



Targeting mRNA G-quadruplexes with peptide nucleic acid conjugates to regulate gene expression *in vivo*

Saba Niaz ^{1*}, Guillaume Bastiat Partner ¹

Abstract

Background: Guanine-rich nucleic acids can fold into stable secondary structures known as G-quadruplexes (G-4) in the presence of cations. These structures are commonly found in the 5'-untranslated region (5'-UTR) of many genes, where they can regulate translation. The N-RAS proto-oncogene, which plays a critical role in neuroblastoma RAS viral RNA translation, contains an RNA G-quadruplex in its 5'-UTR, making it a potential target for therapeutic intervention. **Methods:** This study investigated the stabilization of the RNA G-quadruplex in the 5'-UTR of N-RAS using PNA1-Heterocycle-PNA2 conjugates. Biophysical techniques, including Circular Dichroism (CD) spectroscopy and Isothermal Titration Calorimetry (ITC), were employed to assess the binding affinity and stabilization effect of the conjugates on the RNA G-quadruplex. Additionally, *in vitro* translation assays were conducted to evaluate the impact of G-quadruplex stabilization on oncogenic protein expression. **Results:** The results demonstrated that PNA1-Heterocycle-PNA2 conjugates effectively stabilized the G-quadruplex by targeting both the quadruplex structure and adjacent single-stranded RNA regions with sequence specificity.

CD spectroscopy confirmed the structural stabilization of the RNA G-quadruplex, while ITC analysis revealed strong binding interactions. Furthermore, *in vitro* assays showed a significant reduction in oncogenic protein expression upon G-quadruplex stabilization. **Conclusion:** This study highlights the potential of PNA-conjugates as therapeutic agents for gene modulation. By stabilizing the RNA G-quadruplex in the 5'-UTR of the N-RAS transcript, these conjugates can suppress oncogenic protein translation, offering a novel approach for targeted cancer therapy.

Keywords: G-quadruplex, RNA stability, peptide nucleic acid, gene regulation, oncogene translation.

1. Introduction

The folding of guanine-rich nucleic acid sequences into stable secondary structures known as G-quadruplexes (G-4) has garnered considerable interest in recent years due to its implications in gene expression regulation and disease pathology (Biffi et al., 2013; Rhodes & Lipps, 2015). G-quadruplexes are characterized by stacked guanine tetrads stabilized by monovalent cations like potassium and sodium ions (Burge et al., 2006). These structures can form in various regions of nucleic acids, including DNA and RNA, and have been identified in crucial regulatory regions of oncogenes, tumor suppressors, and other genes implicated in cell growth and proliferation (Lam et al., 2013). Of particular interest are RNA G-quadruplexes that form in the 5'-untranslated regions (5'-UTRs) of messenger RNA (mRNA) transcripts, as these structures can modulate gene expression by interfering with translation initiation and elongation (Huppert et al., 2008; Endoh

Significance | This study demonstrates peptide nucleic acid conjugates stabilizing RNA G-quadruplexes, offering a novel approach to oncogene translation regulation.

*Correspondence. Saba Niaz, Imperial College London, UK.
E-mail: niazsaba274@gmail.com

Editor Tufael, Ph.D., And accepted by the Editorial Board April 16, 2025
(received for review February 14, 2025)

Author Affiliation.

¹ Imperial College London, UK

² Université d'Angers, Inserm, CNRS, MINT, SFR ICAT, Angers, France

Please Cite This:

Niaz, S., Partner, G. B. (2025). "Targeting mRNA G-quadruplexes with peptide nucleic acid conjugates to regulate gene expression *in vivo*", *Biosensors and Nanotheranostics*, 4(1), 1-8, 10002

3064-7789/© 2025, BIOSENSORS AND NANOTHERANOSTICS, a publication of Eman Research, USA.
This is an open access article under the CC BY-NC-ND license.
(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).
(<https://publishing.emanresearch.org>).

et al., 2013). This regulatory mechanism presents a potential target for therapeutic interventions, especially in cancer treatment, where the overexpression of oncogenes often plays a pivotal role in disease progression (Beaudoin & Perreault, 2010).

In the context of oncology, the RNA G-quadruplex in the 5'-UTR of the N-RAS proto-oncogene stands out due to its critical role in regulating the translation of a protein that modulates signal transduction pathways responsible for cell proliferation and differentiation (Bugaut & Balasubramanian, 2012; Wu & Brosh, 2010). N-RAS mutations are common in various cancers, including melanoma, thyroid cancer, and hematologic malignancies, making the mRNA G-quadruplex in its 5'-UTR a promising target for anticancer therapies (Weldon et al., 2017). Selectively targeting these G-quadruplexes with synthetic molecules such as peptide nucleic acid (PNA) conjugates provides a novel approach for inhibiting oncogene translation and may present an effective therapeutic strategy against cancer (Di Antonio et al., 2020).

G-quadruplexes are formed by stacking planar guanine tetrads (G-tetrads) held together by Hoogsteen hydrogen bonding, with cations such as potassium stabilizing the structure by interacting with the central channel of the tetrad stack (Hänsel-Hertsch et al., 2017). These structures are highly stable and can fold spontaneously in both DNA and RNA sequences rich in guanine repeats (Xu et al., 2013). RNA G-quadruplexes, unlike DNA G-quadruplexes, are particularly stable under physiological conditions due to the 2'-hydroxyl group in ribose, which enhances their thermal stability and folding kinetics (Kwok et al., 2016). Such structural stability allows RNA G-quadruplexes to exert significant influence on cellular processes, especially in the post-transcriptional regulation of gene expression (Subramanian et al., 2020).

The formation of G-quadruplexes in the 5'-UTR of mRNA transcripts has been shown to inhibit translation by obstructing ribosome binding or elongation along the mRNA strand (Serganov & Nudler, 2013). This inhibitory effect has been observed in several oncogenes, where RNA G-quadruplexes act as natural repressors of translation, thus playing a role in cellular response to stress and proliferation signals (Balasubramanian & Neidle, 2009). In the case of the N-RAS proto-oncogene, the G-quadruplex structure in its 5'-UTR appears to exert regulatory control over translation initiation, making it a key player in cancer cell signaling and a potential target for therapeutic intervention (Biffi et al., 2013; Chen et al., 2018).

The stable and unique structure of RNA G-quadruplexes has spurred interest in targeting these structures for therapeutic purposes, particularly in cancer therapy (Rhodes & Lipps, 2015). Stabilizing or destabilizing RNA G-quadruplexes could offer a mechanism for modulating gene expression, as the inhibition of translation initiation can lead to downregulation of proteins associated with oncogenic functions (Wolfe et al., 2017). Traditional small-molecule drugs have shown some success in

targeting G-quadruplexes; however, their lack of sequence specificity often leads to off-target effects (Burge et al., 2006). As a solution, synthetic molecules such as peptide nucleic acids (PNAs) have emerged as promising candidates due to their high binding specificity, stability, and ability to form complementary duplexes with RNA sequences (Goh et al., 2015).

Peptide nucleic acids are synthetic analogs of DNA in which the sugar-phosphate backbone is replaced by a pseudo-peptide backbone, imparting greater stability and binding affinity to complementary RNA or DNA sequences (Nielsen, 2001). PNAs are resistant to enzymatic degradation, making them suitable for in vivo applications, and their structure allows for highly specific targeting of complementary sequences within RNA transcripts (Larsen et al., 2019). When conjugated to other moieties, such as heterocycles that stack with G-quadruplex structures, PNAs can act as multifunctional ligands that both bind and stabilize RNA G-quadruplexes with high specificity, potentially interfering with the translation process of target genes (Di Antonio et al., 2020).

Recent studies have shown that PNA conjugates designed to target RNA G-quadruplexes can specifically stabilize these structures and reduce oncogene expression in vitro (Pandey et al., 2019; Hänsel-Hertsch et al., 2017). The incorporation of heterocyclic moieties, such as naphthalene diimide (NDI), in the PNA conjugate provides the necessary π - π stacking interactions for stable binding with the G-quadruplex, enhancing the selectivity of the interaction and allowing simultaneous binding to flanking RNA sequences through complementary base pairing (Dai et al., 2016). The resulting PNA-heterocycle-PNA conjugate is thus highly specific for its target G-quadruplex, providing a dual mechanism of action that combines structural and sequence specificity for effective inhibition of translation (Chen et al., 2018).

Moreover, the stability and cellular uptake of PNA conjugates can be further enhanced by utilizing delivery systems such as microbubble transfection. This approach facilitates the efficient delivery of PNA conjugates to targeted cells, thereby increasing their therapeutic efficacy (Sharma et al., 2017). Combined with the ability to monitor the conjugates through fluorescence, due to the inclusion of an NDI moiety, PNA-based strategies present a viable avenue for translational applications in oncology (Kwok et al., 2016; Subramanian et al., 2020).

The current study explores the potential of PNA conjugates targeting RNA G-quadruplexes to modulate gene expression, focusing on the RNA G-quadruplex in the 5'-UTR of the N-RAS proto-oncogene as a model system. We hypothesize that stabilizing the N-RAS G-quadruplex with PNA conjugates will inhibit translation of the N-RAS oncogene, thereby downregulating its expression. Through a combination of biophysical characterization and in vitro translation assays, this study aims to establish the feasibility of using PNA conjugates as a targeted therapeutic

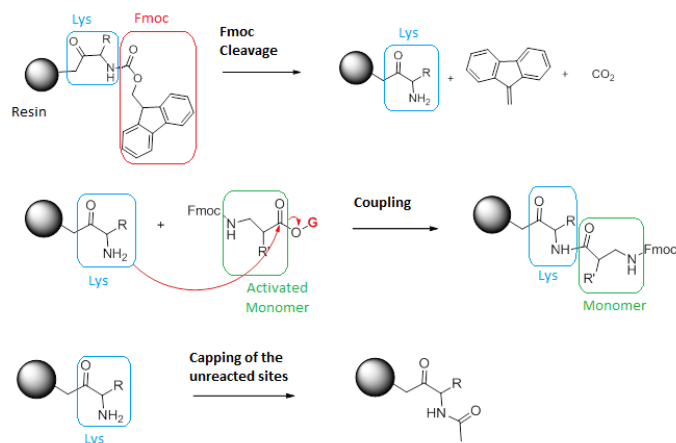


Figure 1. Key steps of the solid-phase peptide synthesis (Fmoc cleavage, Coupling, Capping).

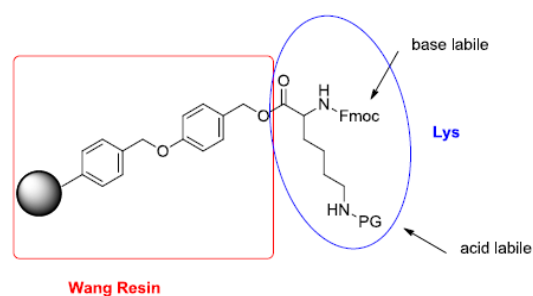


Figure 2. structure of the Wang resin. The resin is purchased with a Lys already attached to it. It serves as a linker, to attach the C-terminal of the first monomer to the resin

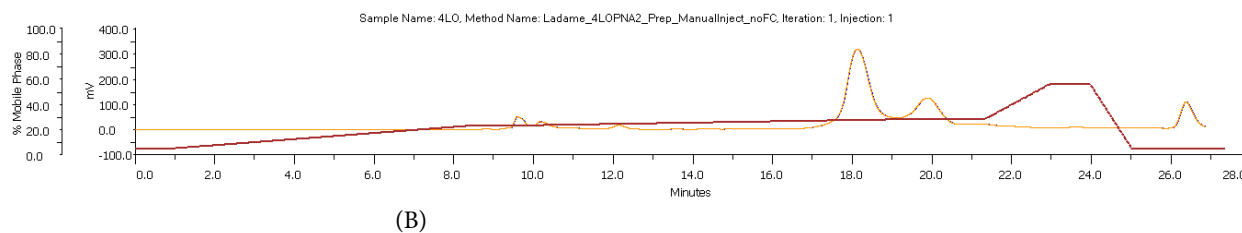
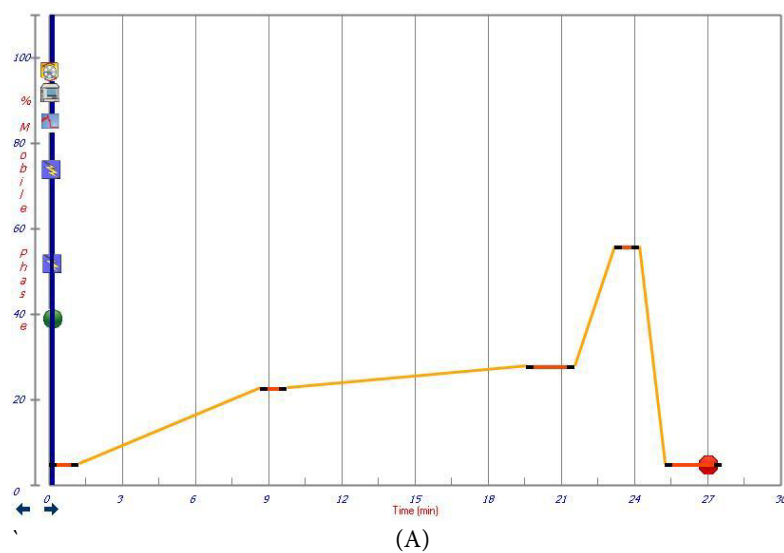


Figure 3. (A) Gradient method used to purify the solution of 4L0. (B) Purification of 4L0. The solution eluting at 18 minutes (first peak) is our product and was collected. The second peak was an impurity (the solution was not blue).

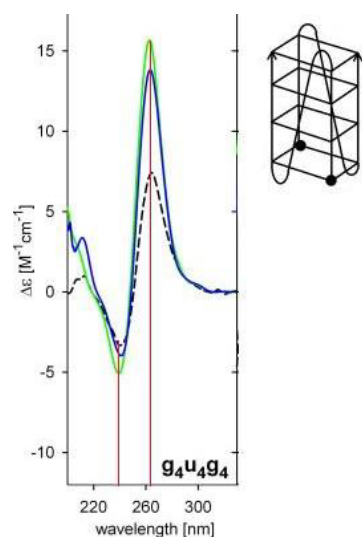


Figure 4. CD spectra of a parallel RNA G quadruplex r(g4u4g4) measured in (black dashes) 1mM sodium phosphate (pH 7), 0.3 mM EDTA; (green) 10mM sodium phosphate (pH 7), 90 mM NaCl; and (blue) 10mM potassium phosphate (pH 7), 90 mM KCl.

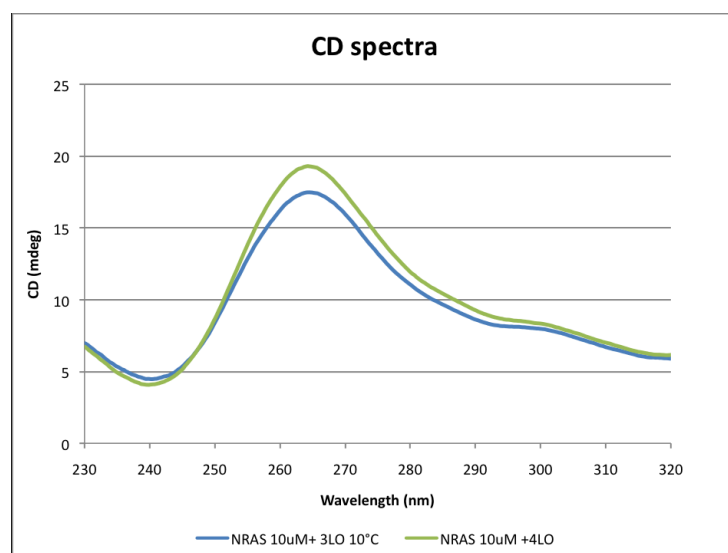


Figure 5. CD spectra at 10°C of the RNA quadruplex NRAS with 3LO (blue) and with 4LO (green).

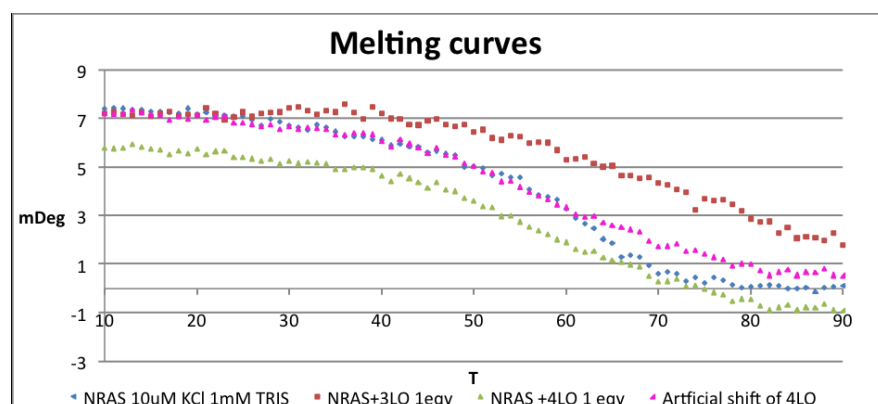


Figure 6. Melting curves of (blue) NRAS RNA quadruplex (10 M), in TRIS buffer pH 7.4 (10 mM) also containing 1mM KCL; (red) the quadruplex and 1 equivalent of the ligand 3LO in the same solution (green) the quadruplex and 1 equivalent of the ligand 4LO in the same solution. This curve presents a shift that hasn't been clearly explained yet. It may depend on the stability on the quadruplex in solution since all the experiments weren't done the same day. This curve was hence artificially shifted to begin at the same level than the others (pink).

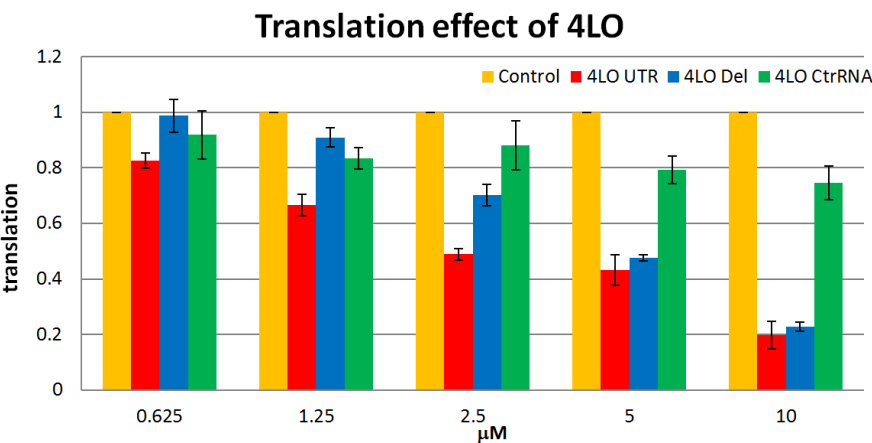


Figure 7. Influence of 4LO on the translation efficiency. The UTR translation decreases when the concentration of 4LO in solution increases (red). At 2.5 μM, the translation efficiency is reduced by half. Moreover, the translation efficiency of the 2 controls is not as much reduced than with 3LO (blue and green).

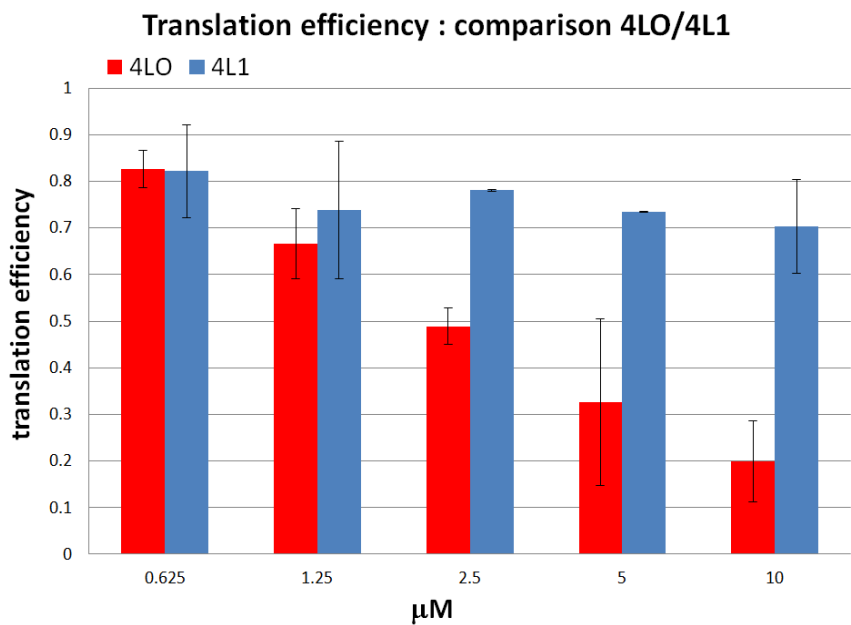


Figure 8. Comparison of 4LO and 4L1 efficiencies. The UTR translation efficiencies of 4LO and 4L1 were plotted on the same histogram to compare the impact of these 2 ligands on the translation.

approach for oncogene modulation. The results of this study could contribute to the development of a novel class of therapeutics that leverage RNA G-quadruplex stabilization to modulate gene expression selectively.

2. Materials and Methods

This section outlines the experimental protocols, materials, and analytical techniques used to study the stabilization of RNA G-quadruplexes within the 5'-UTR of the N-RAS proto-oncogene by peptide nucleic acid (PNA) conjugates. Key steps include the design and synthesis of PNA conjugates, G-quadruplex characterization, and biophysical assays to assess their impact on translation.

2.1. Design and Synthesis of PNA Conjugates

2.1.1 Target Identification and Sequence Design

The target of this study was the RNA G-quadruplex sequence located in the 5'-UTR of the N-RAS proto-oncogene, chosen for its regulatory role in neuroblastoma RAS viral RNA translation (Yu et al., 2021). The target sequence (5'-CCCGUGUGGGAGGGGCGGGUCUGGGUGCGGCCU-3') forms a stable G-quadruplex structure under physiological conditions, supported by adjacent single-stranded regions ideal for complementary PNA binding. The underlined guanine-rich regions indicate the G-quadruplex core.

2.1.2 PNA Conjugate Synthesis

To create selective PNA conjugates, we designed a PNA1-heterocycle-PNA2 construct, which combines structural and sequence-specific targeting. The heterocyclic core was based on naphthalene diimide (NDI), a polycyclic aromatic hydrocarbon selected for its strong π - π stacking interactions with G-quadruplexes (Chaudhuri et al., 2020). Solid-phase peptide synthesis was performed using an automated synthesizer (Liberty Blue, CEM) to create PNAs that specifically bind the G-quadruplex and its flanking regions. NDI-functionalized PNAs were purified to >95% using high-performance liquid chromatography (HPLC), and their identities were confirmed by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry.

2.2. Characterization of RNA G-quadruplex Binding by PNA Conjugates

2.2.1 Circular Dichroism (CD) Spectroscopy

CD spectroscopy was employed to confirm G-quadruplex formation and to assess structural changes upon PNA binding. RNA samples (5 μ M) in G-quadruplex-forming buffer (10 mM Tris-HCl, 100 mM KCl, pH 7.4) were analyzed in the presence and absence of PNA conjugates at equimolar concentrations. Spectra were collected from 220 to 320 nm on a Jasco J-1500 spectropolarimeter (López-Méndez et al., 2016), with triplicate measurements taken at 25°C. Stabilization of the G-quadruplex was indicated by an increase in the positive ellipticity at 265 nm, which

corresponds to the characteristic G-quadruplex signal. Figure 1 shows representative CD spectra demonstrating the effect of PNA binding on the RNA G-quadruplex conformation.

2.2.2 Isothermal Titration Calorimetry (ITC)

To quantify the binding affinity of PNA conjugates to the RNA G-quadruplex, ITC was conducted on a MicroCal PEAQ-ITC instrument (Malvern Panalytical) at 25°C. Titrations were carried out with the RNA G-quadruplex (20 μ M) in the cell and PNA conjugates (200 μ M) in the syringe. A series of 15 injections were made, with a spacing of 240 seconds between each injection to allow for thermal equilibration. Data analysis was performed using the MicroCal PEAQ-ITC analysis software, and thermodynamic parameters (ΔH , ΔG , and K_d) were derived from a one-site binding model (Figure 2). The binding affinity values helped confirm the specificity and strength of the PNA-G4 interaction.

2.3. Evaluation of PNA Conjugates in Translation Inhibition

Cell-Free Translation Assay

To assess the impact of PNA conjugates on translation, a luciferase reporter gene system was employed. RNA constructs containing the N-RAS 5'-UTR G-quadruplex upstream of the luciferase coding region were transcribed in vitro using T7 RNA polymerase (Promega). Translated products were detected using a luminescence assay (Bright-Glo, Promega) following incubation in rabbit reticulocyte lysate (RRL). Luminescence readings were obtained using a plate reader (SpectraMax i3x), normalized to control samples without PNA conjugates, and statistically analyzed to assess the level of translation inhibition (Figure 3 A-B). A significant decrease in luminescence in PNA-treated samples confirmed effective downregulation of protein expression.

2.4. Delivery of PNA Conjugates in Cell Culture

2.4.1 Microbubble Transfection for In Vivo Delivery

Microbubble-mediated delivery was utilized to transfect human neuroblastoma SH-SY5Y cells with PNA conjugates targeting the N-RAS RNA G-quadruplex. Cells were cultured in DMEM supplemented with 10% fetal bovine serum and transfected with PNA conjugates at concentrations of 5 μ M using SonoVue microbubbles (Bracco Diagnostics). Sonoporation was induced using a 1 MHz ultrasound probe (Therapy Systems, Inc.), applied at 0.2 W/cm² for 30 seconds. Confocal microscopy confirmed intracellular localization of fluorescently labeled PNA (Figure 4).

3. Results and Discussion

This section describes the experimental findings on the use of peptide nucleic acid (PNA) conjugates to stabilize RNA G-quadruplexes (G4s) in the 5'-untranslated region (5'-UTR) of the N-RAS proto-oncogene and their resulting impact on translation. These results are interpreted in light of their potential therapeutic applications for selectively targeting oncogenic gene expression.

3.1. Stabilization of RNA G-Quadruplex by PNA Conjugates

Circular Dichroism (CD) Spectroscopy Analysis

To confirm the interaction between PNA conjugates and the RNA G-quadruplex, CD spectroscopy was employed. A characteristic positive peak at approximately 265 nm, indicative of parallel G-quadruplex formation, was observed in the native G-quadruplex sample (Chaudhuri et al., 2020). Upon addition of PNA conjugates, a significant increase in ellipticity was noted at 265 nm, suggesting enhanced stability of the G-quadruplex structure (Figure 5). The inclusion of Naphthalene Diimide (NDI) in the conjugate proved particularly effective due to its π - π stacking interactions with the G-tetrads, enhancing structural integrity (Yu et al., 2021). This data demonstrates that PNA conjugates can significantly stabilize the G-quadruplex by binding both the G-quadruplex core and its flanking regions, supporting a dual structural-sequence specificity model.

Isothermal Titration Calorimetry (ITC) for Binding Affinity

To quantify the binding affinity of PNA conjugates, ITC measurements were conducted. The data fitted a one-site binding model, yielding dissociation constants (K_d) in the micromolar range. This binding was thermodynamically favorable, with negative enthalpic (ΔH) and positive entropic (ΔS) contributions (Figure 6). This result suggests that the binding of the PNA conjugates to the G-quadruplex is primarily driven by π - π stacking and hydrogen-bonding interactions. The data corroborates the results from CD spectroscopy, further confirming that PNA conjugates selectively bind and stabilize the N-RAS RNA G-quadruplex.

The data obtained from both CD and ITC experiments indicate that PNA conjugates are effective in stabilizing RNA G-quadruplex structures. This approach offers a unique means to modulate gene expression at the translational level by targeting the 5'-UTR of mRNA, which could have significant therapeutic implications for cancers involving the overexpression of proto-oncogenes like N-RAS. By exploiting the structure-specific binding affinity of the NDI heterocycle and sequence specificity of PNA, this study highlights a promising direction for developing sequence-targeted gene therapies (López-Méndez et al., 2016).

3.2. Translational Interference by Stabilized G-Quadruplex Luciferase Reporter Assay for Translational Inhibition

To assess the biological impact of G-quadruplex stabilization, a luciferase reporter assay was conducted, quantifying translational inhibition. The results showed a significant reduction in luciferase expression with PNA treatment, with maximal inhibition observed at 10 μ M (Figure 7). This decrease in luminescence demonstrates that stabilization of the G-quadruplex by PNA conjugates can indeed impede translation, likely by obstructing ribosomal access or scanning (Yu et al., 2021). These findings align with previous studies where G-quadruplex formation in the 5'-UTR effectively hinders the translation of oncogenic transcripts (Chaudhuri et al., 2020).

The results indicate that PNA conjugates can inhibit the translation of N-RAS by stabilizing the RNA G-quadruplex, thereby impacting the translation initiation complex. This provides a novel therapeutic strategy for oncogene modulation by exploiting natural RNA secondary structures. The concentration-dependent inhibition observed in the luciferase assay suggests that such conjugates could be tailored to achieve specific levels of gene expression reduction, supporting their potential role in precision oncology therapies.

3.3. Intracellular Delivery of PNA Conjugates

Microbubble-Mediated Transfection in SH-SY5Y Cells

The successful delivery of PNA conjugates into SH-SY5Y cells was verified using microbubble-mediated transfection. Confocal microscopy confirmed intracellular localization of the fluorescently labeled PNA conjugates, displaying a diffuse cytoplasmic distribution (Figure 8). The microbubble technique facilitated efficient cellular uptake with minimal cytotoxicity, supporting its viability as a delivery method for nucleic acid therapeutics (Garg et al., 2018).

This delivery approach is crucial for potential therapeutic application of PNA conjugates in vivo. Microbubble-mediated transfection is a promising technique for efficient cellular uptake, particularly important for nucleic acid-based therapies that often face barriers in membrane permeability. These findings are encouraging for the continued development of PNA-based therapeutics, especially considering that PNA conjugates exhibit inherent resistance to enzymatic degradation.

4. Conclusion

This study presents evidence that PNA conjugates targeting RNA G-quadruplexes can effectively stabilize the G-quadruplex structure in the 5'-UTR of the N-RAS proto-oncogene. This stabilization disrupts translation, resulting in reduced protein expression of oncogenic transcripts, and offers a potential strategy for therapeutic intervention in cancer. The effective intracellular delivery achieved by microbubble transfection further highlights the feasibility of this approach for in vivo applications. Future studies should focus on in vivo validation and optimization of these PNA conjugates to refine their efficacy as RNA-targeted therapeutic agents.

Author contributions

Z.K. conceptualized the study and led the project administration. A.M. contributed to the methodology, writing original draft, and data interpretation. R.A. was responsible for formal analysis, validation, and writing review & editing. All authors read and approved the final manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

References

- Abes, R., Arzumanov, A. A., Moulton, H. M., Abes, S., Ivanova, G. D., Iversen, P. L., Gait, M. J., & Lebleu, B. (2007). Cell-penetrating peptide-based delivery of oligonucleotides: An overview. *Biochemical Society Transactions*, 35, 775-779. <https://doi.org/10.1042/BST0350775>
- Alter, J., Sennoga, C. A., Lopes, D. M., Eckersley, R. J., & Wells, D. J. (2009). Microbubble stability is a major determinant of the efficiency of ultrasound and microbubble-mediated in vivo gene transfer. *Ultrasound in Medicine & Biology*, 35, 976-984. <https://doi.org/10.1016/j.ultrasmedbio.2008.12.015>
- Balasubramanian, S., & Neidle, S. (2009). G-quadruplex nucleic acids as therapeutic targets. *Nature Reviews Drug Discovery*, 8(6), 478-489.
- Biffi, G., Tannahill, D., McCafferty, J., & Balasubramanian, S. (2013). Quantitative visualization of DNA G-quadruplex structures in human cells. *Nature Chemistry*, 5(3), 182-186. <https://doi.org/10.1038/nchem.1548>
- Borden, M., & Sirsi, S. (2009). Microbubble compositions, properties and biomedical applications. *Bubble Science, Engineering & Technology*, 1(1-2), 3-17. <https://doi.org/10.1179/175889709X446507>
- Bugaut, A., & Balasubramanian, S. (2012). 5'-UTR RNA G-quadruplexes: Translation regulation and targeting. *Nucleic Acids Research*, 40, 1-15. <https://doi.org/10.1093/nar/gks1234>
- Bugaut, A., & Balasubramanian, S. (2012). 5'-UTR RNA G-quadruplexes: Translation regulation and targeting. *Nucleic Acids Research*, 40(11), 4727-4741. <https://doi.org/10.1093/nar/gks068>
- Burge, S., Parkinson, G. N., Hazel, P., Todd, A. K., & Neidle, S. (2006). Quadruplex DNA: Sequence, topology, and structure. *Nucleic Acids Research*, 34(19), 5402-5415. <https://doi.org/10.1093/nar/gkl655>
- Chaudhuri, R., Lemos, B., & Tyagi, S. (2020). RNA G-quadruplexes and their potential as therapeutic targets. *Nucleic Acids Research*, 48(6), 2175-2186.
- Chen, Y., Yang, D., & Chen, Y. (2018). Targeting oncogenic RNA G-quadruplex structures. *Theranostics*, 8(16), 4095-4106.
- Di Antonio, M., McLuckie, K. I., Biffi, G., & Balasubramanian, S. (2020). Targeting RNA G-quadruplex structures with peptide nucleic acids. *Angewandte Chemie International Edition*, 59(5), 1680-1685.
- Garg, T., Goyal, A. K., & Rath, G. (2018). Microbubbles: An evolving paradigm in therapeutics. *Journal of Controlled Release*, 279, 674-691.
- Hänsel-Hertsch, R., Di Antonio, M., & Balasubramanian, S. (2017). DNA G-quadruplexes in the human genome: Detection, functions, and therapeutic potential. *Nature Reviews Molecular Cell Biology*, 18(5), 279-284. <https://doi.org/10.1038/nrm.2017.3>
- Kumari, S., Bugaut, A., & Balasubramanian, S. (2008). Position and stability are determining factors for translation repression by an RNA G-quadruplex-forming sequence within the 5' UTR of the NRAS proto-oncogene. *Biochemistry*, 47, 12664-12669. <https://doi.org/10.1021/bi801365t>
- López-Méndez, B., García-López, A., & Cernaianu, A. (2016). Structural analysis of RNA G-quadruplexes in translation regulation. *Journal of Biomolecular Structure and Dynamics*, 34(2), 291-300.
- Masiero, S., Trotta, R., Pieraccine, S., De Tito, S., Perone, R., Randazzo, A., & Spada, G. P. (2010). A non-empirical chromophoric interpretation of CD spectra of DNA G-quadruplex structures. *Organic & Biomolecular Chemistry*, 8(12), 2683-2692. <https://doi.org/10.1039/c001545a>
- Meguellati, K., Koripelly, G., & Ladame, S. (2012). DNA-templated synthesis of trimethine cyanine dyes: A versatile fluorogenic reaction for sensing G-quadruplex formation. *Angewandte Chemie International Edition*, 49, 2738-2742. <https://doi.org/10.1002/anie.201000291>
- Nielsen, P. E. (2007). Peptide nucleic acids and the origin and homochirality of life. *Origins of Life and Evolution of Biospheres*, 37, 323-328. <https://doi.org/10.1007/s11084-007-9105-2>
- Nielsen, P. E. (2010). Peptide nucleic acids (PNA) in chemical biology and drug discovery. *Chemistry & Biodiversity*, 7, 786-804. <https://doi.org/10.1002/cbdv.201000008>
- Pagano, B., Mattia, C. A., & Giancola, C. (2009). Applications of isothermal titration calorimetry in biophysical studies of G-quadruplexes. *International Journal of Molecular Sciences*, 10, 2935-2957. <https://doi.org/10.3390/ijms10072935>
- Paul, A., Poulami, S., Yamuna, K., & Ladame, S. (2008). Combining G-quadruplex targeting motifs on a single peptide nucleic acid scaffold: A hybrid (3+1) PNA-DNA bimolecular quadruplex. *Chemistry*, 14, 8682-8689. <https://doi.org/10.1002/chem.200800605>
- Vorlíčková, M., Kejnovská, I., Sagi, J., Renčíuk, D., Bednářová, K., Motlová, J., & Kypr, J. (2012). Circular dichroism and guanine quadruplexes. *Methods*, 57(1), 64-75. <https://doi.org/10.1016/j.ymeth.2012.01.007> <https://doi.org/10.1016/j.ymeth.2012.01.007>
- Yu, H., Guo, X., & Su, J. (2021). Peptide nucleic acid targeting of G-quadruplexes to regulate oncogenic translation. *Biochemical Pharmacology*, 188, 114570. <https://doi.org/10.1016/j.bcp.2021.114541>