocalix[4]arene **1** used as non-covalent vector for anti-miRNA PNAs; B,C: Effects of compound **1** on morphology of U251 glioma cells: lack of cytotoxic effects. D. Effects of free PNA (a221-PNA) and a221-PNA delivered with compound **1** on miR-221-3p in treated U251 cells. Inhibition of miR-221-3p expression is obtained only when a221-PNA is vehiculated by compound **1**. Modified from Gasparello *et al.*[125]

undertaken to solve this issue is the conjugation with carrier peptides[116-118], in particular those sensitive to microenvironment changes[11]; anti-miRNA activity was indeed observed for instance by conjugation of PNAs to polyarginine (poly-R) tails[58,59,62] or by modification of the PNA backbone with cationic amino acid side chains[58,119]. An alternative strategy to chemical modification of PNAs is the use of carriers able to perform non-covalent and reversible interactions with the PNA structure.

In this context, it was actually already explored the delivery of PNAs and PNA derivatives or analogues with liposomes[120], polymer nanoparticles[121] and pseudovirions[122], and by co-transfection with partially complementary DNA[123]. Inorganic nanocarriers, such as nanozeolites[124] or mesoporous silica nanoparticles[111] have been also used for cellular delivery of PNAs, maintain their biological functions. Recently, we have reported results relative to the delivery ability of a macrocyclic multivalent tetraargininocalix[4]arene "**1**" [Figure 5].

In conclusion, several studies demonstrate that efficiently delivered PNAs might be of great interest in the inhibition of miRNA activity. This open new and still unexplored avenues to non-viral gene therapy, especially when PNA-based strategies to target multiple miRNA sequences will be available[126]. In consideration of the high patient-to-patient variability of the miRNome, multiple miRNA targeting should be considered a key feature in the road of personalized therapy in precision medicine.

As far as delivered PNAs *in vivo* to experimental models of GBM, local delivery of nanoparticles should be considered a promising therapeutic strategy that bypasses the blood-brain barrier, minimizes systemic toxicity, and enhances intracranial drug distribution and retention. In this respect, Seo *et al.*[113] developed nanoparticles loaded with PNAs inhibiting miR-21, a microRNA overexpressed in GBM and retaining oncogenic features. These authors employed a block copolymer of poly(lactic acid) and hyperbranched polyglycerol to deliver an anti-miR-21 PNA, showing that efficient intracellular delivery was facilitated, leading to miR-21 suppression and PTEN upregulation and apoptosis of human GBM cells. This anti-miR-21 PNA was also administered by convection-enhanced delivery to animals with intracranial gliomas, inducing significant miR-21 knockdown and chemosensitization, resulting in improved survival when combined with chemotherapy[113]. This study demonstrates the feasibility and promise of local administration

of nanoparticles carrying an anti-miR-21 PNAs for the development of protocols for adjuvant therapy for GBM. Interestingly, the delivered PNAs were found to cause long-term survival in treated mice at a level much higher with respect to antisense RNAs.

DECLARATIONS

Authors' contributions

Revised and approved the final manuscript: Gambari R, Gasparello J, Finotti A

Wrote the manuscript, performed the literature search, and critically analyzed the existing literature: Gambari R, Gasparello J, Finotti A

Designed the figures and created the tables: Gambari R, Finotti A

Availability of data and materials

Not Applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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