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.
Molecular recognition of nucleic acids

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**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$_{50}$ 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.
Molecular recognition of nucleic acids

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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.
Molecular recognition of nucleic acids
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Molecular recognition of nucleic acids
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Key publications

Year of publication 2019

DNA junction ligands trigger DNA damage and are synthetic lethal with DNA repair inhibitors in cancer cells
Journal of the American Chemical Society : XXXX : XXX-XXX : DOI : 10.1021/jacs.9b11150

Xiao Xie, Michela Zuffo, Marie-Paule Teulade-Fichou, Anton Granzhan (2019 Aug 6)
Identification of optimal fluorescent probes for G-quadruplex nucleic acids through systematic exploration of mono- and distyryl dye libraries

Oksana Reznichenko, Alicia Quillévére, Rodrigo Prado Martins, Nadège Loaëc, Hang Kang, María José Lista, Claire Beauvineau, Jorge González-García, Régis Guillot, Cécile Voisset, Chrysoula Daskalogianni, Robin Fåhraeus, Marie-Paule Teulade-Fichou, Marc Blondel, Anton Granzhan (2019 May 23)
Novel cationic bis(acylhydrazones) as modulators of Epstein–Barr virus immune evasion acting through disruption of interaction between nucleolin and G-quadruplexes of EBNA1 mRNA

Coralie Caron, Xuan N T Duong, Régis Guillot, Sophie Bombard, Anton Granzhan (2019 Feb 6)
Interaction of Functionalized Naphthalenophanes with Abasic Sites in DNA: DNA Cleavage, DNA Cleavage Inhibition, and Formation of Ligand-DNA Adducts.

Michela Zuffo, Xiao Xie, Anton Granzhan (2018 Dec 6)
Strength in Numbers: Development of a Fluorescence Sensor Array for Secondary Structures of DNA.

Year of publication 2018

Abhijit Saha, Sophie Bombard, Anton Granzhan, Marie-Paule Teulade-Fichou (2018 Oct 27)
Probing of G-Quadruplex Structures via Ligand-Sensitized Photochemical Reactions in BrU-Substituted DNA.
Scientific Reports : 8 : 15814 : DOI : 10.1038/s41598-018-34141-z
Molecular recognition of nucleic acids

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