

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)

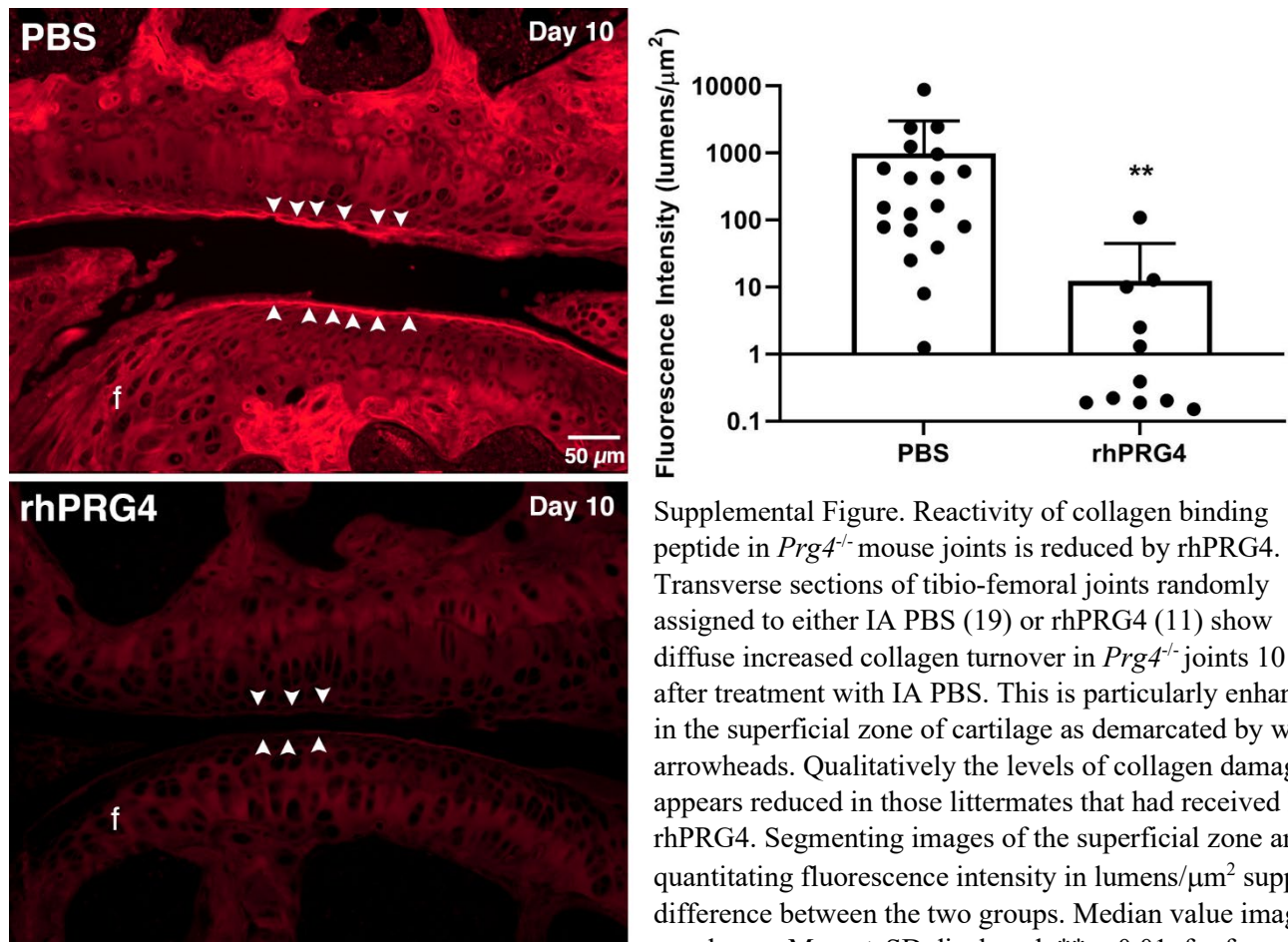
| Symbol | Gene name | Gene Function |
|---|--|--|
| Upregulated & Downregulated Genes in Male Mice rhPRG4 vs PBS | | |
| <i>Scube 1</i> | Signal peptide, CUB domain and EGF like domain containing 1 | Protein Expression |
| <i>Wif1</i> | WNT Inhibitory Factor 1 | Cell Signaling |
| <i>Matn3</i> | Matrilin 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>Prp2</i> | Proteoglycan 2, Pro Eosinophil Major Basic Protein | Extracellular carbohydrate binding |
| <i>Sfrp2</i> | Secreted Frizzled Related Protein 2 | Modulator of Wnt Signaling |
| <i>Col2a1</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>Hmg5</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>Cdc33</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 | snoRNA affiliated gene |
| <i>Vault5</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 | CCTCTTCGATCAAGCTTTTCG | 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 | GACACCCCGTGACACTTG | 186 |
| | | R | CCACCACACGTA CTGCTCG | |
| <i>Ngf</i> | Nerve growth factor | F | GCAGCATGGTGGAGTTTGG | 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 | GCTCCACGAGGACTAACTAGG | 236 |
| | | R | GAATGCGCTCCGAGAGGTAA | |

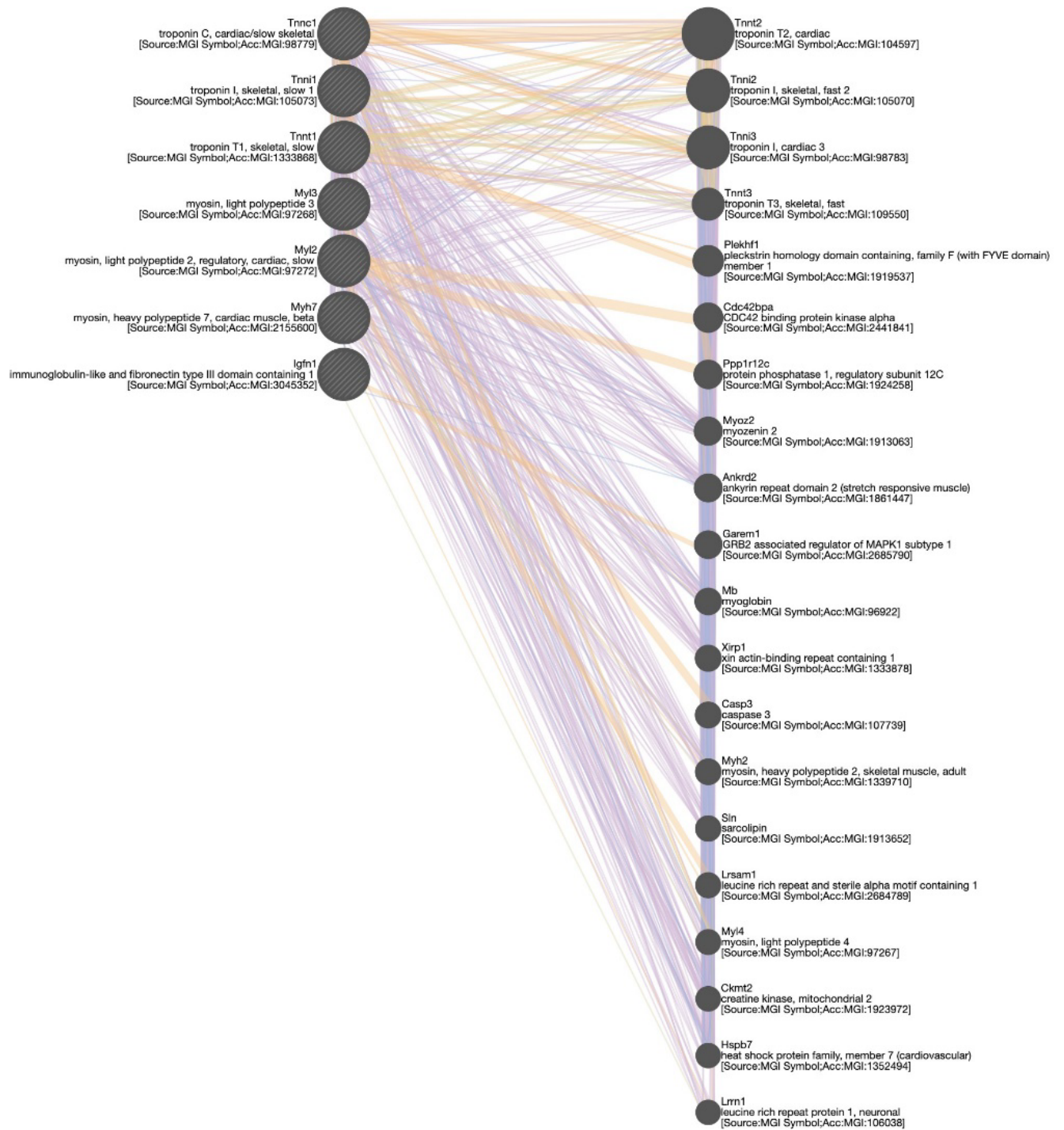
Size in base pairs (BP) is predicted unless indicated* and measured from agarose electrophoresis. Not available (NA) refers to a commercial or academic source described in Materials and Methods with an unknown amplicon size.

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/ μm^2 support a difference between the two groups. Median value images are shown. Mean \pm 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.