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Presentation of the team

The main missions of our team include the design, synthesis, and studies of novel small-molecule ligands and probes able to recognize unusual DNA and RNA structures (in particular, damaged DNA structures representing intermediates in enzymatic DNA repair), as well as elucidation of their biological effects in cellular models. We assume that these compounds could interfere with the native functions of nucleic acids or enzymatic DNA repair, thereby finding applications in cancer therapy.

Recognition of pairing defects in double-stranded DNA

Recognition of DNA mismatches and ligand control of DNA hybridization: We developed a family of distance-constrained polyazacyclophane macrocycles (also termed cyclobisintercalators), a unique series of DNA ligands whose very particular geometry results in enhanced binding to DNA pairing defects, such as mismatched base pairs and abasic sites in double-stranded DNA. In a collaboration with Muriel Jourdan (Grenoble), we investigated the structural details of the recognition of thymine-thymine (T-T) mismatches by these macrocycles using high-resolution NMR spectroscopy. More recently, we demonstrated that their unique DNA-binding properties could be exploited for a controlled modulation of the hybridization state of mismatch-containing DNA duplexes. Thus, hybridization of DNA strands containing multiple T-T mismatches can be induced at room temperature through addition of a stoichiometric amount of the macrocycle. Moreover, this process can be reversibly controlled by addition or sequestration of copper(II) cations, which capture the ligand in a non-DNA-binding, dinuclear metal complex. This mechanism allows implementation of reversible DNA switches and machines.
Recognition of abasic sites and inhibition of DNA repair: Small-molecule recognition of another type of DNA pairing defects, namely abasic sites, can be harnessed to induce modulation of enzymatic DNA repair pathways. In particular, we showed that binding of macrocyclic ligands to abasic sites leads to efficient inhibition of the cleavage of the latter by human AP endonuclease 1 (APE1) via a substrate-masking mechanism (“indirect” inhibition), with IC\textsubscript{50} values comparable to the best APE1 inhibitors acting on the protein itself. Thus, substrate masking by non-covalent abasic-site ligands represents an attractive strategy for inhibition of APE1. Moreover, with a native abasic site substrate, the APE1 inhibition effect of the macrocycle is accompanied by the enzyme-independent cleavage of the DNA substrate by the ligand per se through another mechanism (β-elimination). Altogether, the ligand shifts the processing of abasic sites from the APE1-induced cleavage (hydrolysis of the phosphodiester bond at the abasic site) to AP lyase-like cleavage (cleavage of the C3’–O-P bond). Thus, these ligands can be considered as promising modulators of cellular DNA repair pathways and represent a potential for anti-cancer therapy in a combination with DNA-targeting drugs.


Fluorescent probes for G-quadruplex DNA structures

Development of fluorescent probes for G-quadruplex (G4) DNA and RNA structures remains an active research area due to the high biological importance of these non-canonical nucleic acid structures, which is still far from being fully understood. Along these lines, we demonstrated that 2,4-distyrylpyridinium dyes (e.g., 1a and analogues) represent an easily available and highly promising scaffold for G4-DNA-selective fluorescent probes with excellent optical properties. Additionally, we established a novel bimodal (colorimetric and fluorimetric) probe BCVP, useful for robust in vitro detection of G4-DNA structures irrespective of their topology and their discrimination from other DNA forms.


Key publications

Year of publication 2021

**Identifying G-Quadruplex-DNA-Disrupting Small Molecules**  
*Journal of the American Chemical Society* : 143 : 12567–1257 : [DOI: 10.1021/jacs.1c04426](https://doi.org/10.1021/jacs.1c04426)

Marc Lavigne, Olivier Helynck, Pascal Rigolet, Rosia Boudria-Souilah, Mireille Nowakowski, Bruno Baron, Sébastien Brülé, Sylviane Hoos, Bertrand Raynal, Lionel Guittat, Claire Beauvineau, Stéphane Petres, Anton Granzhan, Jean Guillon, Geneviève Pratviel, Marie-Paule Teulade-Fichou, Patrick England, Jean-Louis Mergny, Hélène Munier-Lehmann (2021 Jul 7)  
**SARS-CoV-2 Nsp3 unique domain SUD interacts with guanine quadruplexes and G4-ligands inhibit this interaction.**  

Yu Luo, Anton Granzhan, Daniela Verga, Jean-Louis Mergny (2021 Apr 1)  
**FRET-MC: A fluorescence melting competition assay for studying G4 structures in vitro**  
*Biopolymers* : 112 : e23415 : [DOI: 10.1002/bip.23415](https://doi.org/10.1002/bip.23415)

Oksana Reznichenko, Anne Cucchiarini, Valérie Gabelica, Anton Granzhan (2021 Jan 14)  
**Quadruplex DNA-guided ligand selection from dynamic combinatorial libraries of acylhydrazones**  

Year of publication 2020

Anton Granzhan, Rodrigo Prado Martins, Robin Fåhraeus, Marc Blondel and Marie-Paule Teulade-Fichou (2020 Jun 30)  
**Quadruplex-interacting compounds for regulating the translation of the Epstein–Barr virus nuclear antigen 1 (EBNA1) mRNA: A new strategy to prevent and treat EBV-related cancers**  
*Quadruplex Nucleic Acids As Targets For Medicinal Chemistry, Annual Reports in Medicinal Chemistry* : Chap 8, 54 : 243-286 : [DOI: 10.1016/bs.armc.2020.05.001](https://doi.org/10.1016/bs.armc.2020.05.001)

Michela Zuffo, Aurélie Gandolfini, Brahim Heddi, Anton Granzhan (2020 Apr 20)  
**Harnessing intrinsic fluorescence for typing of secondary structures of DNA**  