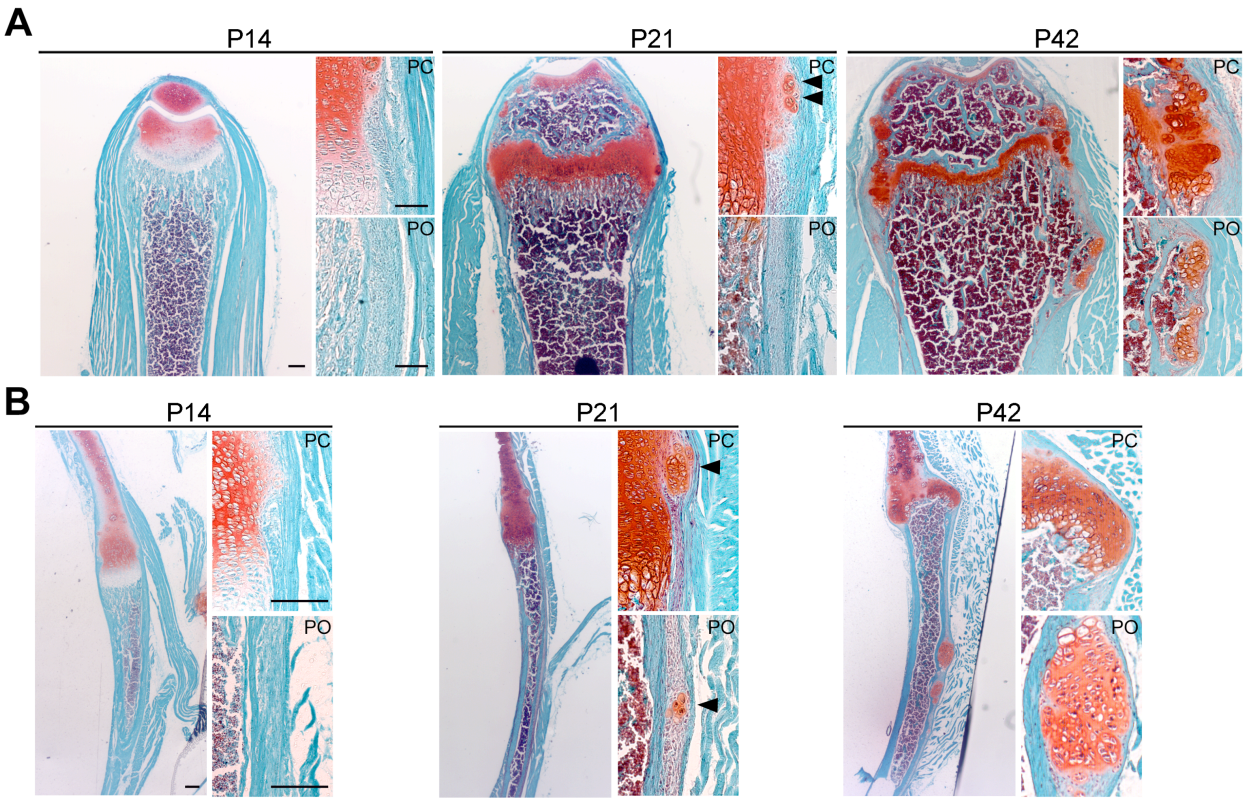

Supplementary Figure 1. Time course of osteochondroma development in *Fsp1^{Cre};Ext1$^{flox/flox}$* mice. Safranin O-stained sections of the distal femur (***A***) and the 10th rib (***B***) of *Fsp1^{Cre};Ext1$^{flox/flox}$* mice at P14, P21 and P42. Small images on the right represent high magnification views of the perichondrium (*PC*) and periosteum (*PO*). Note that no abnormalities are observed at P14. Small abnormal chondrocyte clusters are first detected at P21 (*arrowheads*

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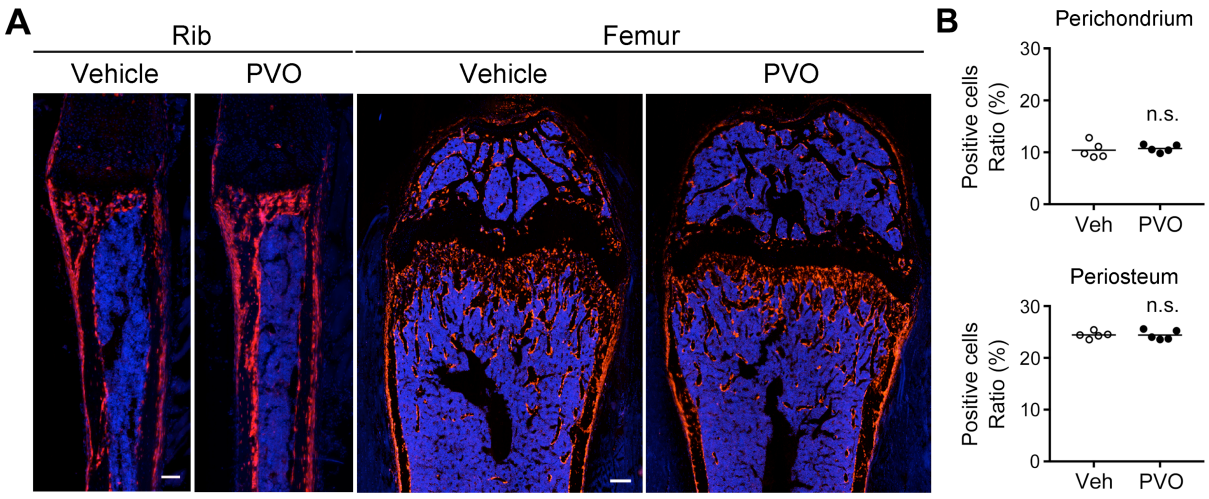

Supplementary Figure 2. PVO does not alter the efficiency or spatial pattern of recombination driven by *Fsp1*^{Cre}. *Fsp1*^{Cre}*;R26*^{tdTomato} mice were treated by daily oral gavage at 1.76 mg/kg of PVO (*PVO*) or vehicle (*Vehicle*) for 21 days starting at P21. (*A*) Sections of the femur and the 10th rib were stained with DAPI (*blue*) and analyzed for the distribution of tdTomato^{+} cells (*red*), which are cells that have undergone *Fsp1*^{Cre}-mediated recombination and their descendants. Note that PVO treatment did not alter the frequency and distribution of tdTomato^{+} cells. Scale bars, 0.1 mm. (***B***) The ratio of the number of recombined (tdTomato^{+}) cells relative to the number of DAPI-stained nuclei in the perichondrium and periosteum. *n.s.*, not significant by Student's *t* test. osteochondroma formation. Scale bars, 0.1 mm (***A***); 0.2 mm (***B***).

Supplementary Table 1. Summary of the results of PVO treatment experiments.

Mouse[1]	Treatment period	Dose [mg/kg/day]	Number of animals (Female/Male)	Body weight at P42 [g]	Number of osteochondromas (% changes relative to vehicle)		Bone length [cm] (% changes relative to vehicle)				
					Long bones[2]	Ribs[3]	Tibia	Femur	Ulna	Radius	Humerus
CKO	P14–P42 (Experiment 1)	0 (vehicle)	11 (5/6)	14.3 ± 2.3	58.5 ± 8.2	91.2 ±13.7	1.27 ± 0.04	1.24 ± 0.05	1.12 ± 0.04	0.90 ± 0.04	1.00 ± 0.04
		0.27	6 (1/5)	14.1 ± 1.6	25.3 ± 3.4*** (56.8% ↓)	38.8 ± 8.4*** (57.5% ↓)	1.29 ± 0.02 (1.6% ↑)	1.27 ± 0.04 (2.4% ↑)	1.11 ± 0.04 (0.9% ↓)	0.92 ± 0.03 (2.2% ↑)	1.01 ± 0.03 (1.0% ↑)
		0.88	8 (5/3)	13.1 ± 1.4	9.0 ± 3.3*** (84.6% ↓)	16.6 ± 3.7*** (81.8% ↓)	1.22 ± 0.04* (3.9% ↓)	0.98 ± 0.04*** (21.0% ↓)	0.98 ± 0.04*** (12.5% ↓)	0.78 ± 0.02*** (13.3% ↓)	0.82 ± 0.02*** (18.0% ↓)
		1.76	7 (3/4)	12.5 ± 1.3	5.2 ± 1.1*** (91.1% ↓)	8.4 ± 3.1*** (90.8% ↓)	1.14 ± 0.03*** (10.2% ↓)	0.97 ± 0.03*** (21.8% ↓)	0.98 ± 0.02*** (12.5% ↓)	0.79 ± 0.02 *** (12.2% ↓)	0.82 ± 0.03 *** (18.0% ↓)
	P21–P42 (Experiment 2)	0 (vehicle)	10 (4/6)	13.9 ± 0.9	50.9 ± 5.8	89.7 ± 9.2	1.24 ± 0.04	1.24 ± 0.03	1.08 ± 0.02	0.91 ± 0.02	0.99 ± 0.03
		0.27	7 (2/5)	14.4 ± 1.1	34.6 ± 3.8*** (32.0% ↓)	59.1 ± 7.2*** (34.1% ↓)	1.27 ± 0.04 (2.4% ↑)	1.25 ± 0.04 (0.8% ↑)	1.11 ± 0.02 (2.8% ↑)	0.92 ± 0.01 (1.1% ↑)	1.02 ± 0.02* (3.0% ↑)
		0.88	7 (2/5)	14.8 ± 1.1	16.4 ± 3.9*** (67.8% ↓)	40.7 ± 7.2*** (54.6% ↓)	1.28 ± 0.04 (3.2% ↑)	1.28 ± 0.03 (3.2% ↑)	1.11 ± 0.05 (2.8% ↑)	0.93 ± 0.03* (2.2% ↑)	1.03 ± 0.02* (4.0% ↑)
		1.76	10 (6/4)	13.7 ± 1.1	5.9 ± 2.8*** (88.4% ↓)	20.1 ± 6.2*** (77.6% ↓)	1.28 ± 0.02 (3.2% ↑)	1.26 ± 0.02 (1.6% ↑)	1.10 ± 0.03 (1.9% ↑)	0.92 ± 0.02 (1.1% ↑)	1.00 ± 0.02 (1.0% ↑)
WT	P21–P42	0 (vehicle)	6 (3/3)	18.6 ± 2.8	0	0	1.44 ± 0.06	1.35 ± 0.05	1.20 ± 0.03	0.99 ± 0.03	1.09 ± 0.04
		1.76	6 (3/3)	17.9 ± 2.0	0	0	1.44 ± 0.03 (0.00%)	1.34 ± 0.04 (0.7% ↓)	1.17 ± 0.05 (2.5% ↓)	0.96 ± 0.03 (3.0% ↓)	1.06 ± 0.03 (2.8% ↓)

[1] *CKO, Fsp1^{Cre};Ext1$^{flox/flox}$*; *WT,* wild-type C57BL6J.

[2] The total number of osteochondromas in five limb long bones (tibia, femur, ulna, radius, humerus) of the right hemi-skeleton per animal.

[3] The total number of osteochondromas in all ribs except for the first rib of the right hemi-skeleton per animal.

* p<0.05, *** p<0.001 relative to the values in corresponding vehicle-treated groups; by one-way ANOVA followed by Bonferroni's post hoc test.