Expanded View Figures

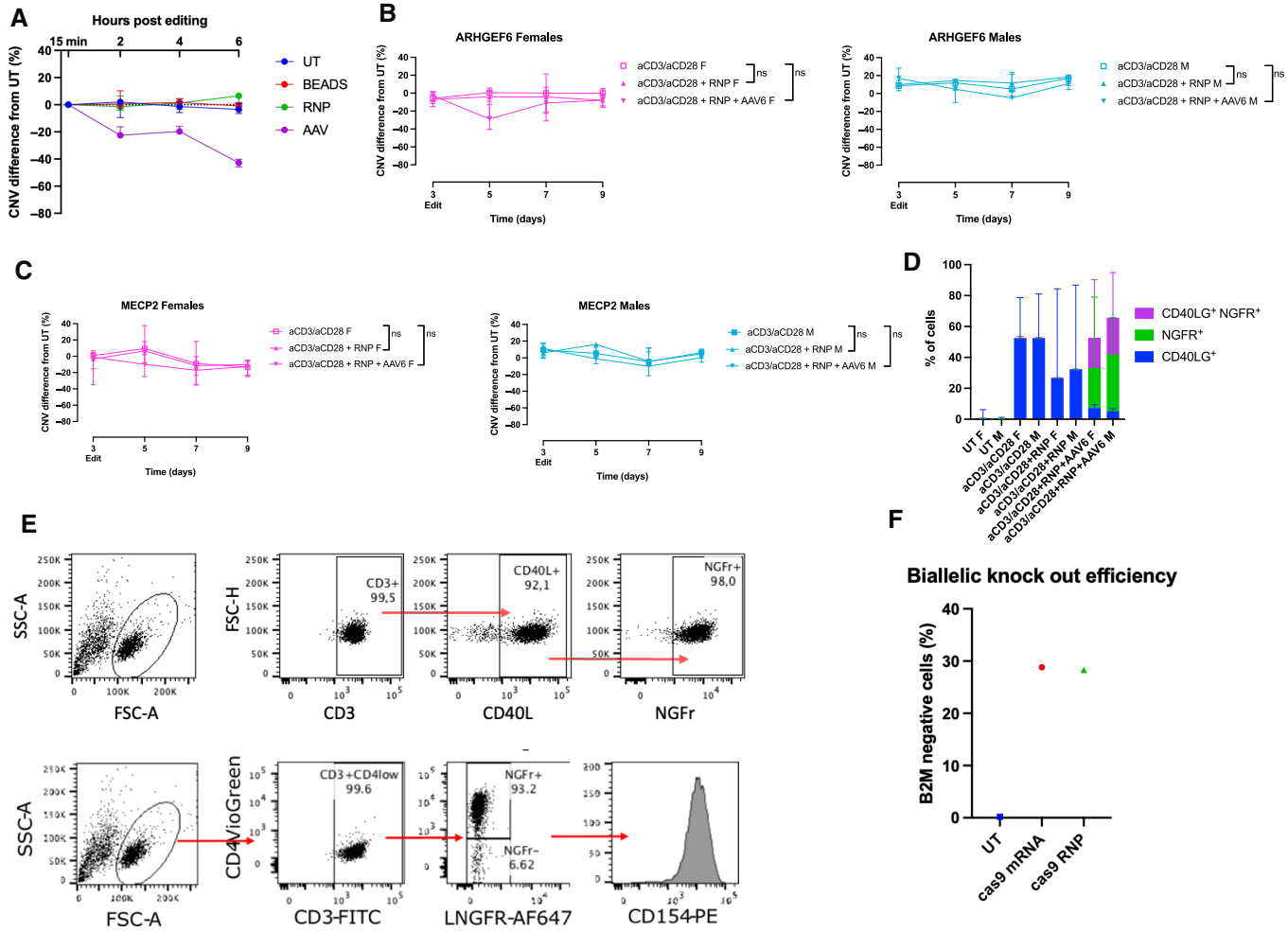

Figure EV1. On-target deletions in edited cells and gating strategies.

A–F Early timecourse of LNC00892 deletions (n = 2 male and 2 female donors; Median + IQR). Variation over time of *ARHGEF6* (B), or *MECP2* (C) copies/diploid genome in males (blue) and females (pink) with respect to untreated samples. Median + IQR. Kruskal–Wallis test for area under the curve, n = 5 males + 5 females (B) or n = 6 males + 6 females (C) Editing efficiency by flow cytometry at day 6–9 of Figs 1E, and EV1B and C. Median and range. M, male; F, female; RNP, ribonucleoprotein. (E) Gating strategies for CD40L and NGFR expression (F) Biallelic B2M knock-out efficiency by flow-citometry in bulk edited cells.

Source data are available online for this figure.

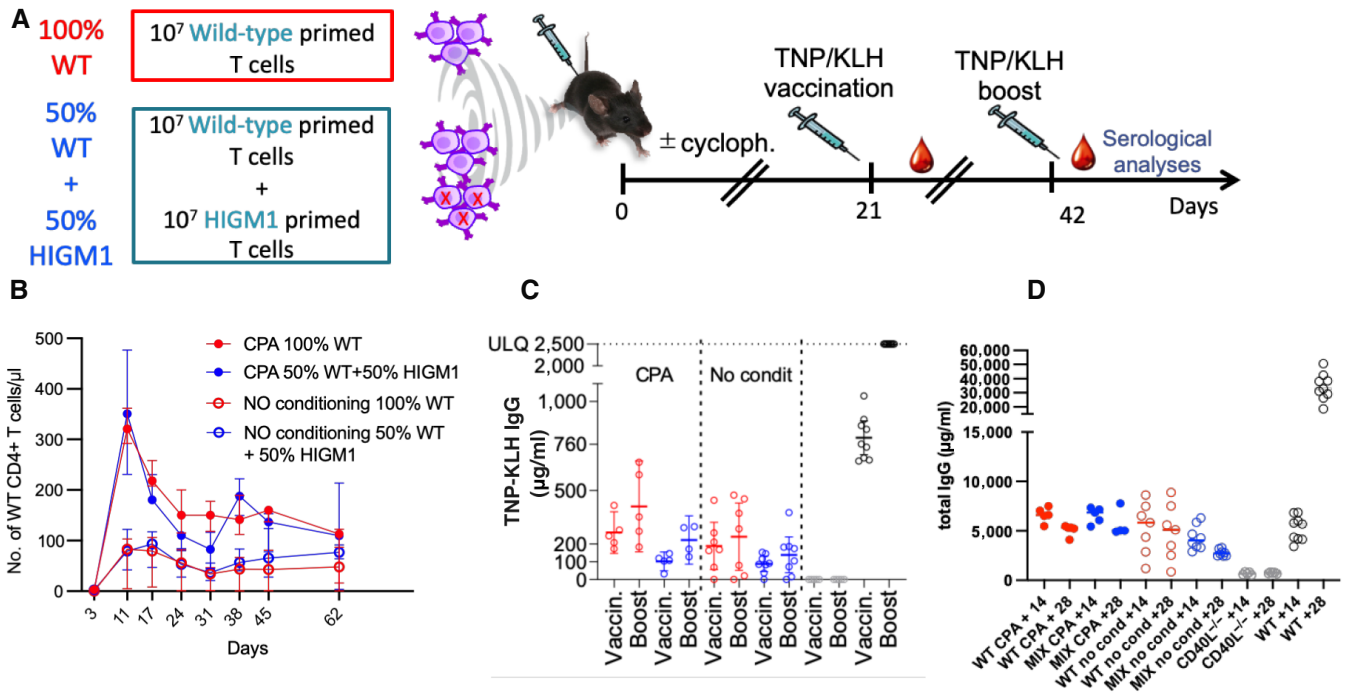

Figure EV2. Modeling selection of corrected cells in the murine model of Hyper IgM1.

A $CD4^+$ T-cells from HIGM1 and wild type (WT) mice were primed *in vivo* against 2,4,6, Trinitrophenyl Keyhole Limpet Hemocyanin (TNP-KLH). Fourteen days after vaccination $CD4^+$ T-cells were isolated from the spleen and activated *in vitro* with anti-CD3/antiCD28 beads as previously reported (Vavassori *et al*, 2021). Recipient HIGM1 mice either received 300 mg/kg of cyclophosphamide (CPA) or not, and were transplanted with 10^7 primed WT $CD4^+$ T-cells alone or 10^7 primed WT $CD4^+$ T-cells admixed with 10^7 primed HIGM1 $CD4^+$ T-cells. Mice were vaccinated with TNP-KLH 21 days and boosted 42 days after $CD4^+$ T cell infusion. Serum was collected 14 days after the first vaccination and 7 days after the second one.

B–D Absolute engraftment levels of WT $CD4^+$ T-cells by flow cytometry (C, D) TNP-KLH specific (C) and total IgG (D) production after the first vaccination (+14 days) and after boosting (+28 days) in the different subgroups. Gray circles indicate untreated HIGM1 mice, black circles untreated WT mice.

Source data are available online for this figure.

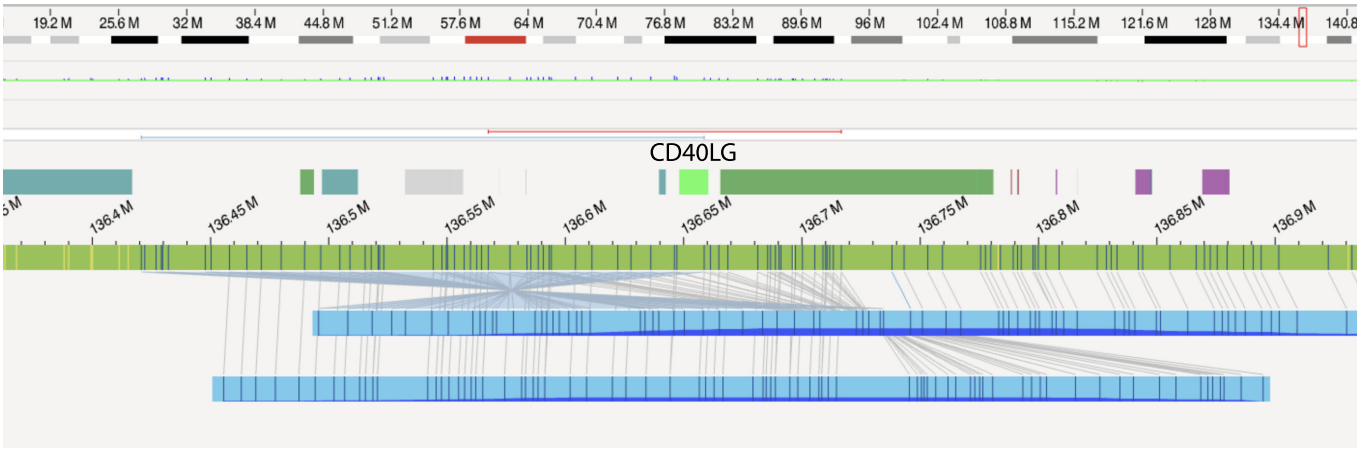

Figure EV3. Partially overlapping inverted duplication (bottom blue bar) and inversion (top blue bar) involving the Xq arm around the *CD40LG* locus.

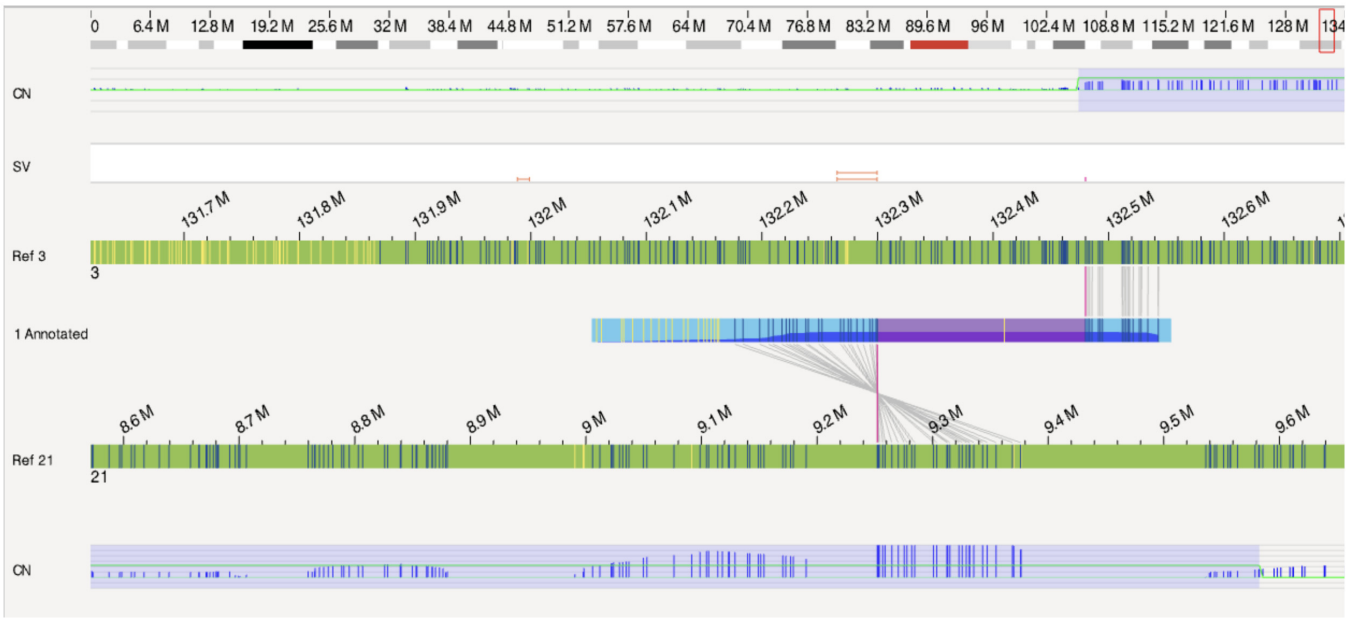

Figure EV4. Translocation between chromosome 3 and chromosome 21 [t(3;21)(q22.1;p11.2)].

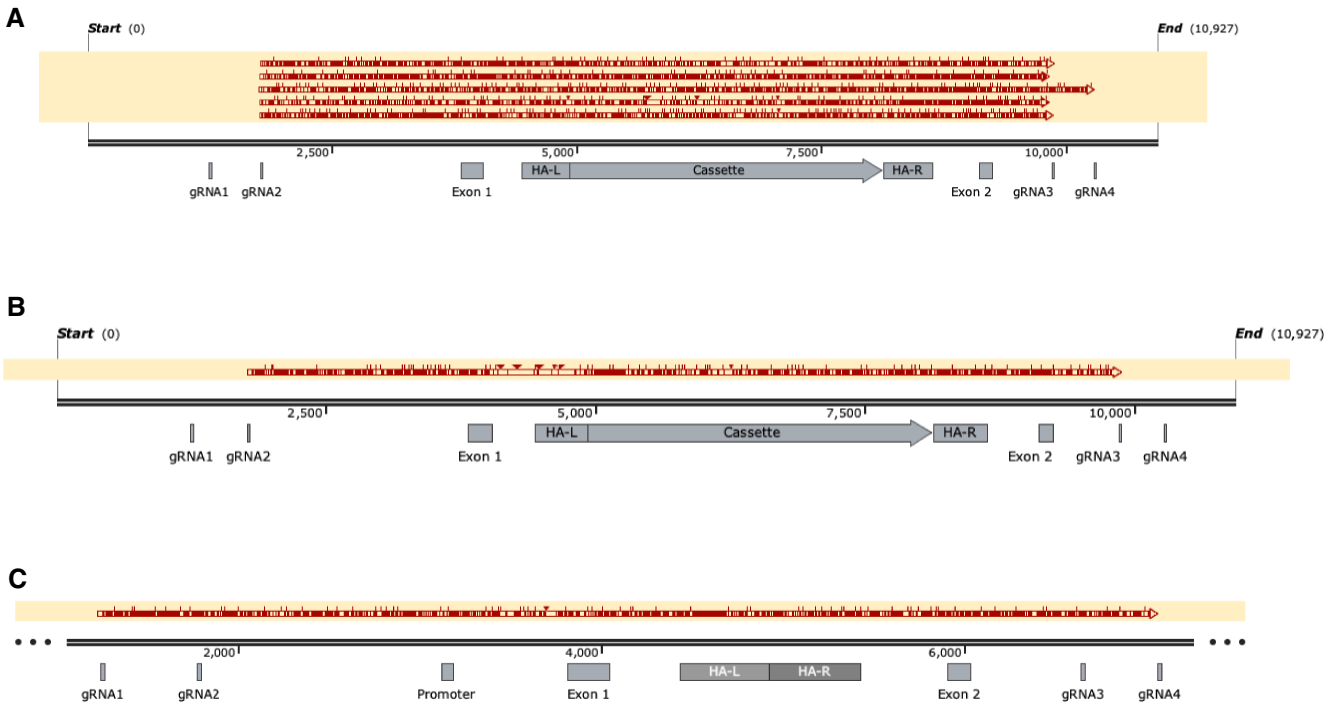

Figure EV5. Sequencing of the target *CD40LG* locus.

A–C Alignment of amplicons retrieved by nanopore sequencing, in red, to HDR (A) imprecise HDR (B) and native gene (C). gRNA1-4 indicate the positions of the gRNAs used for target sequence enrichment.