



Approach to Target Exact Nucleic Acid alternative structures (ATENA)

ATENA (Approach to Target Exact Nucleic Acid alternative structures) is a CRISPR-based platform that enables unprecedented, site-specific targeting of individual DNA G-quadruplex and i-motif structures in living cells to precisely interrogate and control gene regulation.

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Intellectual property information

[WO2025/172696A1](#) – A PCT application titled “*G-Quadruplex*” was filed 12 February 2025

Inventor information

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Proposed Uses

ATENA is designed as a research and target-validation platform for pharmaceutical, biotechnology, and life-science researchers seeking to identify, validate, and de-risk novel therapeutic targets linked to DNA secondary structures. By enabling selective targeting of individual G-quadruplexes (G4s) or i-motifs (iMs) at defined genomic loci, the technology allows users to directly link specific DNA structures to transcriptional outcomes. This capability supports mechanism-of-action studies, ligand screening, functional genomics, and early drug discovery, particularly in oncology and transcription-driven diseases.

Problem addressed

DNA G-quadruplexes and i-motifs are widespread regulatory structures implicated in transcriptional control, genome stability and cancer. However, current targeting approaches rely on small-molecule ligands that lack inter-structure selectivity, leading to global genome effects, ambiguous biological interpretation, and poor translational confidence. As a result, it has been impossible to determine the therapeutic relevance of individual G4s or iMs, severely limiting their exploitation as drug targets. This lack of precision has slowed target validation, increased attrition, and constrained clinical progress in this promising area.

Technology Overview

ATENA technology is built on a catalytically inactive Cas9 (dCas9) that is chemically functionalised with structure-selective small-molecule ligands or peptides using HaloTag chemistry, while genomic specificity is provided by programmable guide RNAs. By combining the spatial precision of CRISPR with the chemical selectivity of DNA-binding ligands, ATENA overcomes a central limitation of conventional G4 and iM ligands which is their inability to discriminate between the tens of thousands of similar structures present across the genome.

The approach has demonstrated that single G-quadruplexes and i-motifs can be individually targeted and functionally interrogated, revealing highly selective and promoter-specific transcriptional effects. The platform shows that targeting a G4s or its complementary iMs at the same genomic locus can produce opposing transcriptional outcomes, and that different ligands bound to the same G4 can elicit distinct biological responses. Importantly, ATENA dramatically reduces off-target transcriptional perturbation compared with free ligands, enabling clean mechanistic insight into DNA secondary-structure biology.

Intellectual property information

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Publications

Nuccio, Sabrina Pia et al. “[Chemically modified CRISPR-Cas9 enables targeting of individual G-quadruplex and i-motif structures, revealing ligand-dependent transcriptional perturbation.](#)” Nature communications vol. 17,1 385. 9 Dec. 2025

Sabrina Pia Nuccio, Michele Stasi, Enrico Cadoni, Marco Di Antonio, “[Function through shape: An overview of DNA G-quadruplexes in transcriptional regulation](#)”, Current Opinion in Chemical Biology, Volume 93, 2026

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Benefits

- Enables selective targeting of individual G-quadruplexes or i-motifs eliminating confounding genome-wide effects.
- Links specific DNA secondary structures to defined transcriptional outcomes
- Discriminates ligand-specific biological responses at the same genomic site, supporting rational lead selection.
- Spatial confinement of ligands via CRISPR guidance dramatically reduces global genome perturbation compared with free ligands, resulting in far fewer differentially expressed genes and cleaner mechanistic readouts.
- A versatile CRISPR-guided system that can be readily reprogrammed to target any G4 or i-motif and paired with diverse ligands, making it scalable for functional genomics, ligand screening, and early therapeutic target discovery.
- Identifies novel disease vulnerabilities by revealing G-quadruplex master regulators of gene expression.