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.


Molecular recognition of nucleic acids


**Key publications**

**Year of publication 2018**

Ludivine Guyon, Marc Pirrotta, Katerina Duskova, Anton Granzhan, Marie-Paule Teulade-Fichou, David Monchaud (2018 Feb 16)
Molecular recognition of nucleic acids
UMR9187 / U1196 - Chemistry, Modelling and Imaging for Biology (CMIB)

TWJ-Screen: an isothermal screening assay to assess ligand/DNA junction interactions in vitro
Nucleic Acids Research : 46 : e16 : DOI : 10.1093/nar/gkx1118

Year of publication 2017

Jiyeon Choi, Mai Xu, Matthew M Makowski, Tongwu Zhang, Matthew H Law, Michael A Kovacs, Anton Granzhan, Wendy J Kim, Hemang Parikh, Michael Gartside, Jeffrey M Trent, Marie-Paule Teulade-Fichou, Mark M Iles, Julia A Newton-Bishop, D Timothy Bishop, Stuart MacGregor, Nicholas K Hayward, Michiel Vermeulen, Kevin M Brown (2017 Aug 1)
A common intronic variant of PARP1 confers melanoma risk and mediates melanocyte growth via regulation of MITF.
Nature genetics : 49 : 1326-1335 : DOI : 10.1038/ng.3927

Naoko Kotera, Régis Guillot, Marie-Paule Teulade-Fichou, Anton Granzhan (2017 Apr 4)
Copper(II)-Controlled Molecular Glue for Mismatched DNA.

Sébastien Lyonnais, Aleix Tarrés-Soler, Anna Rubio-Cosials, Anna Cuppari, Reicy Brito, Joaquim Jaumot, Raimundo Gargallo, Marta Vilaseca, Cristina Silva, Anton Granzhan, Marie-Paule Teulade-Fichou, Ramon Eritja, Maria Solà (2017 Mar 9)
The human mitochondrial transcription factor A is a versatile G-quadruplex binding protein.
Scientific reports : 7 : 43992 : DOI : 10.1038/srep43992

Year of publication 2016

Katy Schäfer, Heiko Ihmels, Cornelia Bohne, Karolina Papera Valente, Anton Granzhan (2016 Nov 2)
Hydroxybenzo[b]quinolizinium Ions: Water-Soluble and Solvatochromic Photoacids.
The Journal of organic chemistry : 81 : 10942-10954 : DOI : 10.1021/acs.joc.6b01991

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