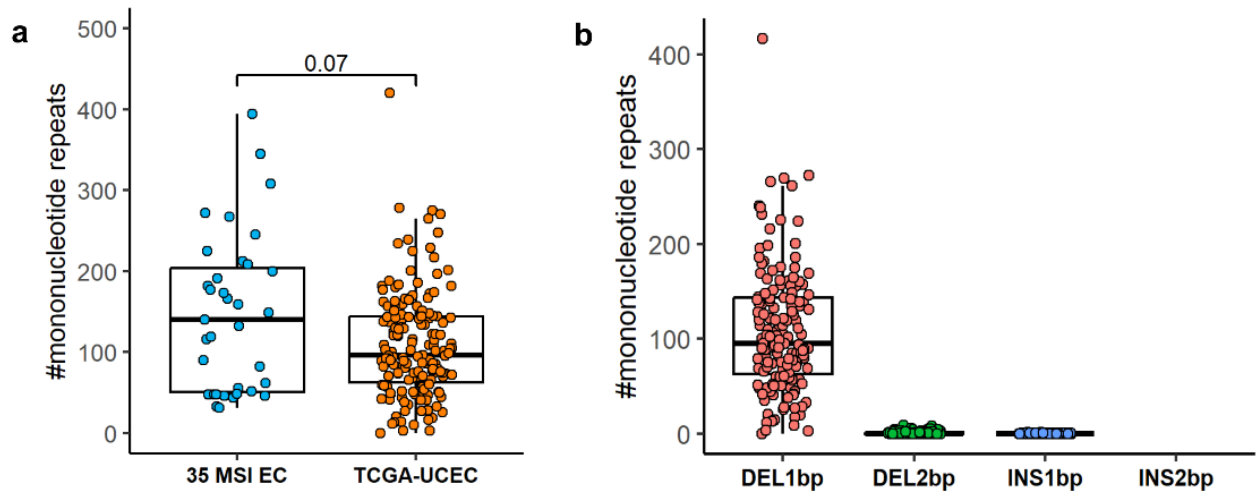


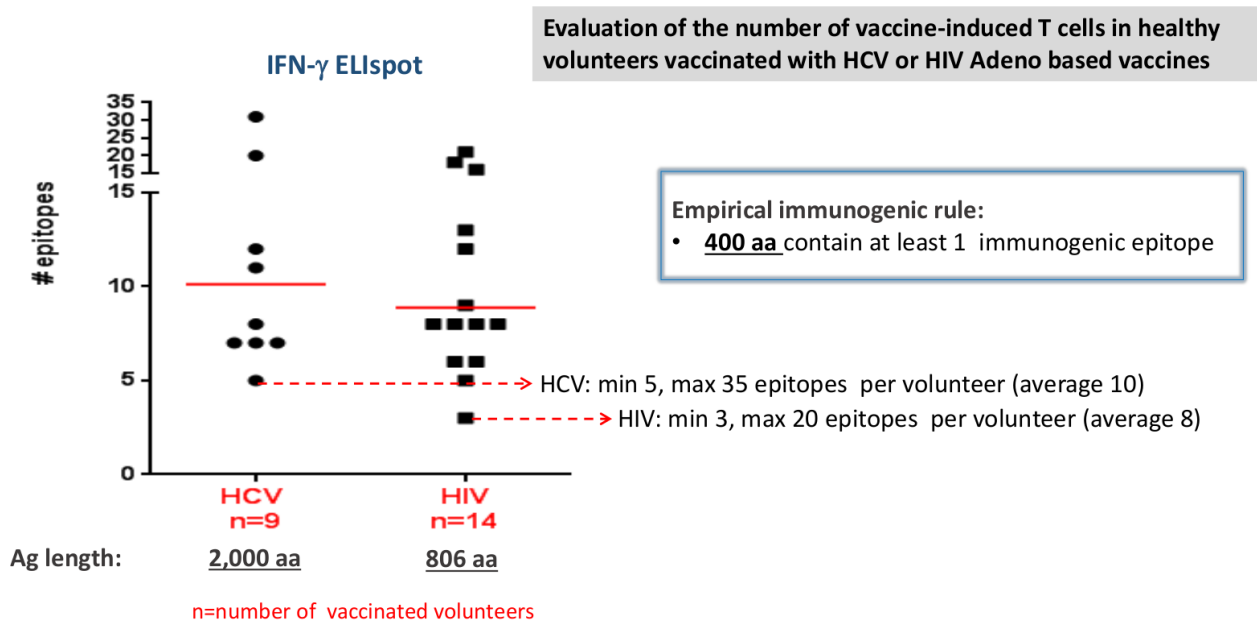
**Supplementary Figure 1. Landscape of mutated MNRs identified in the 35 MSI-h EC and endometrial TCGA cohorts.**

Panel a) Boxplot of MNRs identified in 35 EC patients and endometrial TCGA cohorts (n=160). Panel b) Boxplots representing the distribution and the abundance of the out-of-frame *indels* detected at mutated MNRs in endometrial TCGA cohort. **Footnotes:** **MNR:** mononuclear repeats; **EC:** endometrial cancer; **MSI:** microsatellite instability.

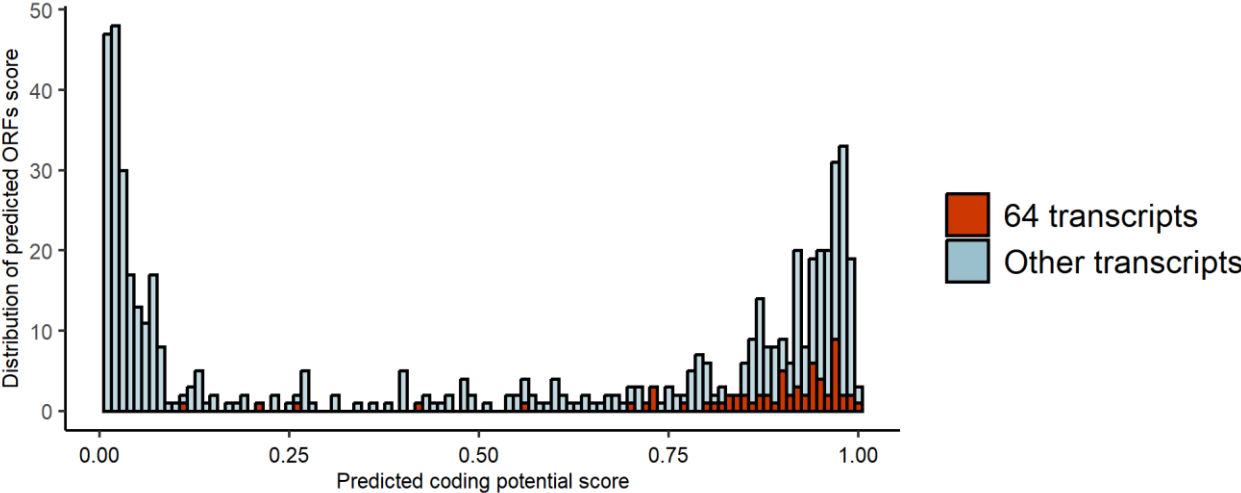


### Supplementary Figure 2. Number of immunogenic epitopes in healthy donors vaccinated with viral antigens.

The plot indicates the number of immunogenic epitopes detected in healthy donors (black dots) vaccinated with viral antigens from HCV and HIV viruses. The length of each antigen (black) and the mean number of immunogenic epitopes (red) are reported.



**Supplementary Figure 3.** 64 predicted ORFs with sequence context pipeline correspond to 38 FSP shared across 35 patients and AN3CA cell line (Exome-seq and Ribo-seq mapping).



**Supplementary table 1.** For each patient, the MMR status by IHC, the *MLH1*-promoter methylation assay, and the PCR-based MSI status were reported.

Patient ID	MMRd status	MLH1-promoter methylation	MSI status
NOU-01	PMS2 loss	-	MSI-L/MSS
NOU-02	PMS2 loss	-	MSI-L/MSS
NOU-03	MLH1/PMS2 loss	Hypermethylation	-
NOU-04	MLH1/PMS2 loss	Hypermethylation	-
NOU-05	MSH2/MSH6 loss	-	MSI-L/MSS
NOU-06	MLH1/PMS2 loss	Hypermethylation	-
NOU-07	MLH1/PMS2 loss	N/A	MSI-H
NOU-08	MLH1/PMS2 loss	Hypermethylation	-
NOU-09	PMS2 loss	-	MSI-H
NOU-10	MSH6 loss	-	Equivocal
NOU-11	MLH1/PMS2 loss	Hypermethylation	-
NOU-12 §	MLH1/PMS2 loss	-	-
NOU-13	MLH1 loss	Unmethylated	Equivocal
NOU-14	MLH1/PMS2 loss	Hypermethylation	-
NOU-15* §	MSH6 loss	-	-
NOU-16*	PMS2 loss	-	MSI-H
NOU-17	MLH1/PMS2 loss	Hypermethylation	-
NOU-18	MLH1/PMS2 loss	N/A	MSI-H
NOU-19	PMS2 loss	-	MSI-H
NOU-20	MLH1/PMS2 loss	Hypermethylation	-
NOU-21	MLH1/PMS2 loss	Hypermethylation	-
NOU-22	MLH1/PMS2 loss	Hypermethylation	-
NOU-23	PMS2 loss	-	MSI-L/MSS
NOU-24	MLH1/PMS2 loss	Hypermethylation	-
NOU-25	MLH1 loss	Hypermethylation	-
NOU-26	MLH1/PMS2 loss	Hypermethylation	-
NOU-27*	MSH2 loss	-	MSI-H
NOU-28	MLH1/PMS2 loss	N/A	MSI-H
NOU-29	MLH1/PMS2 loss	N/A	MSI-H
NOU-30*	MLH1/PMS2 loss	Unmethylated	MSI-H
NOU-31	MLH1 loss	Hypermethylation	-
NOU-32	MLH1/PMS2 loss	Hypermethylation	-
NOU-33	MLH1 loss	Hypermethylation	-
NOU-34	MLH1/PMS2 loss	Hypermethylation	-
NOU-35	PMS2 loss	-	MSI-H

\* Germline test for mismatch repair multigene panel available. The NOU-15 resulted as carrier of a *MSH6* germline mutation.

§ Tissue sample not available

**Footnotes:** **MMRd:** Mismatch Repair deficiency; **MSI-L/MSS:** instability at a single locus or no instability at any of the loci; **MSI-H:** microsatellite instability at  $\geq 2$  loci; **IHC:** immunohistochemistry; **N/A:** Not Available.

**Supplementary table 2.** In table is reported the frequency of observation of NOUS209 targeted mutations in the cohort of 35 MSI EC.

<b>NOUS209 FSP</b>	<b>#Pts</b>	<b>Percentage</b>
<b>FSP_RPL22_1_chr1:6257785-6257785</b>	15	42,9
FSP_SETD1B_1_chr12:122242658-122242658	13	37,1
FSP_SMAP1_1_chr6:71508370-71508370	13	37,1
FSP_JAK1_1_chr1:65306997-65306997	12	34,3
FSP_COBL1_1_chr2:165551296-165551296	11	31,4
FSP_DOCK3_1_chr3:51417604-51417604	10	28,6
FSP_NBEAL1_1_chr2:203922058-203922058	9	25,7
FSP_NDUFC2_1_chr11:77784147-77784147	9	25,7
FSP_SLC35G2_1_chr3:136573486-136573486	9	25,7
FSP_ABCC5_1_chr3:183665257-183665257	9	25,7
FSP_PHACTR4_1_chr1:28785730-28785730	8	22,9
FSP_UVRAG_1_chr11:75694431-75694431	8	22,9
FSP_THAP5_1_chr7:108205526-108205526	8	22,9
FSP_RNF43_1_chr17:56435161-56435161	7	20,0
FSP_INPPL1_2_chr11:71948748-71948748	7	20,0
FSP_TEAD2_1_chr19:49850473-49850473	7	20,0
FSP_PHF2_1_chr9:96422612-96422612	7	20,0
FSP_MXRA8_1_chr1:1290110-1290110	6	17,1
FSP_SRPR_1_chr11:126137087-126137087	6	17,1
FSP_RAD50_1_chr5:131931452-131931452	6	17,1
FSP_GLTSCR1_1_chr19:48197891-48197891	6	17,1
FSP_KMT2C_1_chr7:151874148-151874148	6	17,1
FSP_JPH4_1_chr14:24040436-24040436	5	14,3
FSP_MNS1_1_chr15:56736723-56736723	5	14,3
FSP_CHD3_1_chr17:7798765-7798765	5	14,3
FSP_GBP3_1_chr1:89473442-89473442	5	14,3
FSP_SGOL1_1_chr3:20216050-20216050	5	14,3
FSP_SYNJ2_1_chr6:158508009-158508009	5	14,3
FSP_TMEM97_1_chr17:26653807-26653807	5	14,3
FSP_DNA2_1_chr10:70182521-70182521	5	14,3
FSP_TTK_1_chr6:80751897-80751897	5	14,3
FSP_DNAH12_1_chr3:57509313-57509313	5	14,3
FSP_ZNF365_1_chr10:64159513-64159513	5	14,3
FSP_ICA1_1_chr7:8198251-8198251	4	11,4
FSP_RFC3_1_chr13:34398063-34398063	4	11,4
FSP_LMAN1_1_chr18:57013194-57013194	4	11,4
FSP_ADD3_1_chr10:111893350-111893350	4	11,4
FSP_TVP23A_1_chr16:10867203-10867203	4	11,4
FSP_DYNC1I2_1_chr2:172549339-172549339	4	11,4
FSP_RGS12_1_chr4:3430399-3430399	4	11,4
FSP_SMAD7_1_2_chr18:46474795-46474795	4	11,4

FSP_ACVR2A_1_chr2:148683686-148683686	4	11,4
FSP_WDTC1_1_chr1:27621108-27621108	4	11,4
FSP_MIS18BP1_1_chr14:45693722-45693722	4	11,4
FSP_MSH3_1_chr5:79970915-79970915	4	11,4
FSP_XPOT_1_chr12:64812755-64812755	4	11,4
FSP_WDR55_1_chr5:140049102-140049102	3	8,6
FSP_TTC3_1_chr21:38524243-38524243	3	8,6
FSP_OFD1_1_chrX:13764946-13764946	3	8,6
FSP_PRRG1_1_chrX:37312611-37312611	3	8,6
FSP_AP1S1_1_chr7:100802405-100802405	3	8,6
FSP_SLC3A2_1_chr11:62649529-62649529	3	8,6
FSP_EBPL_1_chr13:50235209-50235209	3	8,6
FSP_TCEB3_1_chr1:24078404-24078404	3	8,6
FSP_LRRIQ3_1_chr1:74575213-74575213	3	8,6
FSP_RBM45_1_chr2:178988920-178988920	3	8,6
FSP_CEBPZ_1_chr2:37454908-37454908	3	8,6
FSP_SREK1IP1_1_chr5:64023941-64023941	3	8,6
FSP_TCERG1_1_chr5:145886723-145886723	3	8,6
FSP_SPINK5_1_2_3_chr5:147499875-147499875	3	8,6
FSP_CCDC28A_1_chr6:139097330-139097330	3	8,6
FSP_TMEM60_1_chr7:77423460-77423460	3	8,6
FSP_BRD3_1_chr9:136918529-136918529	3	8,6
FSP_CD3G_1_chr11:118220583-118220583	3	8,6
FSP_PRDM2_1_chr1:14108749-14108749	3	8,6
FSP_KIAA2026_1_chr9:5968044-5968044	3	8,6
FSP_KCNMA1_1_chr10:78729786-78729786	3	8,6
FSP_KNOP1_1_chr16:19725706-19725706	3	8,6
FSP_CHRM3_1_chr1:240072444-240072444	3	8,6
FSP_IGF2R_1_chr6:160485488-160485488	3	8,6
FSP_UPF3A_1_chr13:115057211-115057211	3	8,6
FSP_CCDC181_1_chr1:169366580-169366580	3	8,6
FSP_FXR1_1_chr3:180666228-180666228	3	8,6
FSP_TBC1D23_1_chr3:100039736-100039736	3	8,6
FSP_EPHB2_1_chr1:23240246-23240246	3	8,6
FSP_MDN1_1_chr6:90432675-90432675	3	8,6
FSP_ATR_1_chr3:142274740-142274740	3	8,6
FSP_LRRC17_1_chr7:102584993-102584993	3	8,6
FSP_VCP_1_chr9:35059647-35059647	3	8,6
FSP_LRPPRC_1_chr2:44145165-44145165	3	8,6
FSP_EIF2B3_1_chr1:45407182-45407182	2	5,7
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FSP_LARP4B_1_chr10:890939-890939	2	5,7
FSP_CWF19L2_1_chr11:107325228-107325228	2	5,7
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FSP_AKAP7_1_chr6:131481276-131481276	2	5,7
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FSP_JARID2_1_chr6:15496722-15496722	2	5,7
FSP_SEC63_1_chr6:108214755-108214755	2	5,7
FSP_ZDBF2_1_chr2:207174428-207174428	2	5,7
FSP_ATF5_1_chr19:50434211-50434211	2	5,7
FSP_ARV1_1_chr1:231131567-231131567	2	5,7
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FSP_WBP1_1_chr2:74687410-74687410	2	5,7
FSP_C9orf114_1_chr9:131591120-131591120	2	5,7
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FSP_NSD1_1_chr5:176675269-176675269	2	5,7
FSP_GLYR1_1_chr16:4862229-4862229	2	5,7
FSP_ZMYM4_1_chr1:35846960-35846960	1	2,9
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FSP_PDS5B_1_chr13:33344580-33344580	1	2,9
FSP_KIAA1024_1_chr15:79750586-79750586	1	2,9
FSP_ZNF563_1_chr19:12430217-12430217	1	2,9
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FSP_CARD11_1_chr7:2968323-2968323	1	2,9
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