SUPPLEMENTARY NOTES

Pre-Ranked CAMERA Pathway Enrichment and Derivation of Biological Axes

For biological evaluation against gene-based resources, UniProt accessions pf proteins were mapped to gene symbols and Entrez identifiers using the genome-wide annotation for human (org.Hs.eg.db version 3.21). Moderated t-statistics from protein-level Limma were extracted and those mapped to the same gene symbol (11 of 5,373 symbols, 0.2%) were averaged across assays to a single value prior to gene set analysis. All 11 affected symbols were inspected and confirmed to represent assays targeting the same protein or closely related isoforms.

To distinguish the relative relevance of biological processes in treatment-mediated myocardial fibrosis, competitive gene set test was conducted by comparing the collective direction of gene-set regulation between treatment groups. Considering the co-regulation tendency of proteins, such coordinated pathway enrichment was evaluated using the CAMERA (Correlation Adjusted Mean Rank) method, which is a competitive gene set test accounting for inter-gene correlation and controlling type I error.

Corresponding gene sets were obtained from MSigDB Hallmark, Reactome, and MatrisomeDB (curated collection of genes encoding extracellular matrix and associated proteins). Prioritizing mechanistic relevance, CAMERA was performed using pre-specified hypothesis-driven gene sets that reflect fibrosis biology by applying keyword filtering based on existing fibrosis and heart failure literature with relevance to sacubitril/valsartan's antifibrotic mechanism. Keywords were derived independently of enrichment results. Pathways containing the following keywords were retained: "IL6", "JAK", "STAT", "INFLAM", "TNFA", "NFKB", "COMPLEMENT", "COAGUL", "PLATELET", "INTEGRIN", "EXTRACELLULAR MATRIX", "ECM", "MATRIX", "COLLAGEN", "TGF", "SMAD", "WOUND", "EMT", "FIBRO". A small number of pathways incidentally matching oncology-related keywords was excluded: "MELANOMA", "MYELOMA", "METAST", "ORIGINS TO A POST REPLICATIVE", "REPLICATION". This resulted in a total of 49 pathways being included in CAMERA computation.

Supplementary Table 1. Curated gene set universe (n=49 pathways) included in CAMERA pathway enrichment analysis.

Pathway	Number of Proteins
HALLMARK IL6 JAK STAT3 SIGNALING	62
REACTOME GENE AND PROTEIN EXPRESSION BY JAK STAT SIGNALING AFTER INTERLEUKIN 12 STIMULATION	15
HALLMARK INFLAMMATORY RESPONSE	100
HALLMARK COAGULATION	80
REACTOME INTEGRIN CELL SURFACE INTERACTIONS	50
REACTOME SIGNALING BY PDGF	30
REACTOME RESPONSE TO ELEVATED PLATELET CYTOSOLIC CA2	69
REACTOME COMPLEMENT CASCADE	36
REACTOME COLLAGEN CHAIN TRIMERIZATION	17
NABA COLLAGENS	17
REACTOME PLATELET HOMEOSTASIS	20
REACTOME METABOLISM OF ANGIOTENSINOGEN TO ANGIOTENSINS	14
REACTOME DOWNREGULATION OF SMAD2 3 SMAD4 TRANSCRIPTIONAL ACTIVITY	13
REACTOME TRANSCRIPTIONAL ACTIVITY OF SMAD2 SMAD3 SMAD4 HETEROTRIMER	14
HALLMARK TNFA SIGNALING VIA NFKB	91
REACTOME INFLAMMASOMES	11
REACTOME ACTIVATION OF MATRIX METALLOPROTEINASES	19
REACTOME HEDGEHOG ON STATE	20
REACTOME COLLAGEN BIOSYNTHESIS AND MODIFYING ENZYMES	24
REACTOME INITIAL TRIGGERING OF COMPLEMENT	14
REACTOME SIGNALING BY TGFBR3	11
REACTOME DOWNREGULATION OF TGF BETA RECEPTOR SIGNALING	12

Pathway	Number of Proteins
REACTOME SIGNALING BY TGFB FAMILY MEMBERS	52
REACTOME RUNX1 REGULATES GENES INVOLVED IN MEGAKARYOCYTE DIFFERENTIATION AND PLATELET FUNCTION	10
NABA ECM GLYCOPROTEINS	103
REACTOME INTEGRIN SIGNALING	11
REACTOME PLATELET ACTIVATION SIGNALING AND AGGREGATION	105
REACTOME SIGNALING BY BMP	14
REACTOME HEDGEHOG OFF STATE	25
NABA ECM REGULATORS	116
REACTOME NON INTEGRIN MEMBRANE ECM INTERACTIONS	37
HALLMARK IL2 STAT5 SIGNALING	96
HALLMARK TGF BETA SIGNALING	24
REACTOME GPCR LIGAND BINDING	108
REACTOME TURBULENT OSCILLATORY DISTURBED FLOW SHEAR STRESS ACTIVATES SIGNALING BY PIEZO1 AND INTEGRINS IN ENDOTHELIAL CELLS	12
REACTOME SIGNALING BY GPCR	184
REACTOME ANTI INFLAMMATORY RESPONSE FAVOURING LEISHMANIA PARASITE INFECTION	26
REACTOME SIGNALING BY TGF BETA RECEPTOR COMPLEX	33
NABA ECM AFFILIATED	85
REACTOME EXTRACELLULAR MATRIX ORGANIZATION	158
REACTOME COLLAGEN FORMATION	34
REACTOME DEGRADATION OF THE EXTRACELLULAR MATRIX	64
REACTOME PLATELET AGGREGATION PLUG FORMATION	18
REACTOME ECM PROTEOGLYCANS	48
REACTOME FACTORS INVOLVED IN MEGAKARYOCYTE DEVELOPMENT AND PLATELET PRODUCTION	46

Pathway	Number of Proteins
HALLMARK COMPLEMENT	111
REACTOME COLLAGEN DEGRADATION	32
REACTOME ASSEMBLY OF COLLAGEN FIBRILS AND OTHER MULTIMERIC STRUCTURES	25
REACTOME TGF BETA RECEPTOR SIGNALING ACTIVATES SMADS	21

Supplementary Table 2. Protein mapping to biological axes.

Biological Axes	Number of Proteins	Proteins on Panel
Neurohormonal & Vasoactive	18	ACE, ACE2, ADM, AGT, ECE1, EDN1, EDNRB, MME, NOS1, NOS2, NOS3, NPPB, NPPC, NPR1, PRKG1, RAMP2, RAMP3, REN
TGF-beta Superfamily & Fibrogenic	27	ACTA2, ACVRL1, BMP10, BMP4, BMP6, BMP7, BMPR1B, CCN1, CCN2, CCN3, CHRDL1, CHRDL2, ENG, GDF15, GDF2, IGFBP7, SERPINE1, SMAD1, SMAD2, SMAD3, SMAD5, TGFB1, TGFB2, TGFBI, TGFBR1, TGFBR2, TGFBR3
PDGF & Fibroblast Proliferation	16	AKT2, FN1, GAB1, HRAS, MAP2K1, NRAS, PDGFA, PDGFB, PDGFC, PDGFD, PDGFRA, PDGFRB, PLCG1, PTPN11, SRC, YES1
MMP/TIMP & ECM Enzymology	19	ADAM12, ADAMTS1, ADAMTS13, ADAMTS4, MMP1, MMP10, MMP12, MMP13, MMP15, MMP3, MMP7, MMP8, MMP9, PLAU, PLG, TIMP1, TIMP2, TIMP3, TIMP4
Structural ECM	18	COL15A1, COL18A1, COL1A1, COL2A1, COL3A1, COL4A1, COL5A1, COL6A3, COL9A1, ELN, FBN2, LAMA1, LAMA4, LAMB1, LAMB2, POSTN, TNC, VCAN
Inflammatory & Immune	35	ARG1, C1QA, C1R, C1S, C3, C4B, C5, C9, CCL2, CCL5, CD163, CFB, CFD, CFH, CFI, CX3CL1, CXCL10, IFNG, IL18, IL1B, IL2, IL2RA, IL2RB, IL2RG, IL6, IL6R, IL6ST, MASP1, MBL2, MRC1, STAT5B, TNF, TNFRSF1A, TNFRSF1B, TRAF2