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PhpC modulates G-quadruplex-RNA landscapes in human cells†

Jérémy Mitteau,^a Sandy Raevens,^a Zi Wang,^b Marc Pirrotta,^a Ibai E. Valverde,^a Robert H. E. Hudson^b and David Monchaud^b *^a

Stabilizing DNA/RNA G-quadruplexes (G4s) using small molecules (ligands) has proven an efficient strategy to decipher G4 biology. Quite paradoxically, this search has also highlighted the need for finding molecules able to disrupt G4s to tackle G4-associated cellular dysfunctions. We report here on both qualitative and quantitative investigations that validate the G4-RNA-destabilizing properties of the leading compound PhpC in human cells.

DNA and RNA G-quadruplexes (G4s) are the focus of significant chemical biology efforts aiming at deciphering the cellular circuitries where G4s might be involved.¹ These peculiar nucleic acid structures, made of four guanine (G)-rich strands held together *via* the formation and self-stacking of consecutive G-quartets, are currently thought to influence gene expression and DNA transactions (replication, transcription and repair). To achieve this level of knowledge, chemical biology hinged on the use of G4-interacting compounds, known as G4 stabilizers or G4 ligands (Fig. S1A, ESI†), including BRACO-19,² PhenDC3,³ pyridostatin (PDS)⁴ or CX-5461⁵ (which recently reached clinical trials),⁶ to name but a few among the hundreds of ligands reported over the past years.⁷ These programs of reversible perturbation of cell biology using G4 ligands provided key cellular readouts amenable to mechanistic interpretations and enabled a comprehensive review of G4 biology.

In light of their ability to exacerbate cellular G4 landscapes in a reversible manner, G4 ligands have been evaluated as potential anticancer agents.⁸ The logic behind the targeting of DNA G4s^{9,10} with *ad hoc* ligands stems from their ability to downregulate the expression of oncogenes such as c-Myc,¹¹ targeting the G4-forming sequence d[^{5'}GAG₃TG₄AG₃TG₄A₂G^{3'}] found in its promoter (Fig. 1A).¹² G4 ligands can also alter the

telomere organization and maintenance (targeting hTelo G4),¹³ and stabilize impediments to DNA transactions, which triggers genetic instability *via* DNA damage induction.^{14,15} As examples, PDS and CX-5461 were shown to trigger DNA damage by trapping physically topoisomerase 2 (Top2) at G4 sites,^{16–18} and both ligands were successfully included in synthetic lethality programs to treat DNA repair-deficient cancer cells.^{19–21} The logic behind the targeting of RNA G4s^{22,23} with *ad hoc* ligands relies on the regulatory roles they play in both coding²⁴ and non-coding RNAs.^{25,26} As examples, PDS was used as a reversible modulator of the translation of NRAS mRNA,²⁷ targeting the G4-forming sequence r[^{5'}G₃AG₄CG₃UCUG₃^{3'}] found in its 5'-UTR (Fig. 1B)²⁸ and part of the cytotoxic activity of BRACO-19 was shown to be mediated by its interaction with both coding (NRAS G4) and long non-coding RNAs (or lncRNA, here MALAT1 G4).²⁹

One unexpected aftermath of these investigations was the demonstration that ligand-stabilized G4s triggered also genetic instability in central nervous system (CNS) cells and premature ageing in both cells and model organisms.^{30–33} This provides a message of caution about using G4 ligands as anticancer agents, as they might accumulate in and damage CNS cells as well. When combined with the severe genomic dysfunctions caused by loss-of-function mutations in genes coding both DNA and RNA G4 helicases,^{34,35} these observations indicate that an over-abundance of G4s might trigger life-threatening instability and emphasize the need for identifying small molecules able to destabilize G4s,³⁵ in order to tackle the G4 threats.

To date, only a few G4 destabilizers have been reported (Fig. S1B, ESI†): the well-known G4 stabilizer TMPyP4 was shown to unfold d[^{5'}(CGG)_n^{3'}],³⁶ r[^{5'}(CGG)_n^{3'}],³⁷ r[^{5'}(G₄C₂)_n^{3'}]³⁸ and r[^{5'}(G₂CU(CG₂)₃A)^{3'}]³⁹ G4s, likely thanks to a higher affinity for random coiled *versus* folded sequences; this property was common to an anthrathiophenedione derivative found to unfold telomeric G4 d[^{5'}(T₂AG₃)₄^{3'}];⁴⁰ triarylpyridines (TAPs) were chemically fine-tuned to lead to TAP1, which efficiently disrupts c-kit G4s;⁴¹ a stiff-stilbene ligand was shown to modulate G4 folding through a combination of groove binding and

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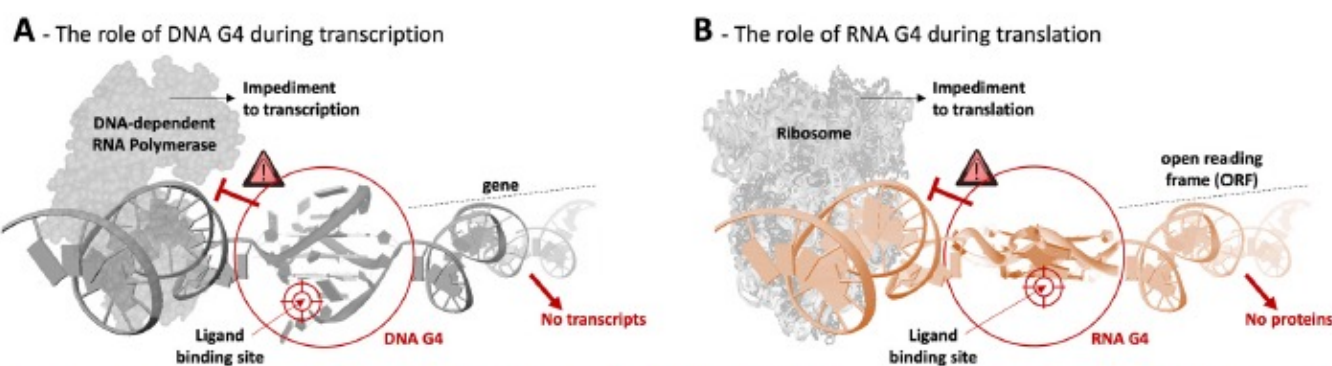


Fig. 1 Schematic representation of one of the roles that DNA (A) and RNA G4s (B) play in the regulation of gene expression at both transcriptional and translational levels: folded G4s hamper proper polymerase processivity and their stabilization by *ad hoc* G4 ligands further restrains the polymerase motion, thereby modulating G4-based regulations in a reversible manner.

intercalation;⁴² and more recently, a large excess of a ruthenium complex was found to unfold $d[{}^{5'}(\text{CGG})_n{}^{3'}]$,⁴³ and of amphiphilic ammonium salts (dodine and derivatives) to destabilize hTelo and c-Myc G4s.⁴⁴

The G4 unfolding properties of these prototypes, though promising, were established on the basis of a limited number of *in vitro* techniques. We invested massive efforts to set up a standardized *in vitro* workflow,⁴⁵ which led to the identification of the G-clamp analogue PhpC (Fig. 2A): the G4-unfolding properties of this molecule were studied *via* the G4-unfold assay, which relies on the study of the hybridization kinetics of a G4-containing oligonucleotide with its complementary strand. PhpC was also shown to help enzymes go through G4 roadblocks, including *Taq* polymerase (qPCR stop assay)^{45,46} and Pif1 helicase (G4-helicase assay).^{45,47} Our hypothesis is that PhpC could clamp a flipping G from the external G-quartet of a G4 when breathing: this weakens the stability of the external G-quartet as already postulated^{39,40} and, in turn, of the whole G4 structure. This hypothesis is supported by both the ability of PhpC to facilitate polymerase processivity whatever the nature of the G4 sequence (Fig. S2 and Tables S1 and S2, ESI†), and by its better interaction with G4 *versus* random coiled DNA (Fig. S3 and Table S3, ESI†). These promising *in vitro* properties must now be confirmed in cells: we recently used a qualitative

approach to assess the way PhpC modulates DNA G4 landscape in HeLa cells⁴⁸ by immunofluorescence using the BG4 antibody;⁴⁹ we here report on our efforts to assess the extent to which it modulates RNA G4 landscape both *in vitro* and *in vivo*, through both qualitative and quantitative approaches.

Our first approach was qualitative in nature, as we tracked the changes in G4 landscape in cells pre-incubated with PhpC by optical imaging (see ESI†). The toxicity of PhpC in MCF7 cells is very low ($\text{IC}_{50} > 300 \mu\text{M}$, Fig. 2B and Tables S4 and S5, ESI†), offering a wide range of possible concentrations for live-cell incubation. The G4 landscape was quantified at a whole-cell scale using the G4-selective, turn-on fluorescence probe N-TASQ ($\lambda_{\text{ex}} = 405 \text{ nm}$; $\lambda_{\text{em}} = 450\text{--}530 \text{ nm}$, Fig. 2A).⁵⁰ N-TASQ was used in live cells ($50 \mu\text{M}$, $\text{IC}_{50} > 300 \mu\text{M}$, 6 h), without or with 2-h pre-incubation with PhpC ($20 \mu\text{M}$). After cell fixation, both the number of N-TASQ foci per cell (ascribed to G4 sites *bona fide*) and the fluorescence intensity per cell were quantified (Fig. 2C and Fig. S4–S7, Table S6, ESI†): in both instances, a good (–30%) to strong (–68%) reduction of the G4 signal was observed upon pre-incubation with PhpC. In contrast, we previously showed that the incubation of HeLa cells with BRACO-19 ($1.8 \mu\text{M}$, 48 h) resulted in a 2.2-fold increase in the number of N-TASQ foci per cell.⁵¹

To rule out a direct competition between N-TASQ and PhpC for G4 binding during live-cell incubation, we quantified the

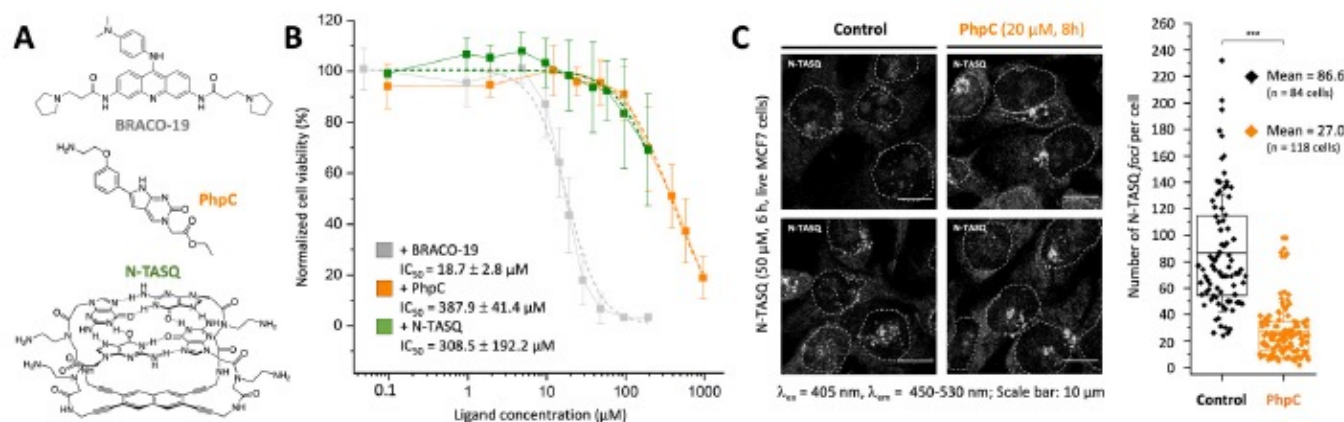


Fig. 2 (A) Chemical structure of the G4-interacting agent BRACO-19, PhpC and N-TASQ used in this study. (B) Antiproliferative activity of BRACO-19, PhpC and N-TASQ in MCF7 cells. (C) G4 imaging in MCF7 cells by N-TASQ without or with pre-incubation with PhpC ($20 \mu\text{M}$, 8 h, left; the nuclei are identified by dotted lines) and related quantification (number of foci per cell, right). Scale bars = $10 \mu\text{m}$; *** $p < 0.001$.

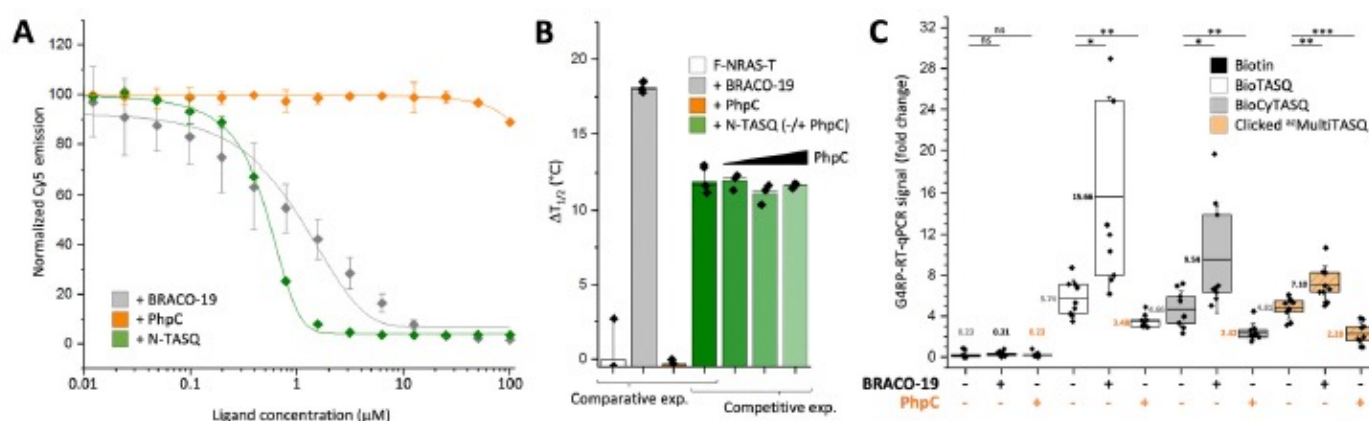


Fig. 3 (A) Apparent affinity of BRACO-19, PhpC and N-TASQ for NRAS G4 assessed by fluorescence quenching assay. (B) FRET-melting experiments performed with F-NRAS-T (0.2 μ M) and BRACO-19, PhpC and N-TASQ (1.0 μ M); competitive FRET-melting experiments performed with F-NRAS-T (0.2 μ M), N-TASQ (1.0 μ M) and increasing amounts of PhpC (up to 20 mol. equiv.); (C) modulation of the G4-containing NRAS transcript by pre-incubation with either BRACO-19 (8.4 μ M, 48 h) or PhpC (90 μ M, 48 h) monitored by G4RP-RT-qPCR using biotinylated TASQs as baits (and biotin as control). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns: not significant.

apparent affinity of both molecules by fluorescence quenching assay (FQA, see ESI†)⁵² using the labelled RNA G4-forming sequence ^{5'}Cy5-NRAS (Fig. 3A and Fig. S8, Tables S1, S7 and S8, ESI†): the >2-log difference between the apparent dissociation constant of N-TASQ ($^{app}K_D = 0.51 \mu\text{M}$) and PhpC ($^{app}K_D > 100 \mu\text{M}$) argue for a decrease in cellular fluorescence originating in a modulation of the G4 landscape rather than a competition between probes. Of note, similar results were obtained with a DNA G4 (^{5'}Cy5-Myc, Fig. S8, ESI†). This lack of competition was confirmed by a competitive FRET-melting experiment⁵³ performed with the doubly labelled F-NRAS-T (Fig. 3B and Fig. S9, Table S9, ESI†): the stabilization imparted by N-TASQ ($\Delta T_{1/2} = 11.9 \text{ }^\circ\text{C}$) was not affected by an excess of PhpC (up to 20 mol. equiv., $\Delta\Delta T_{1/2} \text{ ca. } 0.8 \text{ }^\circ\text{C}$). Similar results were obtained with a DNA G4 (hTelo F21T, Fig. S9 and Table S10, ESI†). However, when incubated in reverse, PhpC mitigates the F-NRAS-T stabilization by N-TASQ (Fig. S10†), yet modestly ($\Delta\Delta T_{1/2} = -0.9 \text{ }^\circ\text{C}$ at 1:1 ratio) but in line with its low activity in this experimental setup (Table S11, ESI†). This indicates that PhpC somehow hampers the proper recognition of G4 by N-TASQ, likely by distorting the G4 target, further confirming that the decrease of N-TASQ fluorescence in cells pre-treated by PhpC does actually stem from that of cellular G4s, and not from just a competition between the probes.

Our second approach was quantitative in nature, as we assessed the modulation of G4s in cells incubated with PhpC by G4RP-RT-qPCR (Fig. 3C).^{29,54,55} The G4RP technique (for G4-RNA precipitation) relies on the affinity precipitation of folded RNA G4s *in vivo* using a biotinylated biomimetic G4 ligand known as TASQ (for template-assembled synthetic G-quartet).⁵⁶ Here, the RT-qPCR version was implemented against NRAS G4 (ESI†), in a manner reminiscent of the pioneering investigations (see above).²⁷ Initially developed with BioTASQ, we performed comparative investigations using two other biotinylated TASQs, BioCyTASQ⁵⁷ and the clicked ³²MultiTASQ (Fig. S1C and Tables S12 and S13, ESI†).⁵⁸ As control, we incubated MCF7 cells with BRACO-19 ($IC_{50} = 18.7 \mu\text{M}$, Fig. 2B and ESI†), as a positive modulator of G4s.

We tracked the G4-containing NRAS, known to be folded and quite abundant in MCF7 cells.^{59,60} The interaction between NRAS G4 and the small molecules used herein (BRACO-19 and TASQs) was confirmed *in vitro* by both FQA and FRET-melting assays (Fig. S8 and S9, ESI†). The incubation of MCF7 cells with BRACO-19 (IC_{20} , 8.4 μM , 48 h) triggered a sharp increase (x1.5–2.7-fold, Fig. 3C) of the G4RP signal of NRAS monitored with the 3 TASQs (using biotin as negative control), in line with our previous optical imaging results.⁴⁶ When treated with PhpC (90 μM , 48 h), the abundance of NRAS G4 was significantly decreased (x0.5–0.6-fold), in agreement with optical imaging results described above. These results thus strongly advocated for a positive modulation of the G4 landscapes by the G4-stabilizer BRACO-19 and a negative modulation by the G4-destabilizer PhpC. They also confirm and further substantiate our preliminary observations with DNA G4s⁴⁸ and, above all, extend them to RNA G4s, making PhpC the very first prototype of what could be referred to as an artificial molecular helicase.

In conclusion, through the implementation of a series of *in vitro* and cell-based investigations (optical imaging and affinity precipitation), we provide here both a qualitative and a quantitative demonstration that PhpC does modulate G4 landscapes in human cells. This series of results places PhpC in an unique position from which reliable strategies to prevent G4-associated genetic dysfunctions could now be devised.

Conflicts of interest

There are no conflicts to declare.

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