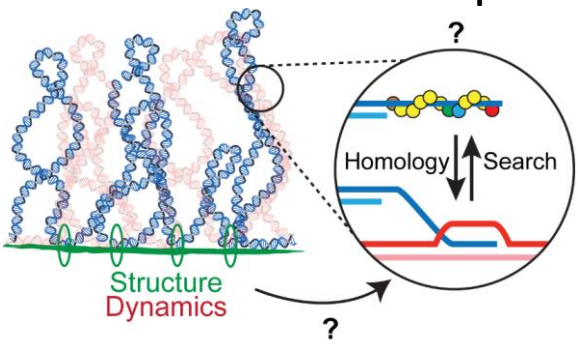
MASTER 2 BMC
PARCOURS GENOPATH
ANNÉE 2021-2022

Titre du sujet de stage :

Dynamic organization of meiotic chromosomes and functional impact on recombinational DNA repair



Nom, adresse de l'Unité d'accueil / Nom du responsable de l'unité :

LBMC UMR5239, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69007 Lyon

Didier Auboeuf

Nom, adresse de l'Equipe d'accueil / Nom du responsable d'équipe :

Equipe "Mécanique du génome" LBMC UMR5239, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69007 Lyon

Aurèle Piazza

Nom, tel, adresse e-mail de l'encadrant de stage :

Aurèle Piazza, +33 4 72 72 80 72 aurele.piazza@ens-lyon.fr
Site web : http://www.ens-lyon.fr/LBMC/equipes/mecanique-du-genome

Sujet de stage :

Meiosis is the specialized cell division at the basis of sexual reproduction. It involves the formation of hundreds of DNA double-strand break (DSBs) in the genome, whose repair by homologous recombination (HR) drives recognition, pairing, and physical attachment via crossover (CO) of the parental homologs for their proper segregation at the first meiotic division. Three outstanding phenomena underlie this HR-driven pairing process (see **Figure 1**):

Homolog bias: how does the repair occurs preferentially on the homologous chromosome rather than the nearby sister chromatid, such as in mitosis?

Obligatory CO: how at least one, and rarely more than one, CO is formed per pair of homolog?

CO interference: how does the local CO designation decision can inhibit formation of subsequent CO at a distance of several dozens to hundreds of kilobases?

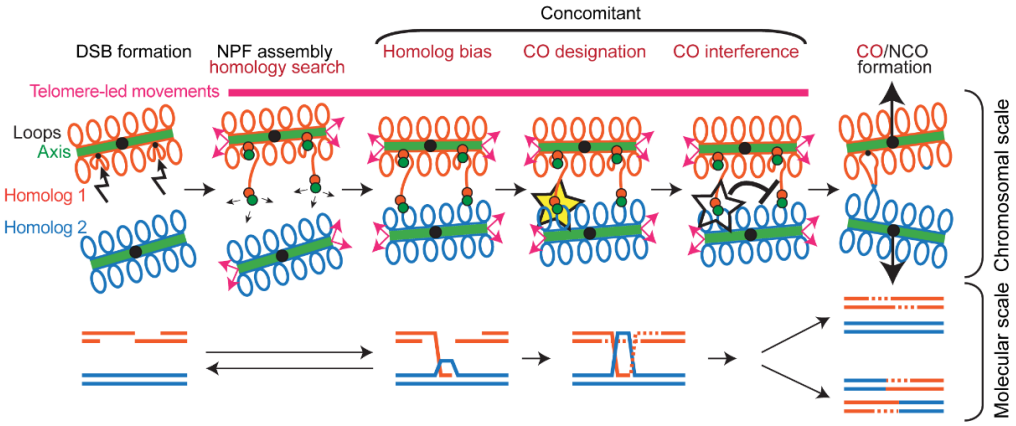


Figure 1: Overview of the molecular and chromosomal events of meiosis.

Our goal is to determine the mechanism(s) underlying these three outstanding phenomena, and the candidate will participate in this endeavor. We know it involves chromosome structure, organized as arrays of chromatin loops anchored on a semi-rigid protein axis, but how this cytological-scale organization mediates or provides input for the molecular-scale DSB repair process remains unknown.

The student will be in a unique position to tackle these great questions of the field, as all the upfront work to develop techniques and build ambitious experimental systems in *S. cerevisiae* are nearing completion: novel physical assays to track early HR intermediates have recently been developed by the team leader (Piazza et al. Cell 2017; Mol Cell 2019), and the assembly of two redesigned chromosomal region of 150-kb (SynIV) dedicated to the study of meiosis with these assays and Hi-C is currently being completed (first version Muller, MSB 2018; Piazza et al. BiorXiv 2020). The approach will consist in simultaneously tracking (i) the genome-wide structuration of chromatin, (ii) the pairing of homologs, and (iii) the progression of the HR reaction at the level of 22 recombination hotspots in the redesigned region during synchronous meiosis in *S. cerevisiae* (**Figure 2**). The student will introduce local perturbation of chromatin folding (*e.g.* loop extrusion block) to address hypothesis regarding the mechanisms of homolog bias, CO designation and interference.

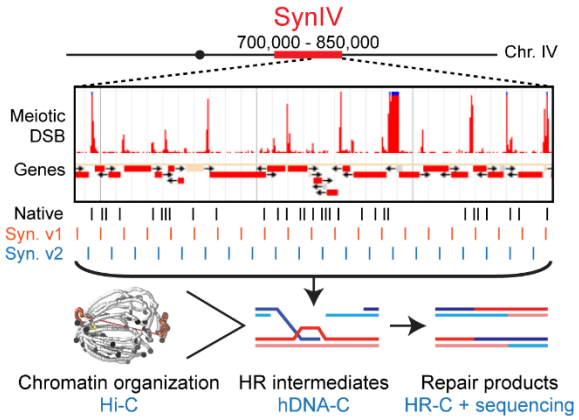


Figure 2: Experimental system to study the chromosomal and molecular events of meiosis over a redesigned region of 150 kb on budding yeast chromosome 4. *Restriction sites have been evenly repositioned over the SynIV regions to enable discriminating the two parental homologs at high resolution. See ref. 2 for more details.*

Supervision: The student will be supervised by Agnes Dumont (IE), expert in Hi-C, Capture-Hi-C and high-throughput sequencing techniques, and myself.

Techniques the candidate will learn: HiC + analysis, capture-HiC, physical assays for high-throughput DNA joint molecules quantification, synthetic biology approaches in yeast.

Technologies utilisées :
Hi-C, séquencage haut-débit, génétique de la levure

Mots clés : DNA repair, 3D genome, meiosis

Publications d'intérêt :

Piazza A*®, Bordelet H*, Dumont A, Thierry A, Savocco J, Girard F, Koszul R®
Cohesin overlays multiple constraints to homology search during recombinational DNA repair
BioRxiv (in revision at Nature Cell Biology) doi: 10.1101/2020.12.17.423195 – co-first and co-corresponding

Piazza, A, Shah, SS, Wright, WD, Gore, SK, Koszul, R, and Heyer, W (2019).
Dynamic processing of displacement loops during recombinational DNA repair
Molecular cell, 73(6):1255–1266.

Muller, H, Scolari, VF, Agier, N, Piazza, A, Thierry, A, Mercy, G, Descorps-Declere, S, Lazar-Stefanita, L, Espéli, O, Llorente, B, and others (2018).
Characterizing meiotic chromosomes' structure and pairing using a designer sequence optimized for Hi-C
Molecular systems biology, 14(7).

Piazza, A, Wright, WD, and Heyer, W (2017).
Multi-invasions are recombination byproducts that induce chromosomal rearrangements
Cell, 170(4):760–773.