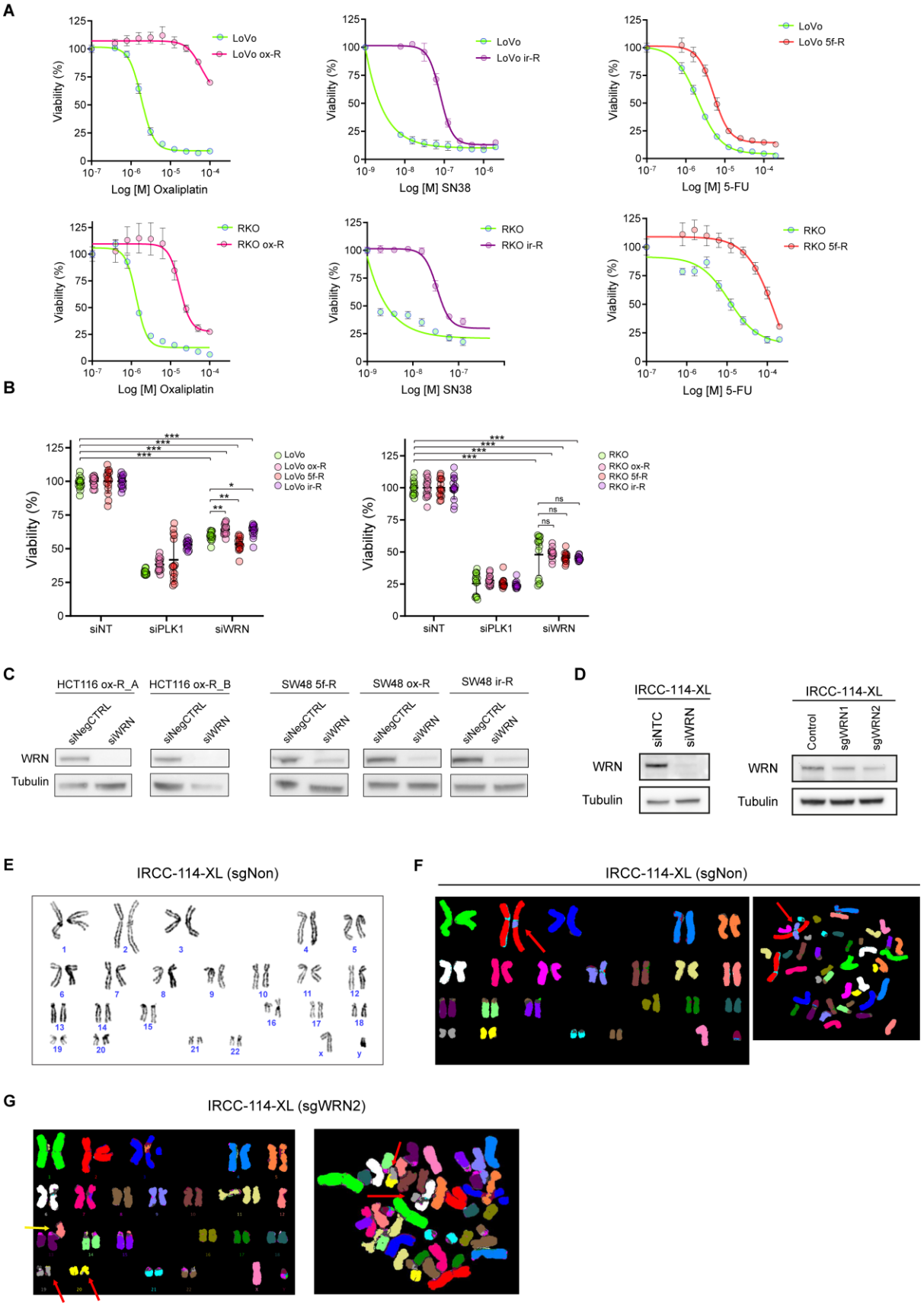


**Supplementary Figure S4:** ***Validation experiments in chemotherapy resistant models and IRCC-114_XL cells following WRN depletion.*** *A, Proliferation assays in Lovo and RKO*

*models of acquired resistance to chemotherapies and parental counterparts. Data are average ± SD of three technical replicates and are representative of three independent experiments. B, Normalized viability of upon siRNA-mediated WRN depletion in LoVo and RKO chemotherapy-resistant sublines. Non-targeting siRNA (siNT) and siPLK1 were used as negative and positive controls, respectively. Data are mean and SD of 2 independent experiments with 4 technical replicates each. Statistical significance was evaluated using a Student's t-test: ns, not significant; ** P≤0.01 *** P≤0.001.* ***C-D*** *Reduction in WRN protein levels in HCT116 and SW48 sublines and IRCC-114-XL cells confirmed by Western blot after siRNA-mediated depletion of WRN (left) or with two WRN-targeting sgRNAs (right) (representative of two independent experiments).* ***E****, Representative image of an IRCC-114-XL metaphase harvested 96h after transduction with non-targeting sgRNA (sgNon), karyotyped based on DAPI-banding patterns and visualized by microscopy. No chromosomal defects were detected.* ***F*** *and* ***G****, Metaphases of IRCC-114-XL cell line transduced with non-targeting sgRNA (F) and WRN-targeting sgRNA (G). Overlaps and complex rearrangements are indicated by red and yellow arrows, respectively. Metaphases have been imaged using SmartCapture and karyotyped using SmartType Karyotyper based on M-FISH and DAPI banding patterns.*