Control of replication stress and mitosis in colorectal cancer stem cells through the interplay of PARP1, MRE11 and RAD51

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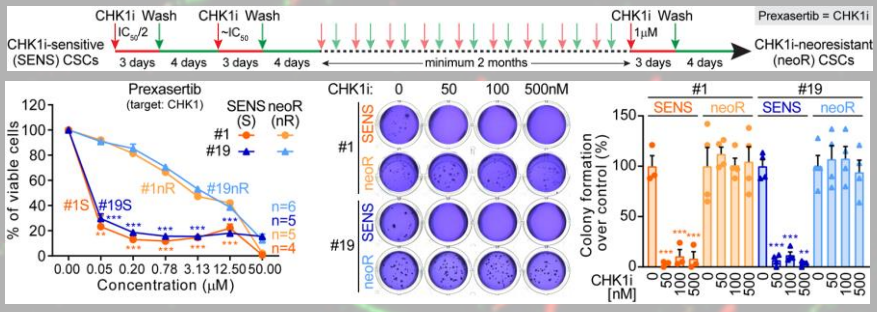
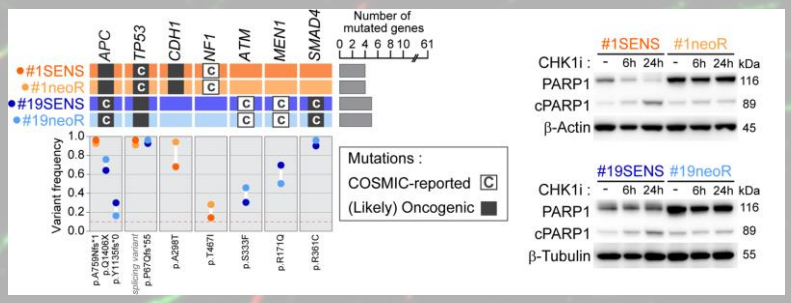
Colerctal cancer stem cells (CRC-SCs) drive tumor initiation, progression and spreading, and are involved in cancer recurrence and therapeutic failure. CRC-SCs display heterogeneous replication stress (RS) levels, but the relevance of the RS response (RSR) centered on the ATR-CHK1 axis is

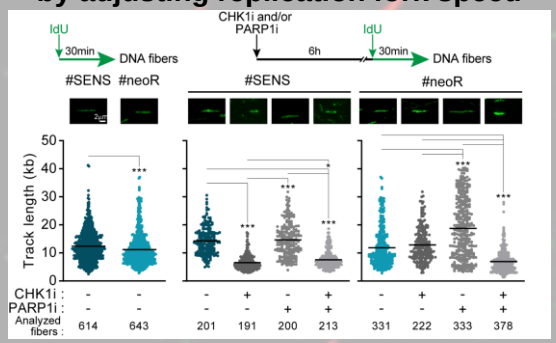
Generation of CRC-SCs resistant to CHK1 inhibitor (neoR)



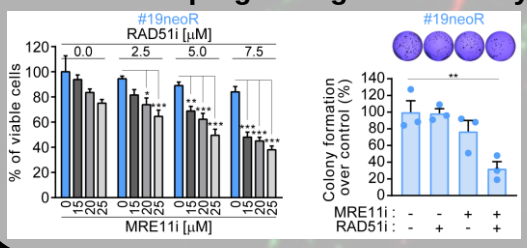
Acquired resistance of neoR CRC-SCs originates from a non-genetic mechanism based on PARP1 upregulation

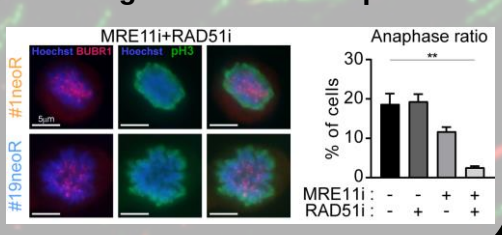


PARP1 limits basal RS levels in neoR CRC-SCs by adjusting replication fork speed

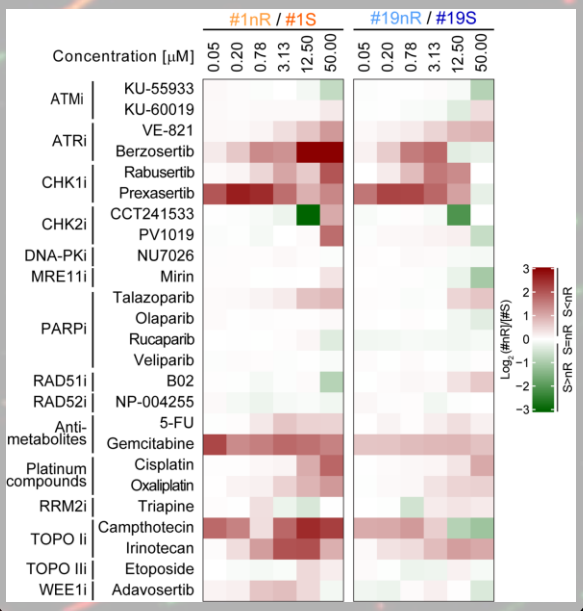


Combined inhibition of MRE11 and RAD51 kills PARP1-upregulating CRC-SCs by inducing mitotic catastrophe

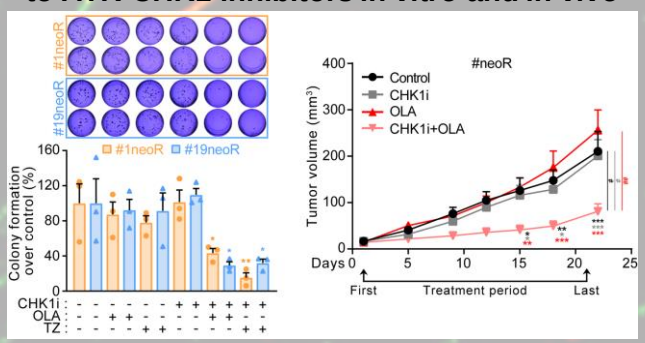




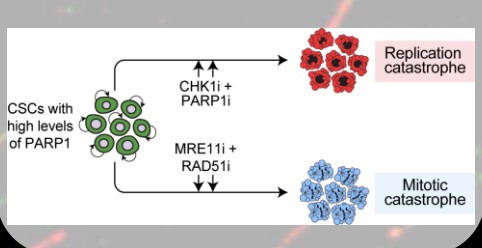
NeoR CRC-SCs display increased resistance to clinically-relevant DNA damage response (DDR) inhibitors and RS inducers



PARP1 inhibition reverts CRC-SC resistance to ATR-CHK1 inhibitors *in vitro* and *in vivo*



Proposed model for CRC-SC eradication



Conclusions: CRC-SCs resistant to therapeutically-relevant DDR inhibitors and RS inducers display low levels of RS and PARP1 upregulation and can be efficiently targeted by the combined inhibition of:
(i) CHK1 + PARP1, which provokes fork degradation and severe RS, resulting in lethal replication catastrophe,
(ii) RAD51 + MRE11, which deregulates RSR and mitosis, resulting in cell death via mitotic catastrophe.