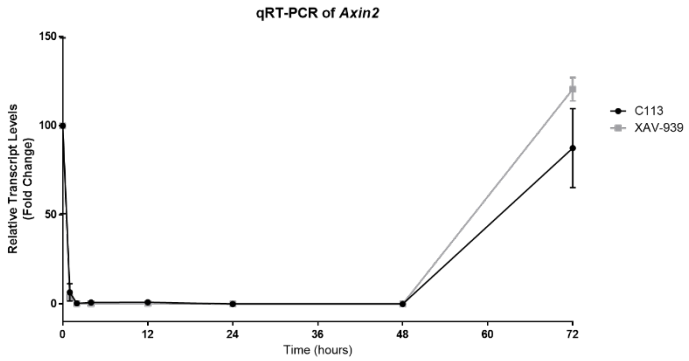
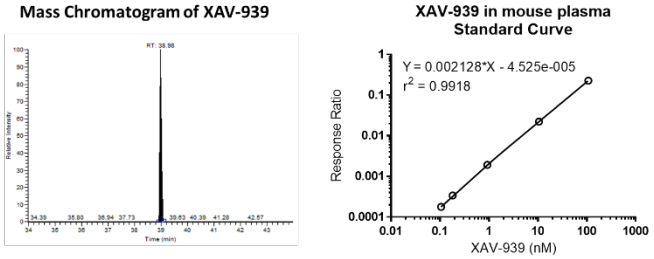
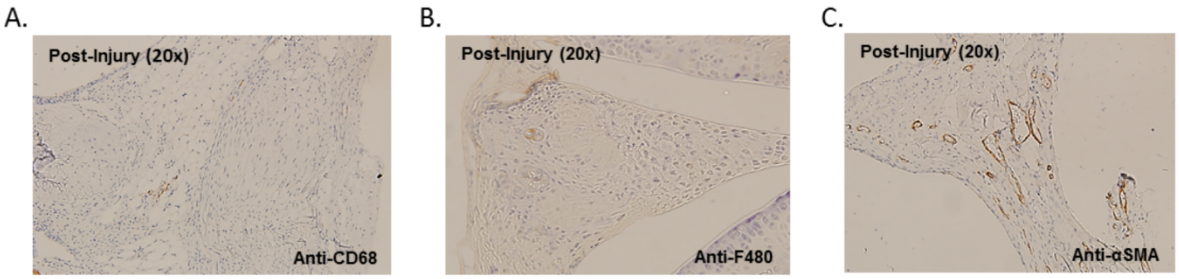
A.



B.

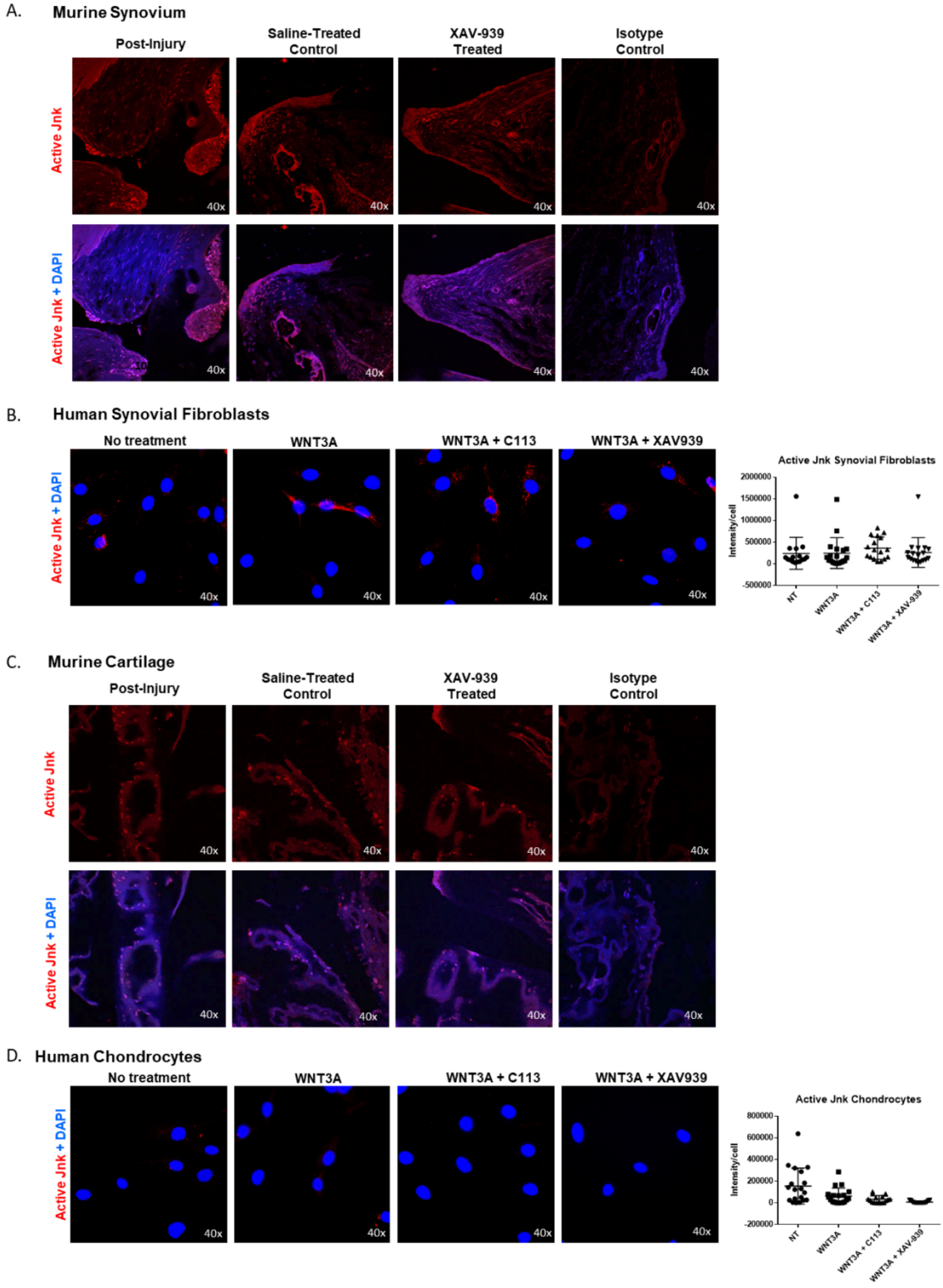


Supplementary Figure 1: (A) *Axin2* transcript levels after treatment with C-113 or XAV-939 in NIH3T3 cells constitutively overexpressing *Wnt3a*. Data is represented as mean ±SD (B) XAV-939 levels measured in plasma by mass spectrometry at 0, 3 and 24 hours post injection of saline or XAV-939 were fitted to a standard curve. The minimal quantifiable limit was 0.100 nM.



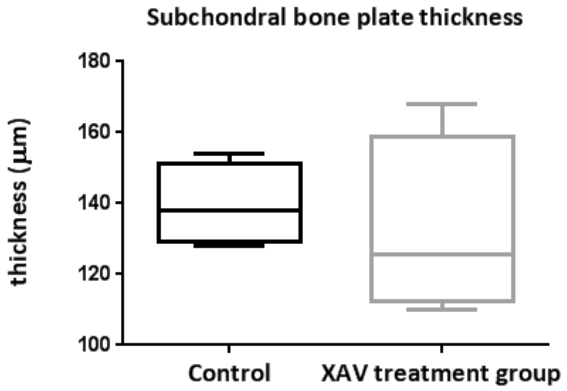
Supplementary Figure 2:

Immunohistochemistry of (A) CD-68 (macrophage) and (B) F480 (macrophage) does not identify any positive cells 10-weeks post DMM surgery. (C) Immunohistochemistry of αSMA of the joint space from control mice 10 weeks following DMM surgery was restricted to pericytes of blood vessels. No significant staining of myofibroblasts is noted.

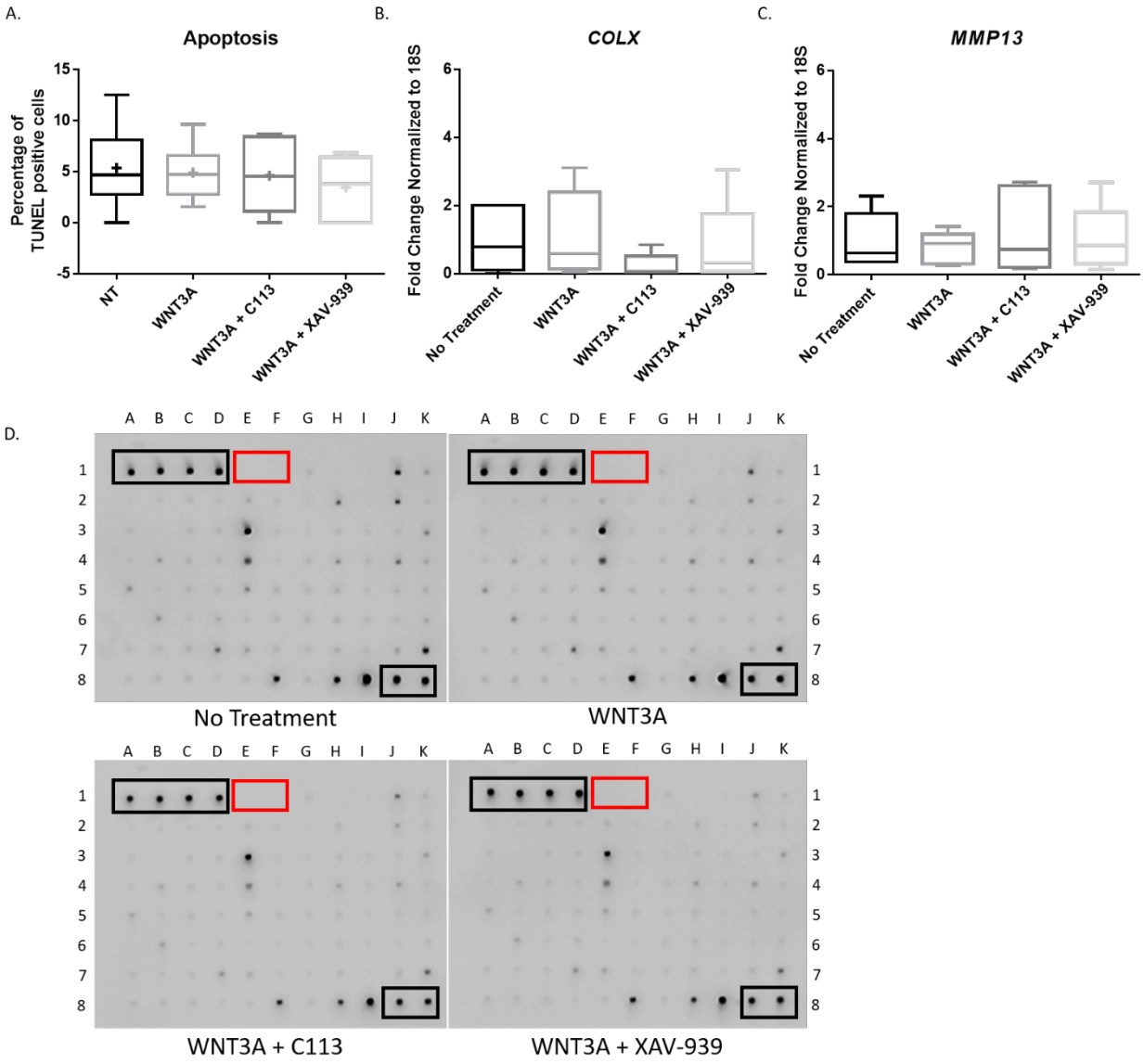


Supplementary Figure 3:

Immunofluorescence of active-Jnk (red) as an indication of non-canonical Wnt signaling, and DAPI (blue). (A) Synovial tissue from mice post injury, with saline treatment, or XAV-939 treatment show similar levels of staining. Isotype controls show low levels of background staining. (B) Human synovial fibroblasts do not show changes in staining. (C) Cartilage from mice post-injury, after saline treatment, or after XAV-939 treatment do not show significant changes in active-Jnk staining. Data was analyzed by one-way ANOVA with Tukey's post-hoc test. Lines indicates mean ± SD, n=16-19. (D) Human chondrocytes similarly show low levels of staining with no differences between treatment groups. Data was analyzed by one-way ANOVA with Tukey's post-hoc test. Lines indicates mean ± SD, n=15-21.



Supplementary Figure 4: The subchondral bone plate thickness was assessed in mice at 10 weeks post XAV or control vehicle treatment in mice subjected to DMM surgery (n = 4 mice per group). For data presented as box-and-whiskers plots, horizontal lines indicate the medians, cross marks indicate the means, boxes indicate the 25th to 75th percentiles, and whiskers indicate the minimum and maximum values of the data set.



Supplementary Figure 5:

Chondrocytes treated with conditioned media from treated synovial fibroblasts show no differences in (A) apoptosis by TUNEL staining, (B) hypertrophy as indicated by *COLX* levels by RT-PCR, or (C) proteinase levels as indicated by *MMP13* RT-PCR. (D) Representative cytokine arrays from treated synovial fibroblasts. Positive controls are shown in black boxes; negative controls are shown in red boxes. Quantification normalized to negative and positive controls is shown in Supplementary Figure 1 by two-way ANOVA, *$p<0.05$, $n=3$. For data presented as box-

and-whiskers plots, horizontal lines indicate the medians, cross marks indicate the means, boxes indicate the 25th to 75th percentiles, and whiskers indicate the minimum and maximum values of the data set.

Supplementary Table 1: Cytokine levels secreted from treated synovial fibroblasts

Location/ Cytokine		No Treatment	WNT3A	WNT3A + C113	WNT3A + XAV-939	NT vs WNT3A	WNT3A vs C113	WNT3A vs XAV939
G1. CXCL5	Mean	517.3333	539.1062	554.7092	474.2809	ns	ns	ns
	SD	464.0758	295.8546	239.7991	180.6758			
H1. G-CSF	Mean	197.3333	76.53072	91.2111	100.5902	ns	ns	ns
	SD	183.9275	80.14999	79.20692	153.5481			
I1. GM-CSF	Mean	35	268.3828	350.9959	132.2794	ns	ns	ns
	SD	60.62178	242.2328	194.3759	47.17378			
J1. GRO α/β/γ	Mean	3251.667	2069.342	3267.763	2000.026	ns	ns	ns
	SD	1830.739	993.1743	909.7786	294.3839			
K1. CXCL1	Mean	665.6667	617.1657	1091.106	770.8978	ns	ns	ns
	SD	611.2907	380.4963	238.9643	363.1515			
A2. CCL1	Mean	172.6667	258.9047	289.436	394.9648	ns	ns	ns
	SD	150.0145	223.3532	46.9348	186.3156			
B2. IL-1α	Mean	139.3333	518.6817	403.949	227.6429	ns	ns	ns
	SD	226.7693	191.2578	76.57477	263.9387			
C2. IL-1β	Mean	372.3333	617.717	544.3953	553.8302	ns	ns	ns
	SD	333.3382	80.22275	165.7887	224.4939			
D2. IL-2	Mean	136.6667	351.1559	365.2579	412.3731	ns	ns	ns
	SD	236.7136	162.9679	162.6996	420.2917			
E2. IL-3	Mean	902.6667	1037.501	756.4279	688.3521	ns	ns	ns
	SD	511.8177	349.5863	113.4829	438.1831			
F2. IL-4	Mean	310.3333	238.6649	234.7083	358.5393	ns	ns	ns
	SD	49.64205	161.6632	207.236	257.4653			
G2. IL-5	Mean	100.3333	115.1274	259.7026	164.8752	ns	ns	ns
	SD	173.7824	118.924	146.3379	172.2562			
H2. IL-6	Mean	4926.334	1490.4	1957.514	1547.184	*	ns	ns
	SD	3539.074	329.4464	1879.609	907.1645			
I2. IL-7	Mean	0	233.5146	81.38654	140.5227	ns	ns	ns
	SD	0	204.5225	107.9491	63.54575			
J2. IL-8	Mean	3188.667	1855.519	2909.773	1912.979	ns	ns	ns
	SD	666.3102	490.8002	1885.114	352.7683			
K2. IL-10	Mean	343	533.8448	509.0786	464.401	ns	ns	ns
	SD	330.3286	161.7478	262.5516	301.1324			

A3. IL-12	Mean	237.3333	483.2774	508.8418	593.9536	ns	ns	ns
	SD	206.413	360.4365	181.1792	122.1686			
B3. IL-13	Mean	32.66667	138.3587	63.36218	128.1339	ns	ns	ns
	SD	56.58033	183.9713	84.32649	221.9344			
C3. IL-15	Mean	591.3333	501.2566	652.8455	550.6301	ns	ns	ns
	SD	257.201	302.8881	139.5835	259.7019			
D3. IFNγ	Mean	160	786.6755	808.5609	578.9036	ns	ns	ns
	SD	342.8863	184.7946	294.7308	236.9119			
E3. CCL2	Mean	12385	10858.88	13155.19	10860.47	ns	*	ns
	SD	1141.888	1194.907	2802.639	3219.656			
F3. CCL8	Mean	330.3333	446.5989	441.7495	156.3083	ns	ns	ns
	SD	102.4711	232.7761	170.2823	135.5998			
G3. CCL7	Mean	57	191.9305	160.9236	190.7821	ns	ns	ns
	SD	98.7269	195.2542	139.3677	255.9009			
H3. M-CSF	Mean	253	475.8377	621.2105	193.933	ns	ns	ns
	SD	279.4799	295.4485	147.7442	176.2811			
I3. CCL22	Mean	310	427	556.5483	409.0943	ns	ns	ns
	SD	357.3835	234.2867	79.52264	192.9981			
J3. CXCL9	Mean	288	577.9829	345.0297	374.9343	ns	ns	ns
	SD	214.2919	289.0363	114.6902	239.233			
K3. CCL4	Mean	1248.333	1504.763	1878.284	1396.57	ns	ns	ns
	SD	629.1219	189.0767	624.9703	675.438			
A4. MIP-1Δ	Mean	84.66666	559.0309	410.554	388.0559	ns	ns	ns
	SD	92.87267	127.0269	235.5571	291.6957			
B4. CCL5	Mean	1111.333	1014.431	1047.036	890.8857	ns	ns	ns
	SD	242.2031	483.2724	441.3416	374.2989			
C4. SCF	Mean	489.3333	630.4211	827.8269	740.2297	ns	ns	ns
	SD	69.92377	339.9217	277.9688	453.6564			
D4. SDF-1α	Mean	374.6667	714.9613	485.6248	407.5582	ns	ns	ns
	SD	60.36831	149.2508	64.63656	298.8162			
E4. CCL17	Mean	5437.334	4928.138	4342.423	4347.376	ns	ns	ns
	SD	1104.408	1035.704	902.1822	1756.308			
F4. TGFβ1	Mean	64.66666	170.4254	247.3459	71.71028	ns	ns	ns
	SD	393.5179	85.65996	231.2122	123.2123			
G4. TNFα	Mean	413.6667	348.986	479.1926	630.8306	ns	ns	ns
	SD	313.497	144.4312	159.9539	142.4667			
H4. TNFβ	Mean	1555	1481.324	1768.048	1259.993	ns	ns	ns
	SD	473.6201	413.5323	607.3929	641.8835			
I4. EGF	Mean	498.6667	463.8719	552.3489	200.5122	ns	ns	ns
	SD	351.7405	118.3646	27.67212	226.9563			
J4. IGF-1	Mean	2129.667	1946.951	2155.689	1389.6	ns	ns	ns
	SD	826.4438	391.4824	517.1813	591.4124			
	Mean	557.3333	522.2246	617.4254	280.6197	ns	ns	ns

K4. Angiogenin	SD	614.3007	338.0037	176.7813	95.77209			
A5. OSM	Mean	1219.667	1610.535	1176.085	1104.478	ns	ns	ns
	SD	611.2163	381.0736	606.635	247.2565			
B5. TPO	Mean	159	521.0551	289.1977	350.4686	ns	ns	ns
	SD	156.8088	201.0601	173.4753	249.7322			
C5. VEGF-A	Mean	434.6667	852.1916	628.1257	675.43	ns	ns	ns
	SD	118.0946	168.4529	140.9209	283.4581			
D5. PDGF-BB	Mean	213.3333	429.1155	545.508	638.74	ns	ns	ns
	SD	486.9808	179.7485	340.9279	421.0736			
E5. Leptin	Mean	2003	1805.84	1889.018	1633.985	ns	ns	ns
	SD	624.8176	238.6378	764.313	786.2117			
F5. BDNF	Mean	631	565.5611	581.7552	739.4893	ns	ns	ns
	SD	390.3165	98.17242	80.77022	315.7466			
G5. CXCL13	Mean	444.6667	468.0326	505.8438	299.826	ns	ns	ns
	SD	198.3364	389.9937	199.8865	123.3178			
H5. CCL23	Mean	724.3333	618.4196	694.6305	771.2009	ns	ns	ns
	SD	256.7106	176.1336	200.2344	38.25303			
I5. CCL11	Mean	183.3333	451.7731	224.9818	578.8217	ns	ns	ns
	SD	189.8008	262.0195	147.969	83.00328			
J5. CCL24	Mean	539	667.4798	449.8715	460.0006	ns	ns	ns
	SD	468.5414	169.8042	269.2074	411.4914			
K5. CCL26	Mean	295.3333	699.3896	487.4492	514.3765	ns	ns	ns
	SD	288.28	231.0463	248.8891	106.2101			
A6. FGF-4	Mean	40	69.87245	142.3749	92.1369	ns	ns	ns
	SD	69.28204	71.5704	75.34004	159.5858			
B6. FGF-6	Mean	1432.333	1590.523	1709.148	1438.604	ns	ns	ns
	SD	722.911	397.9203	647.6685	649.3059			
C6. FGF-7	Mean	226	246.1549	153.9658	275.2236	ns	ns	ns
	SD	268.6317	281.4367	118.5367	205.8933			
D6. FGF-9	Mean	579.3333	788.138	499.3641	620.3659	ns	ns	ns
	SD	458.8162	431.6348	115.9928	370.3884			
E6. FLT-Ligand	Mean	184	463.0848	285.4066	122.2616	ns	ns	ns
	SD	167.3111	318.3135	211.2077	142.465			
F6. CX3CL1	Mean	407.3333	461.7466	602.1606	212.0667	ns	ns	ns
	SD	212.1658	383.7504	226.5944	208.5442			
G6. CXCL6	Mean	653	566.786	320.5384	392.6656	ns	ns	ns
	SD	95.24705	284.3901	44.22207	87.81561			
H6. GDNF	Mean	758	678.3712	494.1227	856.3358	ns	ns	ns
	SD	187.0642	146.9467	32.62173	350.9413			
I6. HGF	Mean	225.6667	542.632	345.8209	455.4476	ns	ns	ns
	SD	225.003	251.4714	94.66505	30.72704			
J6.	Mean	508.3333	385.0254	436.8597	546.0181	ns	ns	ns

IGFBP-1	SD	165.4036	258.5357	148.306	193.1065			
K6. IGFBP-2	Mean	549	541.9671	508.2943	836.2022	ns	ns	ns
	SD	276.1358	257.771	101.3983	373.8076			
A7. IGFBP-3	Mean	333.3333	318.304	553.2021	497.1392	ns	ns	ns
	SD	292.9733	126.22	329.6389	308.8108			
B7. IGFBP-4	Mean	197.3333	403.1744	422.1639	145.7046	ns	ns	ns
	SD	269.2013	329.7807	86.18457	38.10611			
C7. IL-16	Mean	580	522.1465	634.9226	303.3663	ns	ns	ns
	SD	438.9795	202.8318	247.5257	139.5344			
D7. CXCL10	Mean	2711.333	2506.545	1946.687	1783.747	ns	ns	ns
	SD	433.7123	636.0097	520.63	646.9572			
E7. LIF	Mean	1186	1325.418	1474.982	1164.159	ns	ns	ns
	SD	259.0927	644.1686	534.7456	674.7619			
F7. TNFSF14	Mean	453.6667	686.9127	543.196	418.9318	ns	ns	ns
	SD	197.5964	217.6527	209.0251	106.3046			
G7. CCL13	Mean	218.3333	490.8565	158.6044	387.3205	ns	ns	ns
	SD	262.096	252.4347	105.987	155.4454			
H7. MIF	Mean	639	803.3098	870.6154	540.5483	ns	ns	ns
	SD	362.1975	283.6836	481.2186	300.463			
I7. MIP-3α	Mean	307.6667	371.3905	231.2672	249.6784	ns	ns	ns
	SD	344.1516	169.7711	152.6773	122.1354			
J7. CXCL7	Mean	991	1030.692	708.7008	780.823	ns	ns	ns
	SD	536.4243	122.1732	315.5588	142.09			
K7. NT-3	Mean	4476	3725.52	4151.466	2853.974	ns	ns	ns
	SD	2491.087	941.5571	1359.68	1252.662			
A8. NT-4	Mean	411	712.811	635.7987	638.7961	ns	ns	ns
	SD	455.0923	119.9568	420.7758	49.7103			
B8. OPN	Mean	436.3333	689.7337	695.6617	409.4119	ns	ns	ns
	SD	135.3711	111.1815	216.2941	239.1576			
C8. OPG	Mean	539.6667	688.0743	783.3864	403.5011	ns	ns	ns
	SD	219.1628	114.0735	212.3228	153.3234			
D8. PARC	Mean	93.33334	308.1012	517.0475	118.0605	ns	ns	ns
	SD	155.6353	294.4397	342.2063	75.61629			
E8. PLGF	Mean	205.3333	525.9961	313.1626	271.4533	ns	ns	ns
	SD	233.5216	256.7698	171.8877	76.20089			
F8. TGFβ2	Mean	8760.667	7291.871	6551.551	6436.653	ns	ns	ns
	SD	2227.716	1073.548	1814.304	3443.874			
G8. TGFβ3	Mean	582.6667	668.7567	501.4561	199.3672	ns	ns	ns
	SD	113.3152	327.2357	70.23309	66.96215			
H8. TIMP-1	Mean	7219	5981.077	5949.739	5194.692	ns	ns	ns
	SD	1463.506	1229.859	1926.377	2144.599			
I8. TIMP-2	Mean	20696	14312.15	14365.53	11665.27	*	ns	*
	SD	3333.575	4117.292	6080.468	3338.078			

Supplementary Table 2: Oligonucleotide primer sequences used for quantitative RT-PCR

Primer	Direction	Sequence
Human AXIN2	Forward	5’-GCA GTG TGA AGG CCA ATG G-3’
	Reverse	5’-GCA GGC GGT GGG TTC TC-3’
Human COL1A1	Forward	5’-GCC AGA TGG GTC CCC GAG GT-3’
	Reverse	5’-GGG GGT CCA GCA GCA CCA AC-3’
Human COL2A1	Forward	5’-GCA GCA AGA GCA AGG AGA AG-3’
	Reverse	5’-GCG TAG GAA GGT CAT CTG GA-3’
Human PRG4	Forward	5’-GAT GCA GGG TAC CCC AAA-3’
	Reverse	5’-CAG ACT TTG GAT AAG GTC TGC C-3’
Human COLX	Forward	5’-TAC CTT GTG CCT CCC ATT CAA-3’
	Reverse	5’-TAC AGT ACA GTG CAT AAA TAA ATA ATA TAT CTC CA-3’
Human MMP13	Forward	5’-ACT GAG AGG CTC CGA GAA ATG-3’
	Reverse	5’-GAA CCC CGC ATC TTG GCT T-3’
18S	Forward	5’-CGC CGC TAG AGG TGA AAT TCT-3’
	Reverse	5’-CGA ACC TCC GAC TTT CGT TCT-3’