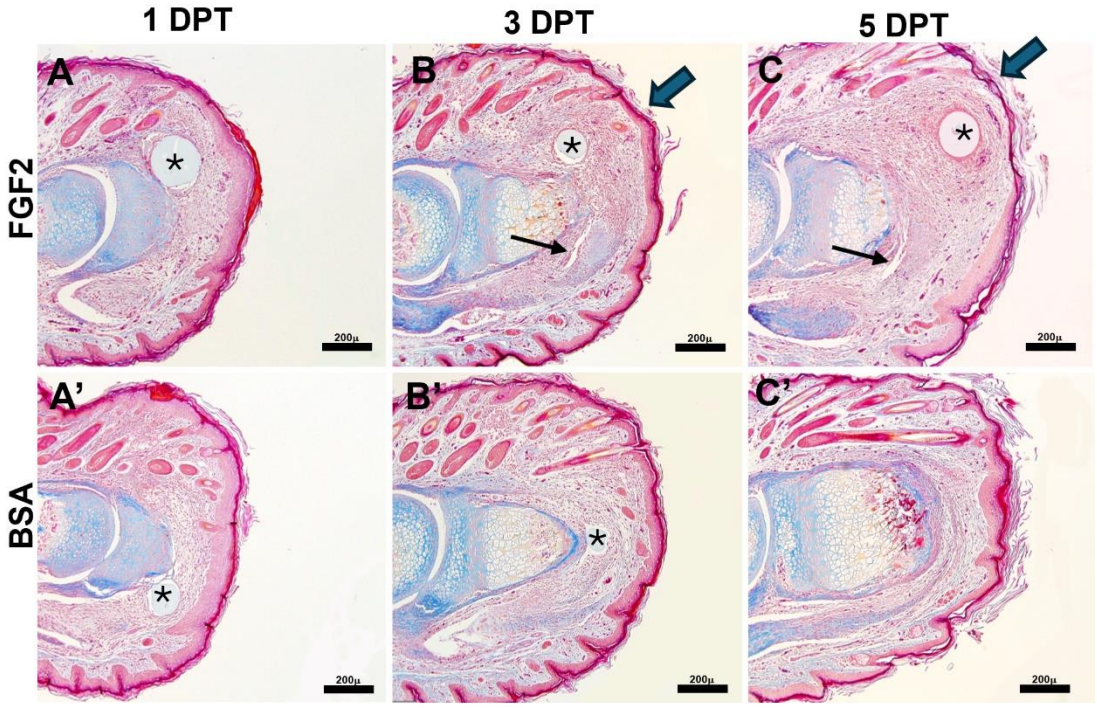
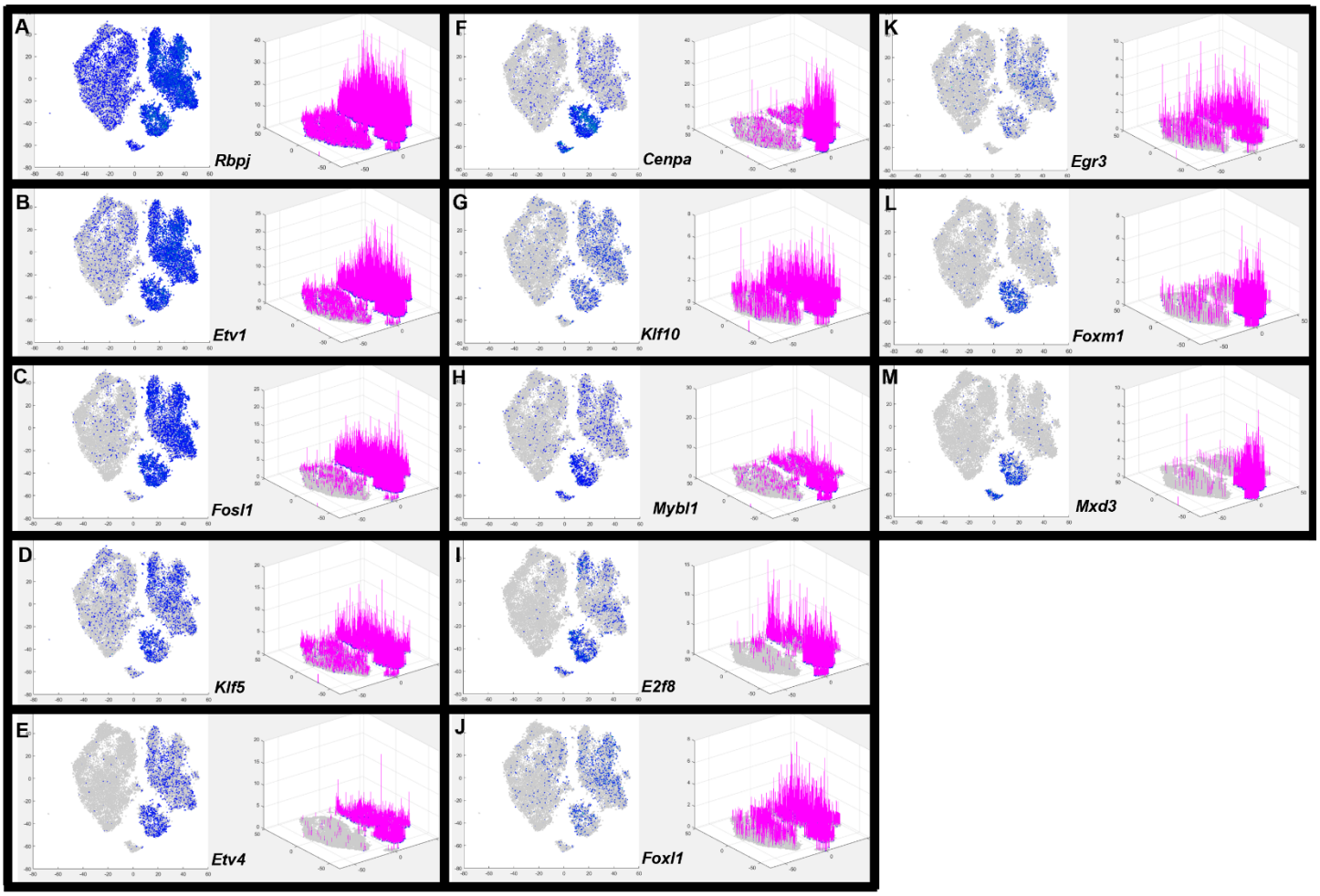
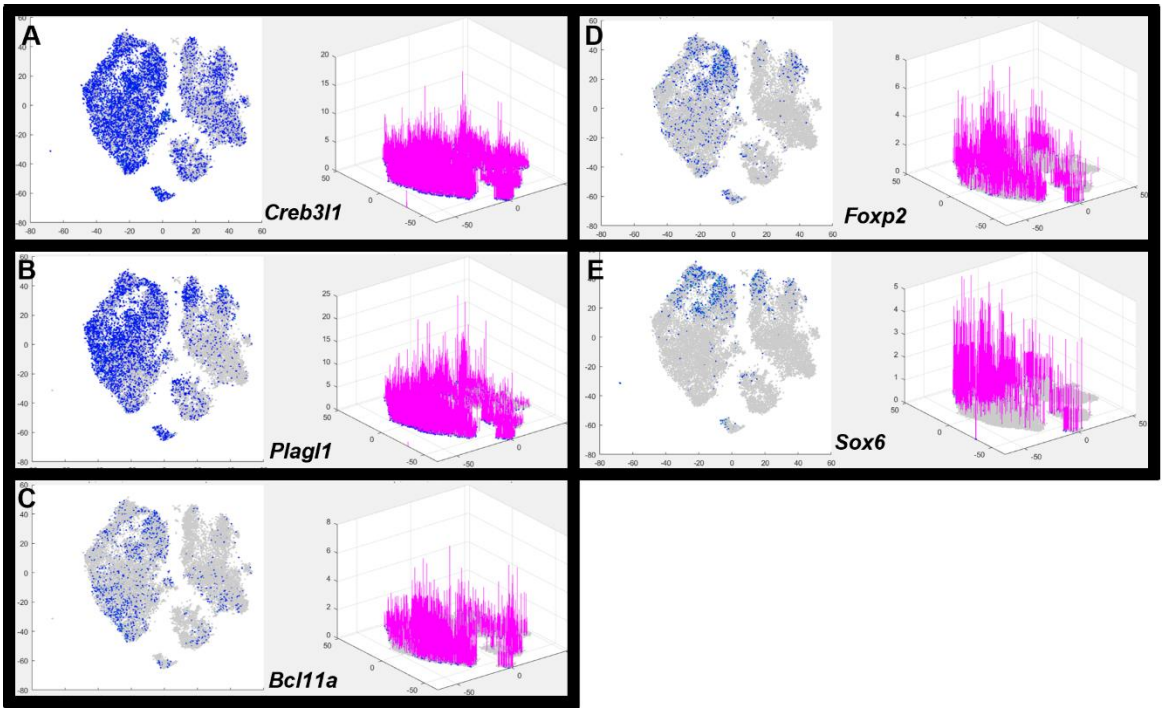


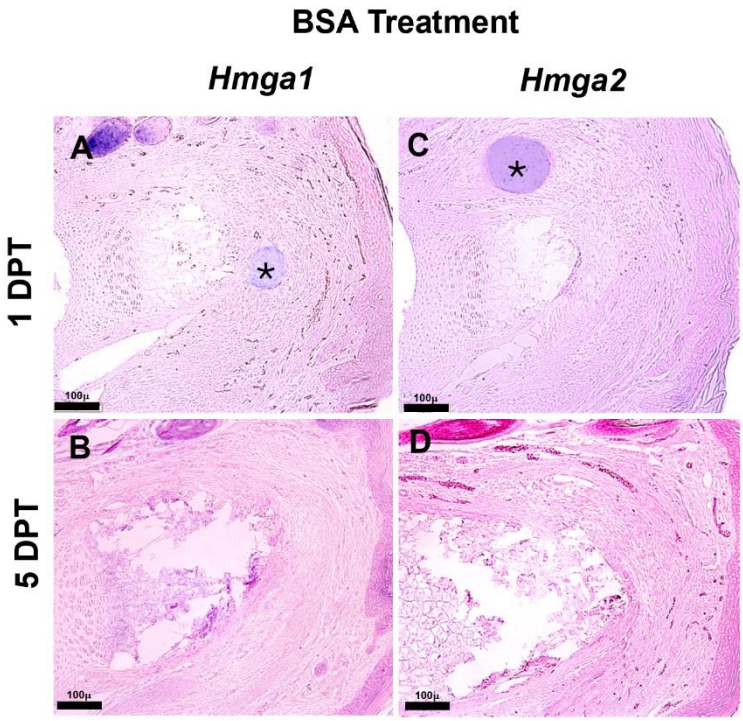
Supplemental Figure 1 – A-C) Progression of FGF2 induced changes of the non-regenerative P2 amputation wound compared with wound healing of control BSA treated digit amputation. A-A') At 1 day post treatment (DPT) the amputation wound of the FGF2 treated digit (A) does not appear different compared to the control BSA treated digit (A'). B-B') At 3 DPT there is a distinct accumulation of mesenchymal cells associated with the FGF2 bead (*) in the dorsal wound (large arrow) and an ectopic chondrogenic nodule associated with a cavity (small arrow) in the ventral region of the wound (B). The BSA control digit (B') is not modified at 3 DPT. C-C') At 5 DPT the accumulation of cells around the FGF2 bead (*) is pronounced (large arrow) and the joint regeneration response (small arrow) continues in the ventral wound region (C) while the BSA control digit (C') is unremarkable.



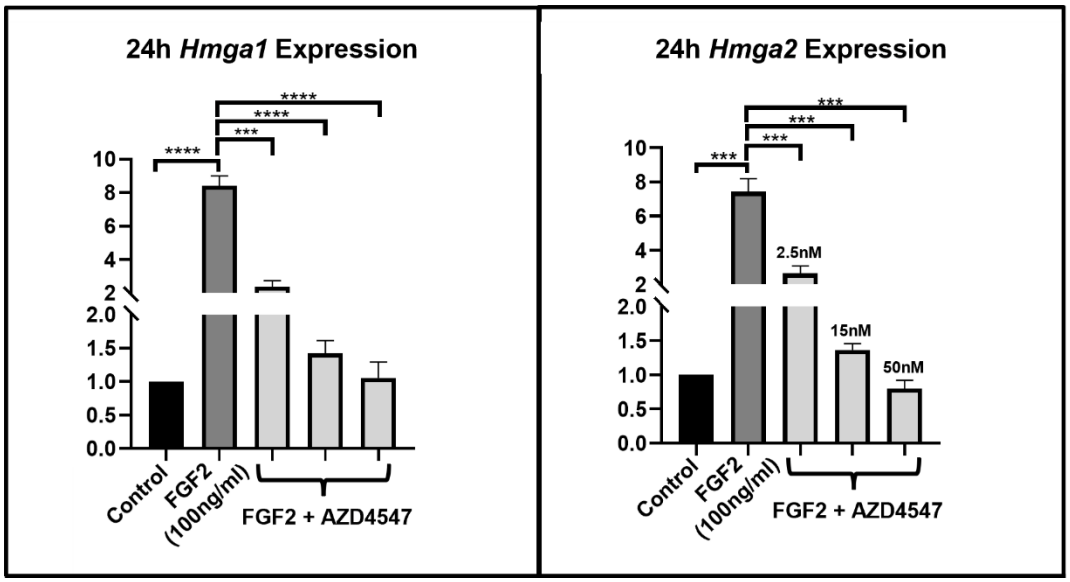
Supplemental Figure 2 – scRNAseq analysis of FGF2 treated amputation wound fibroblasts. A-M) t-SNE projections of 13 of the 15 DEGs for FGF2 induced transcriptional regulators. The dot plot (left) identifies expressing fibroblasts and the stem plot (right) represents the transcript level of each cell. Greater than 50% of the FGF2 induced fibroblasts express *Rbpj*, *Etv1* and *Fosl1* (A-C) whereas the remaining genes (D-M) are induced in less than 50% of the treated fibroblasts.



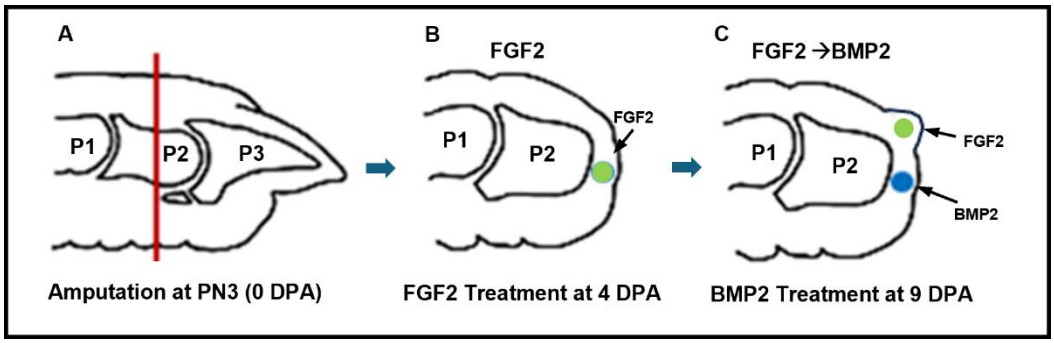
Supplemental Figure 3 – . scRNAseq analysis of FGF2 treated amputation wound fibroblasts. A--E) t-SNE projections of the 5 DEGs for FGF2 repressed transcriptional regulators. The dot plot (left) identifies expressing fibroblasts and the stem plot (right) represents the transcript level of each cell.



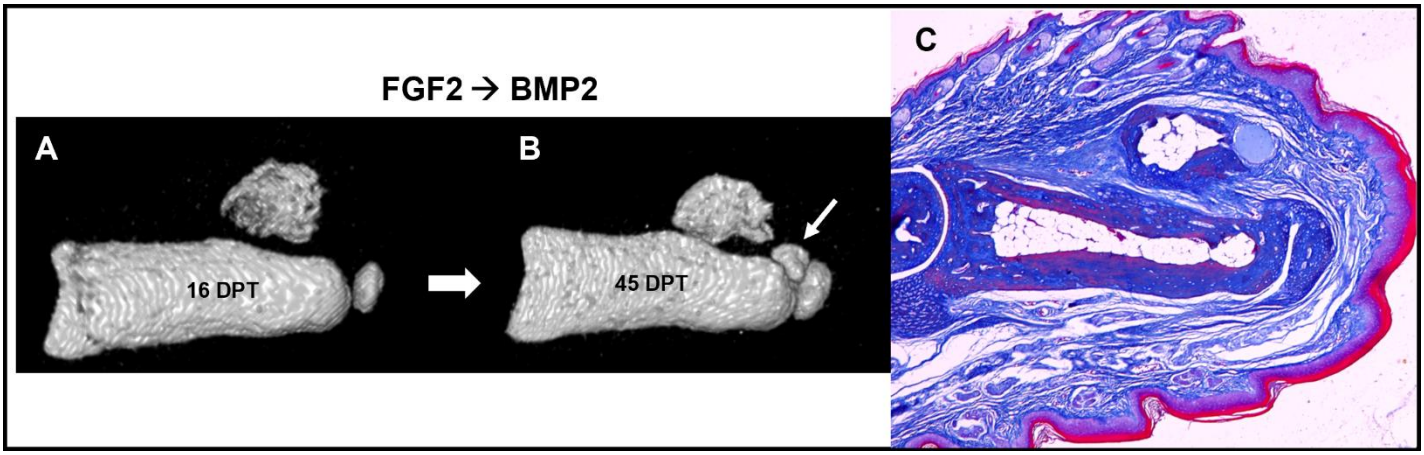
Supplemental Figure 4. Control *in situ* hybridization to localized *Hmga1* (A,B) or *Hmga2* (C,D) transcripts on paraffin sections of digit amputation wounds 1 day (A,C) and 5 days (B,D) after BSA bead (*) implantation. *Hmga1* and *Hmga2* transcripts were not expressed in control amputation wounds that heal by fibrosis.



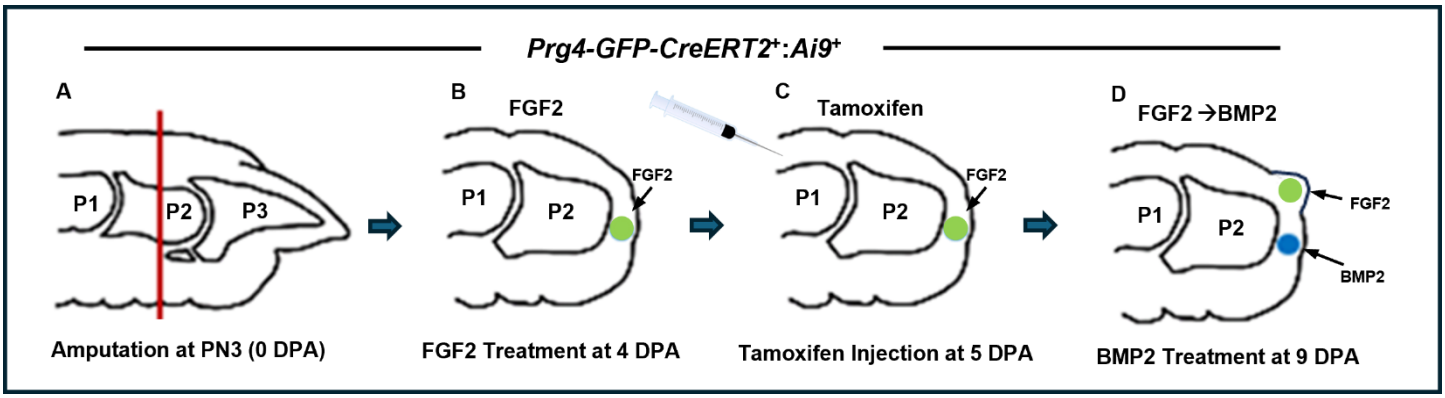
Supplemental Figure 5 – FGFR inhibition studies**.** Pre-treatment of cultured amputation wound fibroblasts with the pan FGF receptor inhibitor, AZD4547 (Selleck Chem LLC) blocks the induction of *Hmga1* (A) and *Hmga2* (B) induced expression by FGF2 in a dose-dependent manner at 24 hours.



Supplemental Figure 6 - Experimental design for sequential FGF2 and BMP2 treatment (FGF2→BMP2) of the amputated digit. A) The digit is amputated on PN3 midway through the P2 bone. B) 4 days post amputation (4 DPA) the amputation wound is closed and an FGF2 bead is implanted into the amputation stump. C) 5 days later (9 DPA) a blastema forms in the distal-dorsal region of the amputation wound and a BMP2 bead is implanted into the center of the amputation stump.



Supplemental Figure 7 – FGF2→BMP2 treated digit amputation that regenerated 3 ectopic skeletal elements at 45 days post treatment (DPT); one large element dorsal and two smaller distal elements. A) At 16 DPI 2 ectopic elements were observed by μCT; a large dorsal element and a small flattened distal element. B) At 45 DPI, a third element (arrow) formed between the stump and the distal element. C) Histological analysis showed that the dorsal element had a large marrow cavity whereas the flattened distal element was associated with a joint cavity.



Supplemental Figure 8 - Experimental design for tamoxifen treatment of FGF2→BMP2 treated amputated digits of *Prg4-GFP-CreERT2*$^{+}$*:Ai9*$^{+}$ neonatal mice. A) The digit is amputated midway through the P2 bone at PN3. B) 4 days after amputation (4 DPA) the amputation wound is closed and an FGF2 bead is implanted into the amputation stump. C) 1 day later (5 DPA) tamoxifen is injected systemically to induce *tomato* expression (TdT) in *Prg4* expressing cells. D) 4 days later (9 DPA) a BMP2 bead is implanted into the center of the amputation stump.

Supplemental Table 1. Primer information for qRT-PCR

Name primer		Sequence information	Name primer		Sequence information
1	*Mouse Ccl2*	Mm00441242_m1	2	*Mouse Cxcr4*	Mm01996749_s1
3	*Mouse Cxcl12*	Mm00445553_m1	4	*Mouse Msx1*	Mm00440330_m1
5	*Mouse PDGFrα*	Mm00440701_m1	6	*Mouse TGFβ1*	Mm01178820_m1
7	*Mouse Sox9*	Mm00448840_m1	8	*Mouse Col2a1*	Mm01309565_m1
9	*Mouse Col10a1*	Mm00487041_m1	10	*Mouse Wnt7a*	Mm00437356_m1
11	*Mouse Lmx1b*	Mm00440209_m1	12	*Mouse Hoxa13*	Mm00433967_m1
13	*Mouse Hoxd13*	Mm00433973_m1	14	*Mouse Prg4*	Mm01284582_m1
15	*Mouse Hmga1*	Mm01302616_g1	16	*Mouse Hmga2*	Mm04183367_g1
17	*Mouse RPL12*	Mm02601627_g1			

Supplemental Table 2 - Differentially Expressed Genes

Genes Up-Regulated by FGF2: *AA467197, Abcb1a, Abcb1b, Adam8, Adora2b, Aif1l, Akr1c18, Aldh1a3, Ank, Anln, Aox1, Apcdd1, Aqp1, Arap2, Arhgap11a, Arhgap22, Arl4c, Asf1b, Aspm, Ass1, Atp6v0e2, Aurka, Aurkb, Baiap2l1, Bcl2l1, Birc5, Bmp2, Brca1, Brip1, Bub1, Bub1b, C77080, Camk1d, Ccdc3, Cck, Ccl2, Ccna2, Ccnb1, Ccnb2, Ccnd1, Ccne2, Ccnf, Cd34, Cd44, Cd80, Cdc20, Cdc25b, Cdc25c, Cdca2, Cdca3, Cdca8, Cdkn3, Cdt1, Cenpa, Cenpe, Cenpf, Cenph, Cenpi, Cenpm, Cenpn, Cenpu, Cep55, Chic1, Chrna1, Chst1, Chtf18, Cip2a, Cit, Ckap2, Ckap2l, Clcf1, Cldn11, Cldn15, Clic5, Clspn, Cplx2, Cx3cl1, Cxcl10, Cyb561, Cyp2f2, Cystm1, Ddias, Depdc1a, Diaph3, Dio2, Dlgap1, Dlgap5, Dnph1, Dok1, Dusp10, Dusp5, Dusp6, E2f8, Ect2, Eda2r, Egr3, Eml5, Entpd1, Epha2, Eps8, Ercc1, Ercc6l, Ereg, Erich2, Ermp1, Errfi1, Esco2, Esm1, Etv1, Etv4, Eva1c, Fam111a, Fam181b, Fam78b, Fbxo5, Fez1, Fignl1, Fjx1, Flrt1, Fosl1, Foxl1, Foxm1, Frzb, Gas2l3, Gask1b, Gch1, Gdf15, Gdf6, Gen1, Gk, Gldn, Gmnn, Gprc5a, Gsdme, Gss, Gtse1, Hbegf, Hectd2, Hmga1, Hmga1b, Hmga2, Hmmr, Igsf9b, Il11, Il16, Il18rap, Il6ra, Inf2, Inka2, Iqgap2, Iqgap3, Itga4, Itga6, Itgb2, Itgb3, Itgb4, Itgb7, Itpr3, Kank3, Kcnn4, Kctd4, Kif11, Kif15, Kif18a, Kif20a, Kif20b, Kif22, Kif23, Kif2c, Kif4, Kifc1, Klf10, Klf5, Klk8, Knl1, Knstrn, Kpna2, Krt18, Lbhd2, Lgr6, Lipg, Lmo2, Lockd, Lrp8, Map3k6, Mapk13, Mastl, Mbnl3, Mcm5, Mcpt8, Mcub, Mdm2, Melk, Met, Mfap3l, Mfsd6, Mgat5, Mis18bp1, Mki67, Morrbid, Mtcl1, Mthfd1l, Mxd3, Mybl1, Myzap, Nav2, Nav3, Ncapd2, Ncapg, Ncaph, Nceh1, Ndc80, Nek2, Nes, Neto2, Notum, Nppc, Nptx1, Nqo1, Nrcam, Nuf2, Nusap1, Nxph3, Odc1, Orai2, Osbpl3, Osbpl6, Pakap, Pbk, Pbld1, Pcgf5, Pclaf, Pdzd2, Perp, Phlda1, Pi16, Pidd1, Pimreg, Pla2g7, Plau, Plaur, Plcg2, Plk1, Plk3, Pmaip1, Pole, Prc1, Prkcb, Prkg2, Prl2c2, Prl2c3, Prr11, Prrg4, Ptchd4, Ptgir, Ptgs1, Ptgs2, Ptk2b, Ptpn22, Ptprn, Pttg1, Pxn, Racgap1, Rad51, Rad51ap1, Raet1e, Rai14, Ramp3, Rapgef3, Raph1, Rassf3, Rbm47, Rbpj, Rem1, Rgmb, Rin1, Ripk3, Rrm2, Rsad2, S100a3, S100a7a, S100a8, Samd12, Schip1, Sema4b, Sema7a, Serpinb2, Sgms1, Sgms2, Sgo1, Sgo2a, Sh3bgrl2, Shcbp1, Ska1, Slc14a1, Slc16a1, Slc16a11, Slc19a2, Slc20a2, Slc25a37, Slc43a2, Slco2a1, Smox, Spag5, Spc24, Spc25, Spdl1, Spink2, Spred2, Spred3, Spry4, Stn1, Stom, Syngr1, Sytl1, Tacc3, Tbc1d2, Tcim, Tes, Tiam1, Tinagl1, Tk1, Tm4sf1, Tmem200a, Tmem47, Tmem51, Tnfrsf12a, Top2a, Tor4a, Tpd52, Tpx2, Trbc2, Trem2, Trib2, Trim7, Trip13, Trpm6, Tslp, Tspan15, Ttk, Ube2c, Ube2t, Ubtd1, Uhrf1, Ulbp1, Unc13c, Upp1, Vldlr, Wnt10a, Zfp365, Zwilch*

Genes Down-Regulated by FGF2: *Abi3bp, Acot2, Acvr2a, Adam12, Adamts15, Adamts9, Adamtsl1, Adh1, Aff3, Agtr1a, Aldh1l2, Ankrd55, Apba2, Arhgap20, Armh4, Aspn, Bcl11a, Bdh2, Bend5, Cadm2, Ccdc30, Ccdc80, Cd24a, Cdc42ep3, Cdkn1c, Cdon, Chodl, Clec3b, Cmbl, Cnn1, Col11a1, Col12a1, Col27a1, Cpxm1, Creb3l1, Cthrc1, Cttnbp2, Cxcl12, Cxcl15, Cybrd1, Cys1, Dact1, Ddr1, Ddx4, Dipk1a, Dipk2a, Dlc1, Dleu2, Dnajb3, Dpep1, Dtx4, Ecrg4, Egfl6, Eln, Epha3, Epha4, Epha5, Eya4, Fat4, Fbln7, Fbn2, Fbxl7, Fgfr2, Fgl2, Fhl1, Fibin, Fmo1, Fmod, Fndc1, Foxp2, Fxyd1, Fzd4, G0s2, Gadd45b, Gadd45g, Galnt13, Galnt9, Gas2, Gdf10, Gdpd2, Ggt5, Gstt1, Gucy1a1, Gulp1, Hmcn1, Hpgd, Hpse2, Hspb2, Htra3, Id4, Igf1, Igfbp5, Il1r2, Islr, Ism1, Kera, Klhl13, Lbp, Ldb2, Lgalsl, Limch1, Lmcd1, Lpl, Lrig3, Lrrc17, Lypd1, Maml2, Matn4, Me3, Megf6, Mest, Mex3b, Mfap4, Mia, Mmp11, Myl9, Mylk, Ncam2, Nckap5, Nedd9, Nhsl1, Nid2, Nkd1, Nrep, Nuak1, Ogn, Olfml1, Omd, Ophn1, Otulinl, Pappa, Parm1, Pcsk5, Pdgfd, Pdgfrl, Pdk1, Phactr1, Phyhd1, Plagl1, Plcxd2, Plekhf1, Plscr2, Podn, Podxl2, Porcn, Ppfibp2, Ppp1r3b, Prelp, Prlr, Prr16, Prss23, Prss35, Pth1r, Ptn, Ptprd, Ptx3, Pygo1, Rab30, Ramp1, Ramp2, Rasl11a, Rbp4, Reps2, Rgs4, Ripor3, Rnf144a, Robo2, Rspo2, Rspo3, Sbspon, Sema3d, Sfrp2, Shroom3, Slc1a3, Slc1a6, Slc24a3, Slc40a1, Slc9a9, Smarca1, Smoc1, Smpdl3a, Sorcs2, Sox6, Spon1, Srpx, St8sia2, Steap4, Susd2, Svep1, Tbxa2r, Tceal3, Tcerg1l, Tenm3, Tent5a, Tgfb2, Thsd7a, Tmeff1, Tmem26, Tnik, Tnmd, Tnn, Tox, Trib3, Unc5c, Vipr2, Vstm4, Wnt16, Wnt5b, Ypel1, Zfp521*