MASTER 2 BMC
PARCOURS GENOPATH
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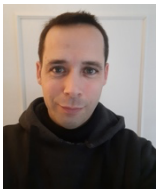
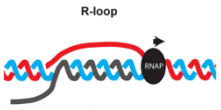


Vincent Vanoosthuyse, DR2 CNRS : vincent.vanoosthuyse@ens-lyon.fr

Équipe P. Bernard, LBMC, ENS-Lyon :
http://www.ens-lyon.fr/LBMC/equipes/architecture-et-dynamique-fonctionnelle-des-chromosomes

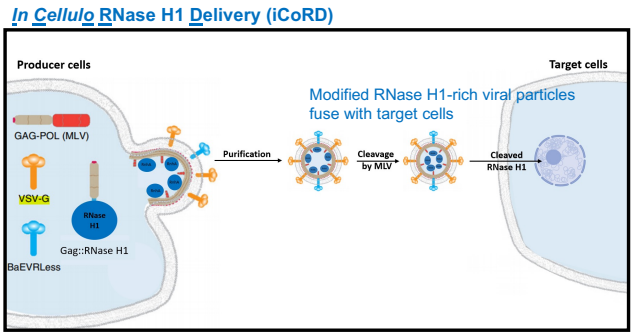
Langues parlées : Anglais/Français

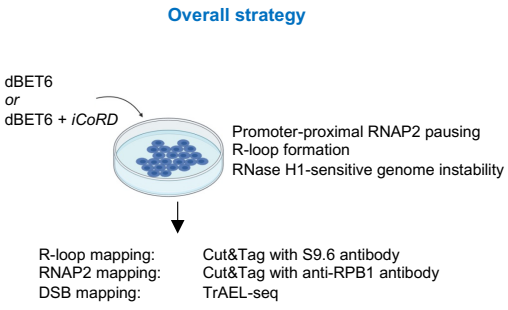
A new innovative approach to understand the primary roles of R-loops in human cells.



R-loops are three-stranded by-products of transcription that result from the abnormal annealing of the nascent RNA to its DNA template (1). Although most R-loops are well tolerated in normal cells (2), changes to the prevalence and distribution of R-loops are predicted to increase genome instability in cancer and it was proposed recently that to modulate R-loop levels could constitute a promising therapeutic strategy in synergy with other cancer treatments (3, 4). It is therefore essential to understand the *primary consequences* of R-loop formation on the surrounding chromatin and to identify the R-loops with the greatest therapeutic potential.

A consensus is emerging that at least a subset of those R-loops causes DNA replication-dependent DNA damage that could be at the origin of undesirable genome rearrangements (1). However, the causal relationship between R-loops and DNA damage has mostly been inferred but never rigorously demonstrated. This is because, until now, no technique was available to quickly manipulate R-loop levels *in vivo*. To circumvent this issue, we have developed *iCoRD*, an innovative strategy that relies on modified viral particles to deplete R-loops from human cells *in vivo* under three hours (see below). *iCoRD* puts us in a prime position to address the primary consequences of R-loop loss. Here we will use this approach to understand the contributions of R-loops to the genome instability phenotypes triggered by small-molecule inhibitors of BET-containing proteins such as BRD4 such as dBET6, which show anti-cancer activity in several pre-clinical models. For the first time, we will establish a list of harmful R-loops that could be interesting therapeutic targets.





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