

**Supplemental Table 1. Periosteal involvement and ossification in synovial sarcomas and other soft-tissue sarcomas.**

age	gender	diagnosis	location	abutting bone	ossification present	volume (cm <sup>3</sup> )
64	male	monophasic SS	arm	(bicipital aponeurosis)		
28	female	monophasic SS	thigh	(intramuscular)	yes	
32	female	monophasic SS	thigh	(intramuscular)	after chemo	
55	female	monophasic SS	thigh	(intramuscular)	on bone scan	
61	female	monophasic SS	thigh	(knee joint capsule)	yes	
40	female	monophasic SS	thigh	(knee joint capsule)	yes	
25	male	monophasic SS	thigh	(knee joint capsule)	yes	
41	female	monophasic SS	calf	(knee joint capsule)		
33	female	monophasic SS	neck	hyoid		8
48	male	monophasic SS	neck	thyroid cartilage		5
31	male	monophasic SS	arm	humerus	after chemo	9
12	male	biphasic SS	forearm	olecranon		45
60	male	monophasic SS	forearm	radius	yes	120
24	male	monophasic SS	forearm	radius	yes	692
61	female	monophasic SS	forearm	ulna	yes	3
28	female	biphasic SS	forearm	ulna	yes	164
9	male	monophasic SS	wrist	hamate		8
32	female	monophasic SS	hand	metacarpal	yes	9
50	female	monophasic SS	chest wall	rib	yes	23

44	female	biphasic SS	chest wall	rib		n/a
20	male	monophasic SS	chest wall	rib		n/a
56	female	monophasic SS	mediastinum	rib		272
81	male	biphasic SS	mediastinum	rib	yes	312
39	male	monophasic SS	flank	spine		274
15	female	monophasic SS	pelvis	ilium		124
23	male	biphasic SS	groin	pubis		151
39	female	monophasic SS	groin	pubis	yes	347
31	female	monophasic SS	thigh	femur	yes	13
28	male	monophasic SS	thigh	femur	yes	27
54	male	biphasic SS	thigh	femur	on bone scan	190
20	female	biphasic SS	thigh	femur	yes	210
11	female	biphasic SS	thigh	femur		288
49	female	monophasic SS	thigh	femur	yes	1016
22	male	monophasic SS	thigh	femur	yes	1062
50	female	monophasic SS	thigh	femur	yes	1271
24	male	monophasic SS	thigh	femur	yes	1765
23	female	biphasic SS	thigh	patella		3
69	male	biphasic SS	calf	fibula	yes	1656
59	male	monophasic SS	calf	fibula		1954
20	male	monophasic SS	calf	tibia	yes	1

37	female	monophasic SS	calf	tibia	yes	10
32	male	monophasic SS	calf	tibia	yes	11
29	female	monophasic SS	calf	tibia		26
33	female	monophasic SS	calf	tibia	yes	65
60	male	monophasic SS	calf	tibia		646
40	female	monophasic SS	ankle	talus		3
4	female	monophasic SS	foot	metatarsal	yes	2
24	male	monophasic SS	foot	metatarsal		n/a
mean size						346
standard deviation						541

**first comparative cohort**

55	female	malignant peripheral nerve sheath tumor	shoulder	none		
44	male	leiomyosarcoma	shoulder	none		
86	male	epithelioid sarcoma	wrist	none		
16	female	pleiomorphic sarcoma NOS	chest wall	none		
62	male	carcinosarcoma	flank	none		
41	male	pleiomorphic sarcoma NOS	back	none		
68	male	solitary fibrous tumor malignant	pelvis	none		
68	female	leiomyosarcoma	pelvis	none		
69	male	pleiomorphic sarcoma NOS	buttocks	none		
60	male	myxofibrosarcoma	thigh	none		
67	male	extraskkeletal myxoid chondrosarcoma	thigh	none		

64	female	pleiomorphic sarcoma NOS	thigh	none		
73	female	dedifferentiated liposarcoma	thigh	none		
86	male	angiosarcoma	thigh	none		
78	male	pleiomorphic sarcoma NOS	thigh	none		
57	male	well-differentiated liposarcoma	thigh	none		
54	male	myxoid liposarcoma	thigh	none		
80	female	extraskeletal myxoid chondrosarcoma	thigh	none		
34	male	epithelioid sarcoma	calf	none		
56	female	myxoid fibrosarcoma	calf	none		
14	female	clear cell sarcoma	shoulder	scapula		55
23	male	MPNST	shoulder	scapula		550
80	male	pleiomorphic sarcoma NOS	shoulder	scapula		4140
55	male	fibrosarcoma	chest wall	spine		106
69	male	pleiomorphic sarcoma NOS	pelvis	ilium		475
57	male	pleiomorphic sarcoma NOS	thigh	femur		1255
62	male	hemangiopericytoma	thigh	pubis		1981
65	male	pleiomorphic sarcoma NOS	calf	tibia		123
mean size						1086
standard deviation						1402

Two-tailed Fisher's Exact Test comparing bone abutment proportion,  $p = 0.00000383$

Student's t-test comparing size of tumors,  $p = 0.015$

**second comparative cohort**

60	female	pleiomorphic sarcoma NOS	neck	none		
41	male	pleiomorphic sarcoma NOS	shoulder	none		
70	male	pleiomorphic sarcoma NOS	shoulder	none		
81	female	pleiomorphic sarcoma NOS	shoulder	none		
70	male	pleiomorphic sarcoma NOS	shoulder	none		
78	male	pleiomorphic sarcoma NOS	arm	none		
55	male	pleiomorphic sarcoma NOS	arm	none		
81	male	pleiomorphic sarcoma NOS	elbow	none		
72	male	pleiomorphic sarcoma NOS	wrist	none		
50	male	pleiomorphic sarcoma NOS	hand	none		
70	male	pleiomorphic sarcoma NOS	chest wall	none		
64	female	pleiomorphic sarcoma NOS	chest wall	none		
70	female	pleiomorphic sarcoma NOS	chest wall	none		
70	female	pleiomorphic sarcoma NOS	chest wall	none		
65	male	pleiomorphic sarcoma NOS	back	none		
66	male	pleiomorphic sarcoma NOS	back	none		
54	male	pleiomorphic sarcoma NOS	groin	none		
82	male	pleiomorphic sarcoma NOS	buttocks	none		
73	female	pleiomorphic sarcoma NOS	thigh	none		
41	female	pleiomorphic sarcoma NOS	thigh	none		

55	female	pleiomorphic sarcoma NOS	thigh	none	yes	
51	female	pleiomorphic sarcoma NOS	thigh	none		
50	female	pleiomorphic sarcoma NOS	calf	none		
47	male	pleiomorphic sarcoma NOS	calf	none		
39	male	pleiomorphic sarcoma NOS	calf	none		
72	male	pleiomorphic sarcoma NOS	thigh	femur		2327
74	female	pleiomorphic sarcoma NOS	thigh	femur		5763
67	male	pleiomorphic sarcoma NOS	thigh	femur		560
mean size						2883
standard deviation						2646

Two-tailed Fisher's Exact Test comparing bone abutment proportion,  $p = 0.00000383$

Student's t-test comparing size of tumors,  $p = 0.000006$

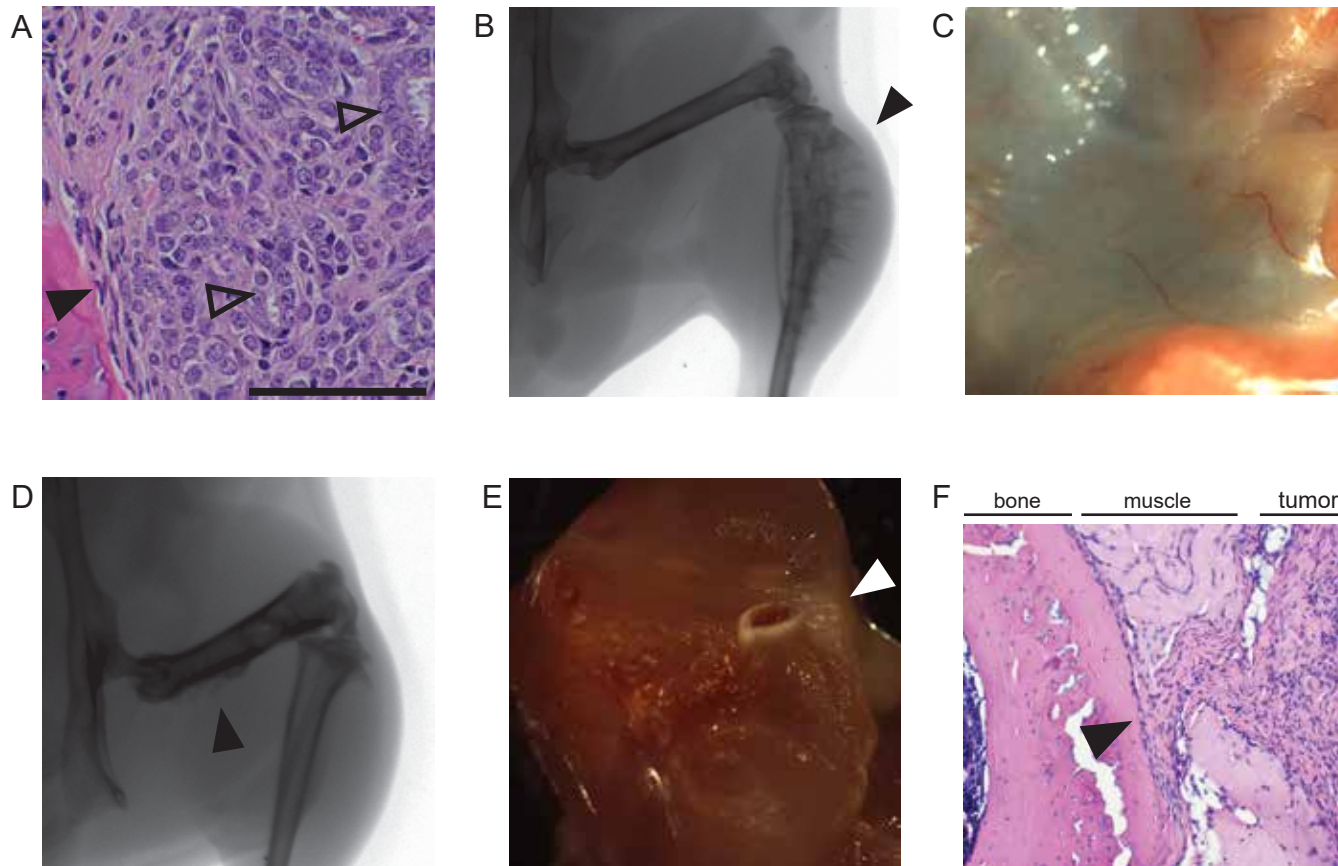
SS = synovial sarcoma

NOS = not otherwise specified

**Supplemental Table 2. Summary of Mouse Genotypes and Phenotypes.**

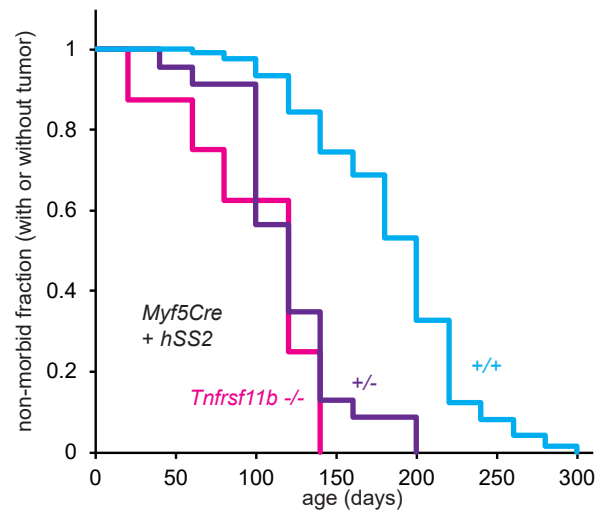
Cre-recombinase activity	Alleles/conditions							
	<i>hSS2T</i> embryonic dox	<i>hSS2T</i> post-natal dox	<i>hSS2/hSS2</i> + <i>Tnfrsf11b</i> <sup>-/-</sup>	<i>hSS2/hSS2</i>	<i>hSS2</i> + rmOPG	<i>hSS2</i>	<i>hSS2</i> + <i>Ctnnb1</i> <sup>ex3fl</sup>	<i>Ctnnb1</i> <sup>ex3fl</sup>
TATCre injection			slower SS growth	faster SS growth	faster early growth	slower early growth	rapid SS growth near bones	*no phenotype
<i>Myf5Cre</i>	SSs develop	no tumors				*SSs develop	*pre-natally lethal	*pre-natally lethal
<i>Pax7Cre</i> <sup>ERT2</sup> + tamoxifen 1-2wk						no tumors		
<i>Pax7Cre</i> <sup>ERT2</sup> + tamoxifen at 2wk						no tumors		
OcCre						P1 lethal + dense bones	pre-natally lethal	pre-natally lethal
Colla1Cre						P15-180 lethal + dense bones	pre-natally lethal	pre-natally lethal
<i>Prx1Cre</i> <sup>ERT2</sup> + tamoxifen at 2wk						jaw SSs develop	complete lineage SSs	periosteal thickening
<i>OsxCre</i> <sup>ERT</sup> + tamoxifen 2-4wk						no tumors	many SSs	osteopetrosis

\*previously reported

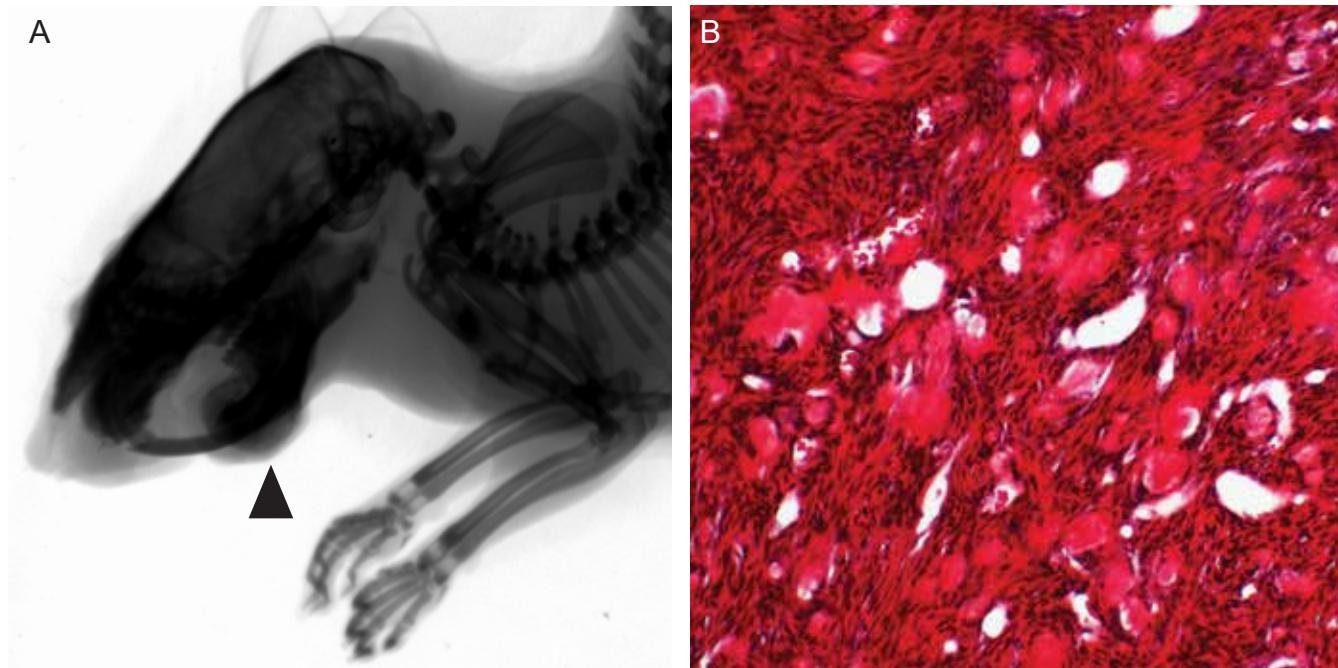


**Supplemental Figure 1. Synovial sarcomagenesis often approximates bone.** (A) Another representative H&E photomicrograph demonstrating a mouse SS immediately involving the periosteum (filled arrow), with classic SS features of epithelial gland formation nearby (open arrows). (B) Radiograph demonstrating pre-tibial tumorigenesis after TATCre injection near the bone. (C) Absence of tumorigenesis on gross photo of abdominal subcutaneous tissues after injection and (D) radiograph, (E) gross photo, and (F) H&E histology of a representative tumor that developed adjacent to bone after injection distant from bone in the thigh musculature. (magnification bar in A and panel width in F are each 100  $\mu$ m length)





**Supplemental Figure 2. Mutant *Tnfrsf11b* is toxic to *Myf5Cre*;*hSS2* mice.** Kaplan-Meier curves demonstrating the non-morbid fraction of mice in each *Tnfrsf11b* genotype combined with *Myf5Cre* and *hSS2*. Notably none of the *Tnfrsf11b* mice reached morbidity due to tumorigenesis, although some had tumors detected at necropsy. Tumor-related morbidity characterized the index morbidity for nearly all of the *Tnfrsf11b* homozygous wildtype mice.



**Supplemental Figure 3. Mandibular abnormality following *Ctnnb1* stabilization alone in pre-osteoblasts.** (A) Lateral radiograph of the single, non-aggressive jaw mass (black arrow) that formed among 7 *OsxCre<sup>ERT</sup>;Ctnnb1<sup>ex3fl/wt</sup>* mice at age 12 months. (B) Masson's trichrome photomicrograph from the mass shows a bland fibroblastic proliferation making islands of osteoid (red) lacking embedded osteocytes.