

Supplemental Table S1. Mapped RNA-Seq reads of *M. musculus* genome

Sample ID	Total Reads	Total Mapped Reads	% Total Mapped Reads	Unique Mapped Reads	% Unique Mapped Reads
LUBF1	36590775	25118712	68.64	15881169	43.40
LUBF2	33448004	19834982	59.30	15180440	45.38
LUBF3	27161382	17669437	65.05	13605463	50.09
LUBM1	34400855	22371720	65.03	16154568	46.96
LUBM2	36315874	23848286	65.67	18141147	49.95
LUBM3	29299012	23200913	79.18	18016334	61.49
PBSF1	39116779	22193698	56.73	14087055	36.01
PBSF2	44562009	21537723	48.33	13867401	31.12
PBSF3	44795502	22244019	49.65	14647927	32.69
PBSM1	32616338	20779813	63.71	15984367	49.00
PBSM2	30432361	21523578	70.72	16808787	55.23
PBSM3	33377599	24679298	73.94	19036823	57.03

Supplemental Table S2. Differentially Regulated Genes Identified by RNA-Seq. Green (Upregulated) & Red (Downregulated)

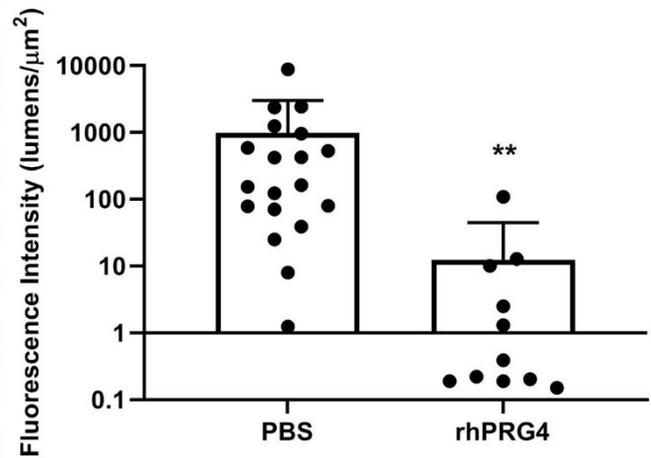
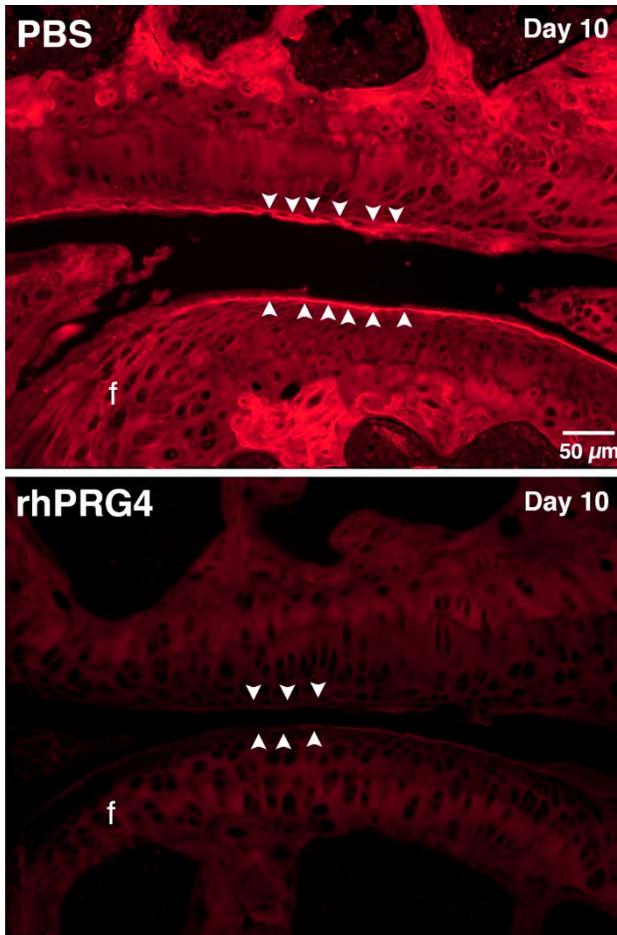
Symbol	Gene name	Gene Function
Upregulated & Downregulated Genes in Male Mice rhPRG4 vs PBS		
<i>Scube1</i>	Signal peptide, CUB domain and EGF like domain containing 1	Protein Expression
<i>Wif1</i>	WNT Inhibitory Factor 1	Cell Signaling
<i>Matn3</i>	Matrilin 3	Extracellular matrix fibrillar protein
<i>Cxcl14</i>	C-X-C Motif Chemokine Ligand 14	Secreted cytokine
<i>Hapln1</i>	Hyaluronan And Proteoglycan Link Protein 1	Extracellular matrix
<i>Mss51</i>	MSS51 Mitochondrial Translational Activator	Mitochondrial protein expression
<i>Col2a1</i>	Collagen Type II Alpha 1 Chain	Extracellular matrix fibrillar protein
<i>Tnn</i>	Tenascin N	Extracellular matrix glycoprotein
<i>Prg2</i>	Proteoglycan 2, Pro Eosinophil Major Basic Protein	Extracellular carbohydrate binding
<i>Sfrp2</i>	Secreted Frizzled Related Protein 2	Modulator of Wnt Signaling
<i>Coll2a1</i>	Collagen 2A1	Extracellular matrix fibrillar protein
<i>Fam129c</i>	Family with sequence similarity 129 member C	Regulates p53-mediated apoptosis
<i>Mmp13</i>	Matrix Metalloproteinase 13	Protease of extracellular matrix
<i>Myh7</i>	Myosin Heavy Chain 7	Extracellular matrix and ATPase
<i>Kdm5d</i>	Lysine Demethylase 5D	Histone H3 Protein Processing
<i>Uty</i>	Ubiquitously Transcribed Tetratricopeptide Repeat Containing, Y-Linked	Histone H3 Protein Processing
<i>Ddx3y</i>	DEAD-Box Helicase 3 Y-Linked	ATP-dependent RNA helicase
<i>Eif2s3y</i>	Eukaryotic translation initiation factor 2 subunit 3, Y-linked	Heterotrimeric GTP-binding protein
<i>Amd1</i>	Adenosylmethionine Decarboxylase 1	Enzyme in polyamine biosynthesis
<i>Igkc</i>	Immunoglobulin Kappa Constant	Secreted glycoprotein
<i>Gbp4</i>	Guanylate Binding Protein 4	Hydrolysis of GTP to GDP and GMP
<i>Xist</i>	X Inactive Specific Transcript	RNA gene involved in X inactivation
Upregulated & Downregulated Genes in Female Mice rhPRG4 vs PBS		
<i>My12</i>	Myosin Light Chain 2	Extracellular matrix and ATPase
<i>Matn3</i>	Matrilin 3	Extracellular matrix fibrillar protein
<i>Rgs9</i>	Regulator Of G Protein Signaling 9	GTPase activating protein
<i>Tnni1</i>	Troponin I1, Slow Skeletal Type	Slow skeletal Actin binding protein
<i>Hmgn5</i>	High Mobility Group Nucleosome Binding Domain 5	Nuclear protein in transcription
<i>Alox12b</i>	Arachidonate 12-Lipoxygenase, 12R Type	Enzyme for Arachidonic acid
<i>Lars2</i>	Leucyl-tRNA Synthetase 2, Mitochondrial	Mitochondrial tRNA synthetase
<i>Ccdc33</i>	Coiled-Coil Domain Containing 33	Protein expression
<i>Map7d2</i>	MAP7 Domain Containing 2	Protein expression
<i>Pkhd1</i>	PKHD1 Ciliary IPT Domain Containing Fibrocystin/Polyductin	Transmembrane protein
<i>Pou4f1</i>	POU Class 4 Homeobox 1	Transcription factor
<i>Igfn1</i>	Immunoglobulin Like And Fibronectin Type III Domain Containing 1	Secreted protein expression
<i>Cyt11</i>	Cytokine Like 1	Protein expression
<i>Mt-tv</i>	Mitochondrially Encoded TRNA-Val (GUN)	tRNA affiliated gene
<i>Mt-t12</i>	Mitochondrially Encoded TRNA-Leu (CUN) 2	tRNA affiliated gene
<i>Mt-tp</i>	Mitochondrially Encoded TRNA-Pro (CCN)	tRNA affiliated gene
<i>Snora73a</i>	Small Nucleolar RNA, H/ACA Box 73A	snoRNA affiliated gene
<i>Snora23</i>	Small Nucleolar RNA, H/ACA Box 23	snoRNA affiliated gene
<i>Snord118</i>	Small Nucleolar RNA, C/D Box 118	snoRNA affiliated gene
<i>Snora21</i>	Small Nucleolar RNA, H/ACA Box 21	snoRNA affiliated gene
<i>Rny3</i>	RNA, Ro60-Associated Y3	Y_RNA affiliated gene
<i>Snord104</i>	Small Nucleolar RNA, C/D Box 104	noRNA affiliated gene
<i>Vaultrc5</i>	vault RNA component 5	Vault_RNA class affiliated gene
<i>Rnu12</i>	RNA, U12 Small Nuclear	snRNA affiliated gene
<i>Rny1</i>	RNA, Ro60-Associated Y1	Expressed ribonucleoprotein
<i>Snord15a</i>	Small Nucleolar RNA, C/D Box 15A	snoRNA affiliated gene
<i>Snora57</i>	Small Nucleolar RNA, H/ACA Box 57	snoRNA affiliated gene
<i>Snora17</i>	Small Nucleolar RNA, H/ACA Box 17	snoRNA affiliated gene
<i>Snord17</i>	Small Nucleolar RNA, C/D Box 17	snoRNA affiliated gene
<i>Snord13</i>	Small Nucleolar RNA, C/D Box 13	snoRNA affiliated gene
<i>Snora78</i>	Small Nucleolar RNA, H/ACA Box 78	snoRNA affiliated gene
<i>Scarna6</i>	Small Cajal Body-Specific RNA 6	snoRNA affiliated gene
<i>Scarna3a</i>	Small Cajal Body-Specific RNA	scaRNA affiliated gene
<i>Asmt</i>	Acetylserotonin O-Methyltransferase	Secreted enzyme
Upregulated Genes in Pooled Sex Mice PBS vs rhPRG4		
<i>Myh7</i>	Myosin heavy chain 7	Extracellular matrix and ATPase
<i>Mt-tn</i>	Mitochondrially Encoded TRNA-Asn (AAU/C)	tRNA affiliated gene
<i>Gm25747</i>	Predicted Gene	
<i>Igfn1</i>	Immunoglobulin Like And Fibronectin Type III Domain Containing 1	Secreted protein expression
<i>Myl2</i>	Myosin light chain 2	Extracellular matrix and ATPase
<i>Myl3</i>	Myosin light chain 3	Extracellular matrix and ATPase
<i>Tnnc1</i>	Troponin C1, slow skeletal and cardiac type	Slow skeletal Actin binding protein
<i>Tnni1</i>	Troponin I1, slow skeletal type	Slow skeletal Actin binding protein
<i>Tnnt1</i>	Troponin T1, slow skeletal type	Actin binding & calcium metabolism

Supplemental Table S3. cDNA Primer Sequences Used in qRT-PCR

Gene	Description	Primer	Sequence (5' – 3')	Size (BP)
<i>Xiap</i>	X-linked inhibitor of apoptosis	F	CTGGCCGGACTATGCTCATT	131
		R	CACGATCACAGGGTTCCCAA	
<i>Bid</i>	BH3 interacting domain death agonist	F	CCTGTGCAAGCTTACTGGGA	243
		R	TTTGTCTTCTCCGACAGGC	
<i>Bcl2</i>	B cell leukemia/lymphoma 2	F	CTTTGAGTTCGGTGGGGTCA	153
		R	AGTTCCACAAAGGCATCCCA	
<i>Gapdh</i>	Glyceraldehyde-3-phosphate dehydrogenase	F	GGAGAGTGTTTCTCGTCCC	202
		R	ACTGTGCCGTTGAATTTGCC	
<i>Cad</i>	Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase	F	GAGCCCTACATAGCGCTG	306
		R	CAGCAGCTTTTGCCTCAGTG	
<i>Icad</i>	Inhibitor of caspase-activated DNase	F	CAGGCCTTGGAGAAAGAGGG	333
		R	TCTGGCTGTGTGAAAAGGCA	
<i>Hsp70</i>	Heat shock protein 70 binding	F	CGACCTGAACAAGAGCATCA	500*
		R	ATGACCTCCTGGCACTTGTC	
<i>Hsp27</i>	Heat shock protein 27 binding	F	CCTCTTCGATCAAGCTTTCG	300*
		R	CTCAGGGGATAGGGAAGAGG	
<i>Hsp90</i>	Heat shock protein 90 binding	F	GAACATTGTGAAGAAGTGCC	320
		R	GAACATTGTGAAGAAGTGCC	
<i>Parp1</i>	Poly (ADP-ribose) polymerase family, member 1	F	GACACCCCGTGCAGACTTG	186
		R	CCACCACACGTA CTGCTCG	
<i>Ngf</i>	Nerve growth factor	F	GCAGCATGGTGGAGTTTTGG	215
		R	CTGTGTACGGTTCTGCCTGT	
<i>Myh7</i>	Myosin heavy chain 7	F	CTCAAGCTGCTCAGCAATCTATTT	NA
		R	GGAGCGCAAGTTTGTATAAGT	
<i>Lars2</i>	Leucyl-tRNA synthetase 2, mitochondrial	F	GCCTTCCATCTGGACAGTGTCT	NA
		R	GGACTTGCTCATCTTCTCCAC	
<i>Myl2</i>	Myosin light chain 2	F	TCCCTGAGTGGGTTTGGGT	416
		R	TTTGCCCTCGGGATCAAACA	
<i>Tnni1</i>	Troponin I1	F	GCTCCACGAGGACTAAACTAGG	236
		R	GAATGCGCTCCGAGAGGTAA	

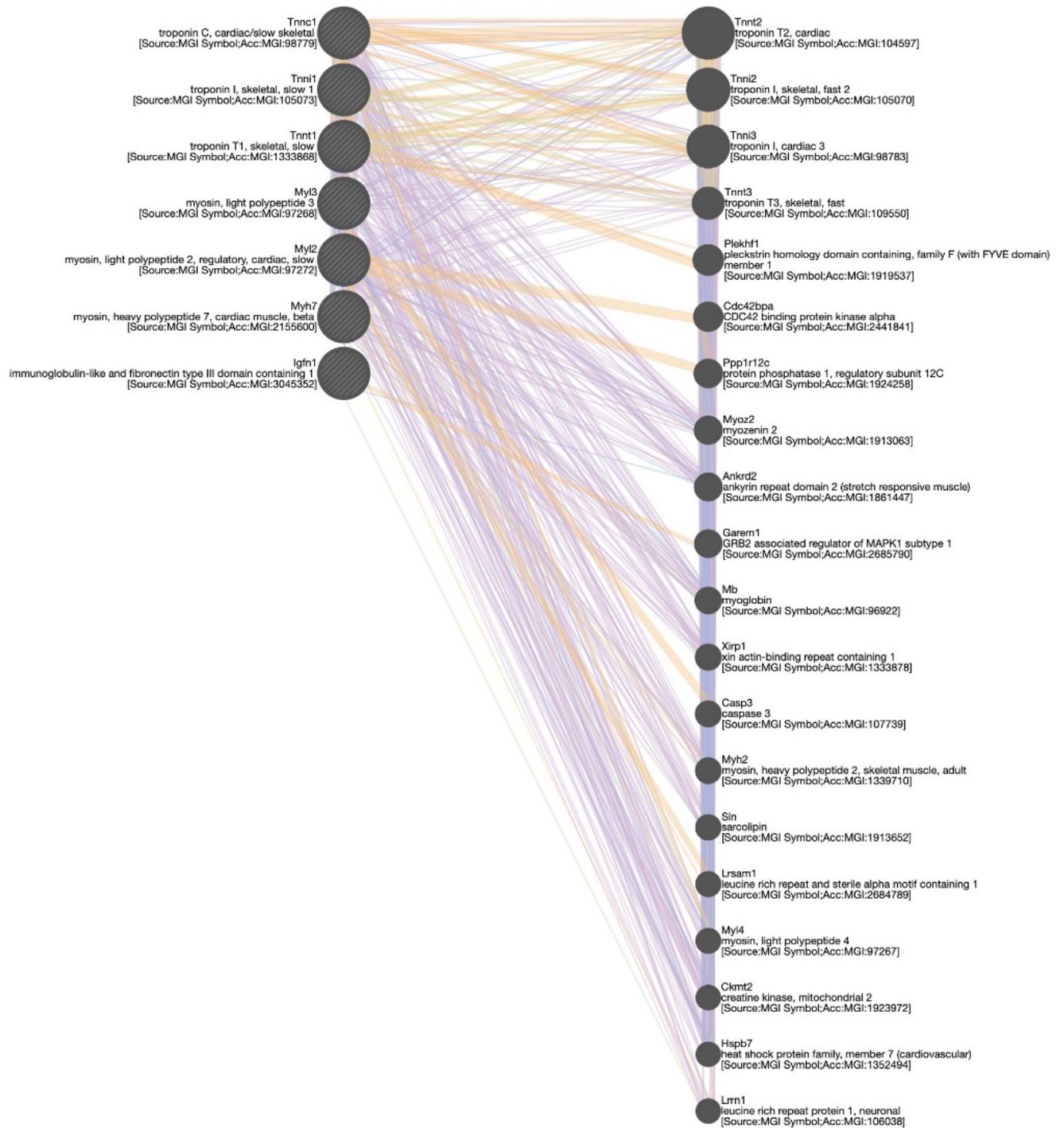
Size in base pairs (BP) is predicted unless indicated* and measured from agarose electrophoresis. Not available (NA) refers to a commercial or academic source described in Materials and Methods with an unknown amplicon size.

Supplemental Figure S1.



Supplemental Figure. Reactivity of collagen binding peptide in *Prg4*^{-/-} mouse joints is reduced by rhPRG4. Transverse sections of tibio-femoral joints randomly assigned to either IA PBS (19) or rhPRG4 (11) show diffuse increased collagen turnover in *Prg4*^{-/-} joints 10 days after treatment with IA PBS. This is particularly enhanced in the superficial zone of cartilage as demarcated by white arrowheads. Qualitatively the levels of collagen damage in appears reduced in those littermates that had received IA rhPRG4. Segmenting images of the superficial zone and quantitating fluorescence intensity in lumens/μm² support a difference between the two groups. Median value images are shown. Mean ± SD displayed, **p<0.01, f = femoral.

Supplemental Figure S2.



Supplemental Figure. GeneMANIA interaction network associated with Fig 3 where individual genes have been identified.