Supplementary Table S1. List of HR and NHEJ targets for siRNA knock-down.

Pathway	Target	References
NHEJ	Ku70/Ku80	Walker et al., 2001
	DNA-PKcs	Allen et al., 2002; Dobbs et al., 2010; Sipley et al., 1995
	LigIV	Critchlow et al., 1997
	Xrcc4	Critchlow et al., 1997; Li et al., 1995
	53BP1	Xie et al., 2007
HR	MDC1	Stucki et al. 2005; Zhang et al. 2005; Lou et al. 2006; Xie et al. 2007
	Rad51	Benson et al. 1994; Baumann and West 1998; Vispé et al. 1998; Arnaudeau et al. 1999
	Rad51B, Rad51C, Rad51D, Xrcc2, Xrcc3	Cartwright et al. 1998; Pittman et al. 1998; Masson et al. 2001; Takata et al. 2001; Lio et al. 2004; Liu et al. 2004; Suwaki et al. 2011
	Rad52	Van Dyck et al. 1998; Van Dyck et al. 1999; Feng et al. 2011
	Rad54	Essers et al. 2002; Heyer et al. 2006
	Brca1	Yoshida and Miki 2004; Cousineau et al. 2005
	Bard1	Wu et al. 1996
	Brca2	Davies et al. 2001; Moynahan et al. 2001; Yoshida and Miki 2004; Liu et al. 2010; Feng et al. 2011
	MRN (MRX in yeast)	Stracker and Petrini 2011
	CtIP	Yu and Chen 2004; Sartori et al. 2007; You et al. 2009
	Cyclin D1	Li et al. 2010; Jirawatnotai et al. 2011

Supplementary Table S2. List of MMEJ targets for siRNA knock-down.

Target	References
MRN (MRX in yeast)	Ma et al. 2003; Zhang and Paull 2005; Lee and Lee 2007; Dinkelmann et al. 2009; Della-Maria et al. 2011
CtIP	Yun and Hiom 2009; Wang et al. 2012
PARP1	Audebert et al. 2004
Ercc1/Xpf (Rad1/Rad10 in yeast)	Ma et al. 2003; Lee and Lee 2007
Ligase I	Liang et al. 2008; Crespan et al. 2012; Paul et al. 2013; Oh et al. 2014
Ligase III (absent in yeast)	Audebert et al. 2004; Liang et al. 2008; Della-Maria et al. 2011; Paul et al. 2013; Oh et al. 2014
Xrcc1 (absent in yeast)	Della-Maria et al. 2011
DNA Polymerase delta subunit 3 (POLD3) (POL32 in yeast)	Lee and Lee 2007; Costantino et al. 2014
DNA Polymerase theta (POLQ) (absent in yeast)	Yu and McVey 2010; Koole et al. 2014; Kent et al. 2015

Supplementary Table S3. siRNA sequences.

Target gene	Name and sequence of the oligo sense strand
Negative control	Neg_1 AGGUAGUGUAAUCGCCUUG Neg_2 GACGACUCACAUACGUAAA Neg_3 GAAUAUAUCGCGAAAUGUA
Ku70	Ku70_1 GGUGCCCUUUACUGAGAAA Ku70_2 AAAGCCCAAGGUAGAGUUA Ku70_3 ACAUUUCCAAGACACAAUU
Ku80	Ku80_1 GAAACUGUCUAUUGCUUAA Ku80_2 CCAUAGGGAAGAAGUUUGA Ku80_3 GGAUUCCUAUGAGUGUUUA
DNA-PKcs	DNA-PKcs_1 GGAUCGAGCUGUUCAGAAA DNA-PKcs_2 AGAUGAUGUUCACUCUAAA DNA-PKcs_3 AUCCAUCGGUAUCUUUAAA
DNA Ligase IV	LigIV_1 AGAGCCUCCUUCAGUUAAU LigIV_2 CUAUACAGCAGGUAAAUGA LigIV_3 AGAGGUAUGAUAUCCUUAA
Xrcc4	Xrcc4_1 AUAUGCUGAUGAAUUGAGA Xrcc4_2 CUGAAAGAUGUCUCAUUUA Xrcc4_3 AUGAGCACCUGCAGAAAGA
53BP1	53BP1_1 UCAGAAUGAUGACAAAGUA 53BP1_2 GAGCAAGGAGACAAUAAUA 53BP1_3 CAAAGACAUCCCUGUUACA
Cyclin D1	CycD1_1 UGGAACUCCUUCUGGUGAA CycD1_2 CGCACUUUCUUUCCAGAGU CycD1_3 UGCCAGAGGCGGAUGAGAA
MDC1	MDC1_1 ACAGCAUGCAGUAAUUGAA MDC1_2 GGAAGAAGAUCCUGAGGAA MDC1_3 CACGGAAAUGGGUGAAGAA
Rad51	Rad51_1 GUGCCAAUGAUGUGAAGAA Rad51_2 GGGAAUUAGUGAAGCCAAA Rad51_3 GGCGUUCAGAAAUCAUACA
Rad51B	Rad51b_1 ACAGCCUAUGAUAUAAAGA Rad51b_2 CAAGUUCUUGGCCAAACAA Rad51b_3 GUACCUGGCUGAGGAAUUU
Rad51C	Rad51c_1 UGAUCAGCCUGGCAAAUAA Rad51c_2 AGAGGAAGCUUUAGAAACU Rad51c_3 GGAUGAAGAACACCAGAAA
Rad51D	Rad51d_1 ACGGAGCAGACCUAUAUGA Rad51d_2 CCCAAGAUGAGGAGAAACA Rad51d_3 GCCUGGACAAACUACUUGA
Xrcc2	Xrcc2_1 GAAGUGUUCUCAGCUCCUA Xrcc2_2 CAACACAAAGUCUAAUGCA Xrcc2_3 AUCAGAGGGUGGACUGCAA

Supplementary Table S3. siRNA sequences (continued).

Rad52	Rad52_1 UGAGAUGUUUGGUUACAAU Rad52_2 ACUGCAUUCUGGACAAAGA Rad52_3 CCCUGAAGACAACCUUGAA
Rad54	Rad54_1 AGAAGACCUGCUAUAUUUA Rad54_2 CAUCAGAUAUCCUCUCUAA Rad54_3 GAAGCUAUGUAACCAUCCA
Brca1	Brca1_1 CCACGUAACUGAAAUUAUA Brca1_2 AAGGCUGAGUUCUAUAAUA Brca1_3 AGAGCCAAAUGAACAAAGA
Bard1	Bard1_1 GAACGGCCAUGUGGAUAUA Bard1_2 ACAGACAAUUGGACAACAU Bard1_3 GCAGCAGAAGAAAUCUUUA
Mre11	Mre11_1 AGAUGCAGUUCGAGGAAAU Mre11_2 AAACAGGUGAAGAGAUCAA Mre11_3 UUACUCAGAGACUAUUGAA
Nbs1	Nbs1_1 GAAACAGCCUCCAGAAAUU Nbs1_2 CAAUUGAUUUGGCUAUAGA Nbs1_3 AAACUGUGCCAUUCUGAUA
Rad50	Rad50_1 UAAUGAGACUUGACAAUGA Rad50_2 ACACUCUUGGGUACAAUAA Rad50_3 ACAGAACUCCUCACUAAGA
CtIP	CtIP_1 GUGCAAGGUUUACAAAUAA CtIP_2 CAAAGUCCCUGCCAAACAA CtIP_3 AGAAUACUCUCCAGGAAGA
PARP1	PARP1_1 AGGAGUUGCUUAUCUUCAA PARP1_2 UAUCCUACCUCAAGAAAUU PARP1_3 UGACACCUGCCUACUAUAU
DNA polymerase θ	Poltheta_1 UCAGUGAAAUUCCCUUAAA Poltheta_2 GUUCAGGGCUACUUAUAAA Poltheta_3 CGAAAGGCCUAAAUUAACA
Pold3	POLD3_1 AACAGAUGCUCUAUGAAUA POLD3_2 CCAAAGCAGAGGCUAAAGA POLD3_3 ACGAAAGCGUGUACUGAAA
Xpf1	Xlf1_1 GUAGAAUACUUGUGGUUGA Xlf1_2 GAACCCUACUGCAGUAUCU Xlf1_3 GAAGUGUGGGUGAAUCUUA
Ercc1	Ercc1_1 ACGGGAGCGAAAUCCAAUA Ercc1_2 GUUUGUGAUCCCACUGGAA Ercc1_3 GCCCUUAUUCAGAUCCUCA
Xrcc1	Xrcc1_1 GCGCUGGGACCGUGUUAAA Xrcc1_2 ACUGGACUUGAAUCUAGAA Xrcc1_3 GCUUAUCCGAUACGUUACA
DNA Ligase I	Ligase 1_1 UUACAAUCCUUCCAAGAGA Ligase 1_2 AGACAUGGUUGGAAGAACA Ligase 1_3 AAGGAAGAAGGAAGAAGAA
DNA Ligase III	LigIII_1 UCACUGGCCUGUCAUAAGA LigIII_2 GCACAAAGACUGUCUACUA LigIII_3 AAUCCUAGCUACAAUACAA

Supplementary Table S4. Sequences of the DNA junctions of Immunoglobulin expression vector genomic integration sites (part 1).

Clone	Integration site #	Junction side		Sequence[1]	Mechanism[2]	Integration in/near a gene[3] expressed (yes/no)	Deletion in the genome (size)	Templated insert[4] (size)
BS01	1	Left	junction	GCGAGCAGAACGGAGACTGAAGGGGTGGGGCCGCGGCCGACAATGGGCGGGGGTCGTTGGGCGGTCAGCCAGGCGGGCCATTTACCGTAAGTTATGTAACGCGGAATGGCGAATGGCAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTAAATCAGCTCATTTTTTAACCAATA	SD-MMEJ (5 nt)	Ssh3 (exon), yes (RPKM=3)	no	yes (66bp)
			genome	...CTATTGTCCTTGCTC(206bp)TGGGGCCGCGGCCGATCGG...	(IR and DR)			
			vector frgm 1	...TTATTGACGTCAATGGGCGGGGGTCGTTGGGCGGTCAGCCAGGCGGGCCATTTACCGTAAGTTATGTAACGCGGAACTCCATATATGGGCTATGA...	MMEJ (3 nt)			
			vector frgm 2	...CCTGAATGGCGAATGGCAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTAAATCAGCTCATTTTTTAA...				
		Right	junction	AAAATACAAAAATTAGCCAGGTGTGTCGAATGGACAACCCGAGAATAACTATAAGACGACGCCACCCGTCCTTGATAGCGACGGTTCCTTTTTCTTGTACAGCAAACTGACGGTGGACAAATCAAGATCGGTGCGAGCTCTGTGGGGCCGGACTGGGCACCAGTC	SD-MMEJ (4 nt)			yes (100bp)
			vector frgm 1	...ACCCTGTCTC(24bp)GGTGTGGTGG...	(DR)			
			vector frgm 2	...AGACATTGCGGTAGAGTGGGAGTCGAATGGACAACCCGAGAATAACTATAAGACGACGCCACCCGTCCTTGATAGCGACGGTTCCTTTTTCTTGTACAGCAAACTGACGGTGGACAAATCAAGATGGCAGC...	MMEJ (3 nt)			
			genome	...GGCCGATCGGTGCGAGCTCTGTGGGGCCGGACTGGGCACCAGTCGGGCCCTTTAAGGGCCGCTCCCGA...				
	2	Left	junction	AAAATCCCCGCCCTTTGCTGGCGGCTCGGCGGTCGATGATGCCTCTTCGCTATTACGCCAGCCCAAGCTACCATGATAAG	SD-MMEJ (10 nt)	Dph1 (exon), yes (RPKM=18)	no	yes (3bp)
			genome	...ATCCCCGCCCTTTGCTGGCGGCTCGGCGGTCGATCG...				
			vector	...ATCGGTGCGGGCCTCTTCGCTATTA(1103bp)CTTGGTTGACGGCAATTTCGATGATGCAGC...				
		Right	junction	TTAAGGTAATCTTAAGTAGAAGAGATAGAGTTTAGAATTTTTTAATCGTGCTGCCTGGGTTCTCCGCGTTCCTCCAGCGC	SD-MMEJ (5 nt)			no
			vector	...AGGTAATCTTAAGTAGAAGAGATAGAGTTTAGAATTTTTTAAATTTATCTCT...	(DR)			
			genome	...CGATCGTGCTGCCTGGGTTCTCCGCGTTCCTCCAGCGCTGCCTTTTTGGTC...				
	3	Left	junction	AAATTATACTGAGTAAGGTAACTCTGGACCAGAAATGAGAATCGACCGATGCCCTTGAGAGCCTTCAACCCAGTCAGCTC	MMEJ (2nt)	intergenic (404.9kb from nearest gene)	n.a.[5]	no
			genome	...TTATACTGAGTAAGGTAACTCTGGACCAGAAATGAGAATGACCTGTGTT...	SD-MMEJ (4 nt)			
			vector	...CAGCAGCATAGGGATCCGTCGATCGACCGATGCCCTTGAG(25bp)CGGTGGGCGCGGGGCATGACTATCGTCG...	(IR or DR)			
	4	Left	junction	GTCCCTACCCGCCTCCTGGCGCTGGTCTCCGACTTGGAGCGGCCCTGCATCTCAATTAGTCAGCAACCATAGTCCCGCCC	SD-MMEJ (4 nt)	10.9kb from lin-54 homolog, yes (RPKM=4)	n.a.	no
			genome	...CCTACCCGCCTCCTGGCGCTGGTCTCCGATCGGTCCTCCAGAGCGCGCG...	(IR or DR)			
			vector	...ACGGGAGGTACTTGGAGCGGCCCTGCATCTCAATTAGTCAGCAAC(68bp)ATCGCTGACTAATTTTTTTT...				
	5	Right	junction	ATGGTAGCTTGGGCTGGCGTAATAGCGAAGAGGCCCGCACCGGCGGGCCAATTTCTTTATGCATATCGCTGTGTCCTAGG	SD-MMEJ (6 nt)	Ankzf1 (exon) , yes (RPKM=2)	n.a.	yes (2bp)
			vector	...TGGGCGGAGTTAGGGGCGGGACTATGGT(103bp)ACCGATCGCCCTT...	(DR)			
			genome	...TTTTCAAAAATGCCCAGGGCCAATTTCTTTATGCATATCGCTGTGTCCTAGGCCCTCGACAGGCA...				
	6	Right	junction	ACATTCGACGATTATGCGATGCATTGGGTTCGTCAGATGAGGCTCTACAAGGTGAAATGTCTTCTTGCAGAGCCTCTCTA	MMEJ (4 nt)	16.5kb from Amigo1, no (RPKM=0)	n.a.	no
			vector	...TTCGACGATTATGCGATGCATTGGGTTCGTCAGGCGCCTGGGAAGGGTC...	SD-MMEJ (6 nt)			
			genome	...TACTCTTTCGAGGGCTCAGTCCTATCAGATGAGGCTCTACAAGGTGAAATGTC(76bp)CTCTCTGACACGACTACCTCTTTCTC...	(IR)			

Supplementary Table S4. Sequences of the DNA junctions of Immunoglobulin expression vector genomic integration sites (part 2).

Clone	Integration site #	Junction side		Sequence[1]	Mechanism[2]	Integration in/near a gene[3] expressed (yes/no)	Deletion in the genome (size)	Templated insert[4] (size)
BS03	1	Left	junction	TAATGCGTCCTTGCTTTGCTCTGAGCGCTTCTTGTCTCGAACAGGGGGGGTGGTCTTGTAGTTGTTCTCGGGCTGTCCGT	SD-MMEJ (5 nt) (IR)			no
			genome	...TGCGTCCTTGCTTTGCTCTGAGCGCTTCTTGTCTCGATCGACACCCT...				
			vector	...GGAGTCCAGCACAGGGGGGGTGGTCTTGTAGTTGTTCTCGGGCTGTCCGTTGGACTCCCATTC...		**17.9kb from Bahcc1,** yes (RPKM=5)	yes (~913 bp)	
		Right	junction	GGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGGGGTGGGGAGCCAAGCCGCGGCGAGAGCGCAAAGCCCGCG	MMEJ (5nt) SD-MMEJ (5 nt) (DR)			no
			vector	...GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCCCACCCCAC...				
			genome	...CGATCGGCCCGCAGGGGGTGGGGAGCCAAGCCGCGGCGAGAGCGCAAAGCCCGCG...				
	2	Right	junction	GGCGAAGGGGCTCCTTAAGCGCAAGGCCTCGAACTCTCCCTCGCTTGAGTGCGGGGTCAGCTCAGGAAACCCTGTCTCTT	SD-MMEJ (5 nt) (DR)			n.a.
			vector	...GAAGGGGCTCCTTAAGCGCAAGGCCTCGAACTCTCCCACCCACTTCC...		**1kb from C17orf70,** yes (RPKM=6)	n.a.[5]	
			genome	...TGGGGCACGATCGCTTGAGTGCGGGGTCAGCTCAGGAAACCCTGTCTCTTAAAAACCTTAAGC...				
Cp33/64	1	Left	junction	GCTTTTCTAACTTAAATTATCTGGTTTCTCTTTAACTACAATGCTGCTGGTTTACAGACCACATGTAGAGTGGCAATGTG	MMEJ (2nt) SD-MMEJ (6 nt) (DR)			no
			genome	...TTTCTAACTTAAATTATCTGGTTTCTCTTTAACTACAATTTGCCTCT...				
			vector	...GGGCATCGGTCGATCGACGGATCCCTATGCTGCTGGTTTACAG(147bp)TTTAGCAAGACAGTGATAATGCTAATATG...		**Cblb (intron),** yes (RPKM=2)	yes (320 bp)	
		Right	junction	TGCCATCCAGCACATTGCCACTCTACATGTGGTCTGTAAACCAGCAGCATACAGCATAAACAAATGTAACACAACTTAAA	SD-MMEJ (5 nt) (DR)			no
			vector	...TGAAATTACAATACAAATGATGAT(100bp)TGTAAACCAGCAGCATAGGGATCCGTCGAT...				
			genome	...CAAATGTTCCACAGCATAAACAAATGTAACACAACTTAAACTAATATTTCACA...				
	2	Left	junction	GCCCTGCCACTTTGAACATACTTTCTTGTTTACTTATTACTATTTTCCTTTTATATGTTTAAATCATCATTTGTATTGTAATTTCATCTTCCA	SD-MMEJ (5 nt) (DR)			yes (1nt)
			genome	...CTGCCACTTTGAACATACTTTCTTGTTTACTTATTATGTTTATCCC...				
			vector	...GAACAATTTTTATTTTCCTTTTATATGTTTAAATCATCATTTGTATTGTAATTTCATCTTCCA...		**intergenic** (118.4kb from nearest gene)	no	
		Right	junction	ACCTCCCGTACCTTAATATTACTTACTTATCATGGTAGCTTGTTTATCCCTTAGTCTTCCCACTCCTGACTTGAATGCTT	MMEJ (2nt) SD-MMEJ (4 nt) (DR)			no
			vector	...TCCCGTACCTTAATATTACTTACTTATCATGGTAGCTTGGGCTGGCG...				
			genome	...TTACTTATTATGTTTATCCCTTAGTCTTCCCACTCCTGACTTGAATGCTTACTCTTTGAGGAG...				

[1] Sequenced plasmid integration junctions are represented by blue (CHO genome) and green (vector sequence) letters, as predicted from whole genome sequencing of Illumina genomic and mate-pair libraries, and as validated experimentally by PCR amplification and direct sequencing of the junctions.

[2] This lists the most probable mechanisms accounting for the junction, consisting of the Microhomology-mediated end-joining (MMEJ) and/or synthesis-dependent MMEJ (SD-MMEJ). The length of the microhomology is indicated in parenthesis. IR and DR indicate the use of inverted or direct repeat as a template for SD-MMEJ, respectively.

[3] Genomic integration site locus. The gene nearest to the integration site is listed in bold. Gene expression was assessed by total RNA sequencing of the parental CHO cells. Reads per kilobase of transcript per million reads mapped (RPKM) are used as a measure of the mRNA level.

[4] Insertion of nucleotides templated from another part of the vector or genome. [5] n.a., not annotated

Supplementary Table S5. Analysis of plasmid integration sites in cells transfected with vectors containing or not the MAR element.

Sample[1]	Integration within genes[2]	Integration near genes[3]	Expressed genes[4]
Polyclonal population without MAR	7/14 (*)[5]	8/14	8/8
Polyclonal population with MAR	6/14	10/14 (*)	5/10
High expressing clones with MAR	6/10 (**)	8/10	7/8

[1] Polyclonal populations of CHO cells transfected with GFP or MAR-GFP plasmids were sequenced by high-throughput sequencing (Pacific Biosciences) and plasmid-to-genome junctions were predicted using bioinformatics tools. Integration sites in high expressing CHO clones transfected with MAR-containing plasmids were PCR-amplified and sequenced using Sanger sequencing.
[2] integration locus inside or within 5kb from an open reading frame (ORF)
[3] integration locus in a gene or within 35kb from a gene
[4] number of expressed genes in the neighborhood (within 35kb) of the integration locus
[5] Statistical significance calculated between each sample set and the corresponding control set using an exact binomial test. Significance levels $p \leq 0.05$ (*), $p \leq 0.01$ (**).

Supplementary References to Tables S1 and S2

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