Drugs and Probes for Nucleic Acids Secondary Structures
UMR9187 / U1196 - Chemistry and Modelling for the Biology of Cancer (CMBC)

Our group works on the design of compounds targeting non-B nucleic acid structures and certain kinases involved in cancer. The group has a broad expertise in bio-organic chemistry and optical spectroscopy with a strong background in supramolecular chemistry and molecular recognition. Our final aims are to open new perspectives in the discovery of anticancer drugs and mechanistic tools.

Context: Our current interest is focused on the design of new nucleic acid targeted compounds for anticancer research and for elucidating DNA-related molecular basis of cancer.

It is well recognized that DNA sequences containing repeats of heterocyclic bases are highly susceptible to aberrant replication and perturbation of other DNA-related processes such as recombination and transcription. These dysfunctions may lead ultimately to modifications of the genetic material) and may have a role in explaining mechanisms linked to cancer development or more largely be involved in pathogenic rearrangements genome-wide. Repeat-containing DNA domains are highly prone to form non-canonical secondary structures due to self-assembly of bases via various H-bonding modes (mismatched pairs, base-triplets or quartets). The generated structures (mismatched sites, hairpins, triplex, quadruplex) are known (for some) or suspected (for others) to be involved in genetic instability and in pathogenic dysfunctions.

Our team is interested in the recognition of these non-canonical structures locally
formed in DNA by means of specifically designed small molecules (i.e. ligands) that will bind the target structure with high specificity. The primary objectives of this research are two-folded, firstly to provide structure probes usable in various in vitro and cellular models for exploring the polymorphism of DNA; secondly to provide functional probes reporting or acting on the target structure (fluorescent signalling, covalent crosslinking). Of note the design and synthesis of targeted fluorescent molecules compatible with cellular imaging represents a subtopic of our research tightly intertwined with the structure-targeting topic. The final objectives of this research are to create new chemical biology tools for studying and controlling the formation of the target structures as well as their processing by proteins. Ultimately we aim at the discovery of better targeted (regiospecific) DNA interactive agents that may become clinical drugs for anticancer chemotherapy.

**Our specific approaches** towards the identification of active scaffolds are based on rational design (shape complementarity- topology adaptation) and on screening methods. Thus we developed home-made assays amenable to high-throughput screening. These are combined with the use of state of the art optical spectroscopy (UV-Vis, fluorescence, circular dichroïsm) and biochemical methods (gel electrophoresis, pull down assay) for quantitative evaluation of NA-ligands interactions. We also intend to a deep understanding of non-covalent interactions at the atomic level by means of molecular modelling analyses.

**Key publications**

**Year of publication 2021**


**Pt-ttpy, a G-quadruplex binding platinum complex, induces telomere dysfunction and G-rich regions DNA damage.**

*Metallomics : integrated biometal science : mfab029, Ahead of Print : DOI : 10.1093/mtomcs/mfab029*

Laura Fourmois, Florent Poyer, Aude Sourdon, Delphine Naud-Martin, Sounderya Nagarajan, Rahima Chennoufi, Eric Deprez, Marie-Paule Teulade-Fichou, Florence Mahuteau-Betzer (2021 May 19)
Modulation of cellular fate of vinyl triarylamines through structural fine tuning: to stay or not to stay in the mitochondria?

Elisa Le Boiteux, Franck Court, Pierre-Olivier Guichet, Catherine Vaurs-Barrière, Isabelle Vaillant, Emmanuel Chautard, Pierre Verrelle, Bruno M Costa, Lucie Karayan-Tapon, Anne Fogli, Philippe Arnaud (2021 Mar 15)

**Widespread overexpression from the four DNA hypermethylated HOX clusters in aggressive (IDHwt) glioma is associated with H3K27me3 depletion and alternative promoter usage.**
*Molecular oncology*: Accepted article: [DOI](https://10.1002/1878-0261.12944).

Alexandre Leduc, Samia Chaouni, Frédéric Pouzoulet, Ludovic De Marzi, Frédérique Megnin-Chanet, Erwan Corre, Dinu Stefan, Jean-Louis Habrand, François Sichel, Carine Laurent (2021 Mar 13)

**Differential normal skin transcriptomic response in total body irradiated mice exposed to scattered versus scanned proton beams.**
*Scientific reports*: 11: 5876: [DOI](https://10.1038/s41598-021-85394-0).


**Competition of ligands and the 18-mer binding domain of the RHAU helicase for G-quadruplexes - orthosteric or allosteric binding mechanism?**

Anouchka Gatin, Isabelle Billault, Patricia Duchambon, Guillaume Van der Rest, Cécile Sicard-Roselli (2021 Jan 3)

**Oxidative radicals (HO• or N3•) induce several di-tyrosine bridge isomers at the protein scale.**