Summary

Expansion of (GAA)n repeats in the first intron of the Frataxin gene is associated with reduced mRNA and protein levels and the development of Friedreich’s ataxia. (GAA)n expansions form non-canonical structures, including intramolecular triplex (H-DNA), and R-loops and are associated with epigenetic modifications. With the aim of interfering with higher order H-DNA (like) DNA structures within pathological (GAA)n expansions, we examined sequence-specific interaction of peptide nucleic acid (PNA) with (GAA)n repeats of different lengths (short: n=9, medium: n=75 or long: n=115) by chemical probing of triple helical and single stranded regions. We found that a triplex structure (H-DNA) forms at GAA repeats of different lengths; however, single stranded regions were not detected within the medium size pathological repeat, suggesting the presence of a more complex structure. Furthermore, (GAA)4-PNA binding of the repeat abolished all detectable triplex DNA structures, whereas (CTT)5-PNA did not. We present evidence that (GAA)4-PNA can invade the DNA at the repeat region by binding the DNA CTT strand, thereby preventing non-canonical-DNA formation, and that triplex invasion complexes by (CTT)5-PNA form at the GAA repeats. Locked nucleic acid (LNA) oligonucleotides also inhibited triplex formation at GAA repeat expansions, and atomic force microscopy analysis showed significant relaxation of plasmid morphology in the presence of GAA-LNA. Thus, by inhibiting disease related higher order DNA structures in the Frataxin gene, such PNA and LNA oligomers may have potential for discovery of drugs aiming at recovering Frataxin expression.

Summary

It is shown by photometric and fluorimetric analysis, along with supporting theoretical calculations, that hydroxy-substituted benzo[b]quinolizinium derivatives display the characteristic features of organic photoacids. Specifically, the experimental and theoretical results confirm the strong acidity of these compounds in the excited state (pKα* < 0). The combination of the prototropic properties of 8- and 9-hydroxybenzo[b]quinolizinium with the particular solvent-solute interactions of the excited acid and its conjugate base leads to a pronounced fluorosolvatochromism, hence the emission maxima shift from 468 nm (8-
Laetitia Saint-Paul, Chi-Hung Nguyen, Anne Buffière, Jean-Paul Pais de Barros, Arlette Hammann, Corinne Landras-Guetta, Rodolphe Filomenko, Marie-Lorraine Chrétien, Pauline Johnson, Jean-Noël Bastie, Laurent Delva, Ronan Quéré (2016 Sep 1)

**CD45 phosphatase is crucial for human and murine acute myeloid leukemia maintenance through its localization in lipid rafts.**

**Oncotarget** : 7 : 64785-64797 : [DOI: 10.18632/oncotarget.11622](https://doi.org/10.18632/oncotarget.11622)

**Summary**

CD45 is a pan-leukocyte protein with tyrosine phosphatase activity involved in the regulation of signal transduction in hematopoiesis. Exploiting CD45 KO mice and lentiviral shRNA, we prove the crucial role that CD45 plays in acute myeloid leukemia (AML) development and maintenance. We discovered that CD45 does not colocalize with lipid rafts on murine and human non-transformed hematopoietic cells. Using a mouse model, we proved that CD45 positioning within lipid rafts is modified during their oncogenic transformation to AML. CD45 colocalized with lipid rafts on AML cells, which contributes to elevated GM-CSF signal intensity involved in proliferation of leukemic cells. We furthermore proved that the GM-CSF/Lyn/Stat3 pathway that contributes to growth of leukemic cells could be profoundly affected, by using a new plasma membrane disrupting agent, which rapidly delocalized CD45 away from lipid rafts. We provide evidence that this mechanism is also effective on human primary AML samples and xenograft transplantation. In conclusion, this study highlights the emerging evidence of the involvement of lipid rafts in oncogenic development of AML and the targeting of CD45 positioning among lipid rafts as a new strategy in the treatment of AML.

Naoko Kotera, Anton Granzhan, Marie-Paule Teulade-Fichou (2016 Aug 16)

**Comparative study of affinity and selectivity of ligands targeting abasic and mismatch sites in DNA using a fluorescence-melting assay.**

**Biochimie** : 128-129 : 133-137 : [DOI: 10.1016/j.biochi.2016.08.004](https://doi.org/10.1016/j.biochi.2016.08.004)

**Summary**

Recently, several families of small-molecule ligands have been developed to selectively target DNA pairing defects, such as abasic sites and mismatched base pairs, with the aims to interfere with the DNA repair and the template function of the DNA. However, the affinity and selectivity (with respect to the well-matched DNA) of these ligands has barely been evaluated in a systematic way. Herein, we report a comparative study of binding affinity and selectivity of a representative panel of 16 ligands targeting abasic sites and a T-T mismatch in DNA, using a fluorescence-monitored melting assay. We demonstrate that bisintercalator-
type macrocyclic ligands are characterized by moderate affinity but exceptionally high selectivity with respect to well-matched DNA, whereas other reported ligands show either modest selectivity or rather low affinity in identical conditions.