Blood transcriptome and clonal T-cell correlates of response and non-response to eltrombopag therapy in a cohort of patients with chronic immune thrombocytopenia

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†HZ and BMZ contributed equally to this work.

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doi:10.3324/haematol.2019.26688
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Supplemental data
Supplemental Methods

Patient enrollment and sample collection

The study was approved by the institutional review boards of Weill Medical College of Cornell University and Stanford University. With informed consent, patients with chronic ITP receiving eltrombopag monotherapy (75 mg daily) during the period of blood sample collections were enrolled in this study (n=19, supplemental Table S1). All patients were diagnosed according to the ASH and Consensus guidelines.\textsuperscript{1,2} ITP is diagnosed in a patient with isolated thrombocytopenia, no abnormalities on physical examination or laboratory results suggestive of another cause of thrombocytopenia. The criteria for response assessment are modified from the International Working Group guidelines.\textsuperscript{3} Response (R) in this study includes both complete response (platelet count >100 x 10\textsuperscript{9}/L and absence of bleeding) and response (platelet count ranges from 30 to 100 x 10\textsuperscript{9}/L, and at least a two-fold increase of the baseline count without bleeding) that defined in the International Working Group guideline. Nonresponse (NR) was defined as platelet count <30 x 10\textsuperscript{9}/L or failed to double baseline platelet count within 90 days of treatment, or bleeding. Peripheral blood samples were collected into PAXgene blood RNA tubes (BD Biosciences, San Jose, CA) at pretreatment, and at 1-week and 1-month on treatment. Patients were stratified by the number/type of prior treatment or duration of disease to assess associations with eltrombopag response.

RNA extraction and Globin mRNA reduction

Total RNA was extracted using EZNA PX blood RNA kit (Omega bio-tek, Norcross, GA), and then concentrated using RNA clean & concentrator-5 (ZYMO research, Irvine, CA). Alpha- and beta-globin mRNAs were depleted from total RNA samples using GLOBINclear-human globin mRNA removal kit (Thermo Fisher Scientific, Waltham, MA) according to manufacturer’s instruction.

3’-end sequencing for expression quantification (3SEQ) and data analysis

3SEQ is a type of RNA-seq that focuses on quantitative analysis of transcriptome by generating a directional sequencing library targeting 3’UTRs and flanking regions in near upstream of poly-A tail and ensuring that one read is produced and measured per transcript. 3SEQ libraries were constructed based on the previously published method\textsuperscript{4} with modifications. Briefly, after globin mRNA reduction, mRNAs were enriched by poly-A selection using Dynabeads mRNA purification kit (Thermo Fisher Scientific, Waltham, MA), and heat-fragmented to 100-200 nucleotides. First-strand cDNAs were synthesized using Superscript III reverse transcriptase with Rd2SP-oligodT primer, followed by second-strand cDNA
synthesis. Adenine was added to the 3’-end of the double-stranded cDNA and then ligated to the P5-R1SP adapter. The ligated product was amplified by PCR for 15 cycles using primers P5-Rd1SP and P7-index-Rd2SP. Six Illumina indexes, each with six bases, were introduced in the P7 primers. Sequence of the primers used in 3SEQ library construction was provided in supplemental Table S7. Qualities of the libraries were examined using Agilent DNA 1000 kit on Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Libraries were quantified by Qubit 2.0 fluorometer using Qubit dsDNA BR assay kit (Thermo Fisher Scientific, Waltham, MA). Six samples with different indexes were pooled together and submitted for sequencing at Stanford Center for Genomics and Personalized Medicine. Index associated 36 bp sequences from the P5 primer end, providing the 5’-end sequences of the polyA-containing mRNA fragments, were generated using Illumina HiSeq 2000 system (Illumina Inc., San Diego, CA). Sequencing data of 46 samples included in this study were deposited to Gene Expression Omnibus (GEO) with the accession number of GSE112278.

Next, using previously described method,5 3SEQ data were filtered and mapped to human transcriptome hg19, and read counts for each gene were generated.

Differentially expressed genes were identified using significance analysis of microarrays-Seq (SAMseq) algorithm using the following cut off criteria: fold change > 2; average transcript per million (TPM) > 0.25; and q-value < .05 for 2 class paired SAMseq analysis between different time points of the same patient group. Samples that were 7-16 days into treatment were analyzed as “1-week” class, and 21-56 days into treatment as “1-month” class. As we performed globin mRNA reduction procedure before 3SEQ library construction, the expressions of hemoglobin subunit alpha 1 (HBA1), alpha 2 (HBA2), and beta (HBB) were excluded from the SAMseq analysis.

Cluster 3.0 (https://www.encodeproject.org/software/cluster/) was used for hierarchical clustering: expression data (in TPMs) of selected genes in designated patient samples were adjusted by “log transform data”, and “center genes-median”, then clustered using “complete linkage” method. The clustered heatmaps were visualized using Java TreeView (Version 1.1.6r4, https://sourceforge.net/projects/jtreeview/files/). Ingenuity Pathways Analysis (IPA)6 (https://www.qiagenbioinformatics.com/products/ingenuitypathway-analysis, Qiagen, Redwood City, CA) was performed to identify potential upstream transcriptional regulators, associated diseases and functions, and enriched canonical pathways of the differentially expressed genes.

**TRB repertoire analysis**

Genomic DNA were extracted from patient blood samples and used for TRB repertoire analysis as previously described.7 Briefly, modified Biomed-2 primers8 were used to amplify the variable-diversity-
joining (VDJ) segments of rearranged TRB genes. The obtained amplicons were used to construct sequencing libraries using KAPA Hyper Prep kit (Kapa Biosystems, Boston, MA), and subjected to paired-end sequencing using MiSeq 500-cycle V2 kit (Illumina). The overlapped paired-end reads were joined using the publicly available software FLASH (Fast Length Adjustment of Short Reads). Subsequently, the obtained TRB sequences were submitted to IMGT/HighV-Quest for rearrangement analysis. For each sample, the unique CDR3 amino acid sequences and their frequencies in the sampled repertoires were summarized based on the IMGT/HighV-Quest results.

**Statistical analysis**

Gene expression levels were presented in TPM. Group values were presented as means ± standard deviation. Statistical analyses were performed using the Mann-Whitney U test for comparisons between responding and nonresponding groups, and paired student t test for longitudinal changes within responding or nonresponding groups. Differences were considered significant at $P < .05$. 
Supplemental Table S1. Patient information and sample usage for various assays included in this study

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<th>SAMseq</th>
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* platelet count was confounded by an adjacent IVIG treatment, and was excluded from pretreatment platelet count statistics listed in the third paragraph in the main text. The baseline platelet count prior to IVIG treatment (R10, R11) or eltrombopag initiation (R7) was provided in the parentheses.

a R4 had a slow response to eltrombopag, but platelet count stayed above 40 x 10⁹/L, and was 90 x 10⁹/L after 8 months of treatment.

b R6 had an interrupted treatment course. Eltrombopag was discontinued after 13 days of treatment when platelet count reached 1000 x 10⁹/L. Treatment resumed later and the sample R6-1mo was collected 28 days after treatment resumed, therefore this time point was not included in longitudinal gene expression analyses.

c platelet count was not available at this time point, but the platelet count was 61 x 10⁹/L after 3 weeks of treatment.

Abbreviations:
SPL: splenectomy; RTX: rituximab (Rituxan X2; Rituxan); VTZ: veltuzumab; Anti-D: WinRho; DZ: danazol; MPSS: Methylprednisolone sodium succinate (Solumedrol); DXM: dexamethasone (dex; Decadron); PDN: Prednisone; LUS: Iusutrombopag (Shionogi S-888711); ROM: romiplostim (Nplate®); AVA: Avatrombopag (E5501; YM477; AKR 501); FOS: Fostamatinib (RIGEL); VIN: Vincristine; AZA: Azathioprine; LVX: Levofloxacin; CTX: Cytoxan (Cyclophosphamide); CsA: cyclosporine; Anti-CD16: Anti-FcyRIII (GMA161); Anti-CD40L: humanized anti-CD40L monoclonal antibody
### Supplemental Table S2. Patient stratification and corresponding response rate to eltrombopag

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<th>Total patient number</th>
<th>Responder (% of total)</th>
<th>Non-responder (% of total)</th>
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<td>≤ 4</td>
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a includes patients who were treated with Rituximab + dexamethasone
### Supplemental Table S3. List of eltrombopag-induced genes in responders

1-week vs pretreatment

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<th>q-value (%)</th>
<th>Average expression (TPM)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Overlap with platelet transcriptome&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>q-value (%)</td>
<td>Average expression TPM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Overlap with platelet transcriptome&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Overlap with nonubiquitous genes of platelet transcriptome&lt;sup&gt;d&lt;/sup&gt;</td>
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<sup>a</sup> for genes GLOD5, CPA2, IGFBP2, KIAA1211, BEST3, and PKHD1L1, as their expression levels at pretreatment time point are mostly below detection limit, the calculated fold changes for these genes are very high and may not represent the real changes of their expression levels.

<sup>b</sup> for each patient, the expression levels of the transcriptome were normalized to transcripts per million (TPM), then the average expression level of each differentially expressed gene across all samples used in the analysis was provided here.

<sup>c</sup> platelet transcriptome genes were obtained from the Table S4 of a previous publication.<sup>11</sup>

<sup>d</sup> nonubiquitous genes of platelet transcriptome were obtained from the Table S5 of a previous publication.<sup>11</sup>
**Supplemental Table S4. Diseases and functions that predicted by Ingenuity Pathways Analysis to be decreased or increased based on the expression changes of eltrombopag-induced genes.**

<table>
<thead>
<tr>
<th>Predicted to be decreased</th>
<th>Diseases or Functions</th>
<th>Annotation</th>
<th>p-Value</th>
<th>Activation z-score</th>
<th>Molecules</th>
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<td><strong>Bleeding time</strong></td>
<td></td>
<td></td>
<td>3.71E-13</td>
<td>-2.377</td>
<td>ABCB4, CD151, F13A1, GP1BA, ITGA2B, ITGB3, MIP6B, PROS1, SELP, TREML1, TUBB1</td>
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<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
<td>1.42E-09</td>
<td>-2.377</td>
<td>E2F1, GFI1B, GP1BA, GP1BB, GP9, ITGA2B, ITGB3, LCN2, MIF, MIP6B, PROS1, PGIR, PTGS1, THBS1, TREML1, TSPAN33, TUBB1</td>
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<tr>
<td><strong>Cytopenia</strong></td>
<td></td>
<td></td>
<td>2.64E-07</td>
<td>-2.377</td>
<td>E2F1, GFI1B, GP1BA, GP1BB, GP9, ITGA2B, ITGB3, LCN2, MIF, MIP6B, PROS1, PGIR, PTGS1, THBS1, TREML1, TSPAN33, TUBB1</td>
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<td><strong>Bleeding</strong></td>
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<td></td>
<td>4.42E-07</td>
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<td>CNN1, E2F1, F13A1, GP1BA, ITGA2B, ITGB3, JAM3, OXR, PDGFA, PROS1, PGIR, PTGS1, SCN1B, SELP, SPHK1, TFPI, THBS1, TREML1, TUBB1</td>
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<td><strong>Inflammation of organ</strong></td>
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<td>3.14E-05</td>
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<td>ABCB4, ALOX12, CD151, CDKN1A, CLU, CXCL5, E2F1, ECM1, EGF, FAH, GFAF, GP1A, ITGB3, KCNN3, LCN2, MGLL, MYL9, MYLK, PDE5A, PDLIM1, PF4, PROS1, PGIR, PTGS1, PTPRN, RET, SCN1B, SELP, SMTN, SPARC, SPHK1, TFPI, THBS1, TPM1, TUBA8, TUBB1</td>
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<td><strong>Apoptosis of epithelial cells</strong></td>
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<td></td>
<td>1.65E-04</td>
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<td>CD151, CDKN1A, E2F1, EGF, FAH, LCN2, MIF, MYLK, PTGS1, SPARC, SPHK1</td>
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<td><strong>Cell death of epithelial cells</strong></td>
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<td></td>
<td>2.41E-04</td>
<td>-2.528</td>
<td>ABCB3, CD151, CDKN1A, DAB2, E2F1, EGF, FAH, LCN2, MIF, MYLK, NRGN, NTRK1, PGIR, PTGS1, SPARC, SPHK1, TGIFB11</td>
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<td><strong>Inflammation of absolute anatomical region</strong></td>
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<td>5.80E-04</td>
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<td>ABCB4, ALOX12, CLU, CXCL5, E2F1, ECM1, FAH, GFAF, ITGB3, KCNN3, LCN2, MGLL, MYLK, PDE5A, PF4, PRKAR1B, PROS1, PGIR, PTGS1, PTPRN, RET, SELP, SMTN, SPARC, SPHK1, TFPI, THBS1</td>
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<td><strong>Inflammation of body cavity</strong></td>
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<td><strong>Organismal death</strong></td>
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<td>ALOX12, CDKN1A, CEL, CETP, CLU, COL10A1, E2F1, ECM1, FAH, FRMD3, GAS2L1, GFAF, HPN, IGFBP2, ITGA2B, ITGB3, ITGB5, LCN2, LY6G6D, PDE2A, PDE5A, PGIR, PTGS1, PTPRN, RAMP3, SCN1B, SELP, SPHK1, TFPI, THBS1, VEPH1</td>
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<th>Diseases or Functions</th>
<th>Annotation</th>
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<th>Molecules</th>
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<td>Migration of breast cancer cell lines</td>
<td>3.10E-05</td>
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<td>CTNNX, CXCL5, ECM1, EGF, IFGBP3, ITGB5, KCNN3, LCN2, NDFUAF3, PDLIM1, PRSS27, TFPI, TGFBI11</td>
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<td>Cell proliferation of breast cancer cell lines</td>
<td>3.48E-05</td>
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<td>CD151, CDKN1A, CLU, DAB2, E2F1, EGF, FOLR1, IFGBP2, ITGB3, ITGB5, MYLK, ND, UFAF3, NTRK1, PARV, PRGMC1, SPHK1, TFPI, TPM1</td>
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<td>Formation of actin filaments</td>
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<td>Microtubule dynamics</td>
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<td>ABC4, ABLM3, ARHGAPE6, ATL1, BACE1, CALD1, CDC42BPA, CLU, CTNNX, ECM1, EGF, ASL21, GFAP, IFGBP2, IFGBP2, ITGB3, ITGB5, KCNN3, LCN2, MAP1B, MGLL, MYLK, NCKAP1, NTRK1, PARV, PCTY1B, PDGFA, PLOXB3, PVAB1, RET, SCN1B, SPARC, SPHK1, THBS1, TGFBI11, THBS1, TFPI, TGFBI11, THBS1</td>
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<td>Organization of cytoskeleton</td>
<td>8.87E-05</td>
<td>2.516</td>
<td>ABC4, ABLM3, ARHGAPE6, ATL1, BACE1, CALD1, CDC42BPA, CLU, CTNNX, ECM1, EGF, ASL21, GFAP, IFGBP2, IFGBP2, ITGB3, ITGB5, KCNN3, LCN2, MAP1B, MGLL, MYLK, NCKAP1, NTRK1, PARV, PCTY1B, PDGFA, PLOXB3, PVAB1, RET, SCN1B, SPARC, SPHK1, THBS1, TGFBI11, THBS1, TFPI, TGFBI11, THBS1</td>
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<td>Transport of molecule</td>
<td>1.00E-04</td>
<td>2.678</td>
<td>ABC3, ABC4, BEST3, CETF1, CLU, CRYM, CTSA, CTNNX, E2F1, EGF, FHL1, FOLR1, FXYD3, ITGB3, KCNN3, LCN2, MAP1B, MGLL, MGLL, NIFAP1, OXTR, PPBP, PPBP, PTGIR, PTGIR, RET, SCN1B, SEPT5, TCL1, TCL2, CTNNX, CTNNX, CTNNX, CTNNX, CTNNX, CTNNX</td>
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<tr>
<td>Invasion of cells</td>
<td>1.05E-04</td>
<td>3.12</td>
<td>CD151, CDC42BPA, CDKN1A, CLU, CMTM5, CTNNX, DAB2, ECM1, EGF, HNP, IFGBP2, ITGB3, JAM3, KCNN3, LCN2, MITF, NCKAP1, PARV, PCSK6, PDGFA, PDLIM1, RAMP3, RET, SELP, SPARC, SPHK1, TFPI</td>
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<tr>
<td>Adhesion of myeloid cells</td>
<td>1.10E-04</td>
<td>2.345</td>
<td>ALOX12, CTNNX, ITGB3, JAM3, MITF, PARV, PCK6, SELP</td>
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<tr>
<td>Chemotaxis of phagocytes</td>
<td>1.14E-04</td>
<td>2.928</td>
<td>CD151, CDKN1A, CXCL5, ITGB3, JAM3, LCN2, PARV, PCK6, PDGFA, PDLIM1, PPR327, RET, SELP, SPARC, SPHK1, THBS1, TGFBI11, THBS1</td>
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<td>Organization of cytoplasm</td>
<td>1.34E-04</td>
<td>2.516</td>
<td>ABC4, ABLM3, ARHGAPE6, ATL1, BACE1, CALD1, CDC42BPA, CLU, CTNNX, ECM1, EGF, ASL21, GFAP, IFGBP2, ITGB3, ITGB5, LAPTMB4, LCN2, MAP1B, MGLL, MYLK, NCKAP1, NTRK1, PARV, PCTY1B, PDE2A, PDGFA, PLOXB3, PVAB1, RET, SCN1B, SPARC, SPHK1, THBS1, TGFBI11, THBS1, TFPI, TGFBI11, THBS1, WASF1</td>
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<td><strong>Endocytosis</strong></td>
<td>1.57E-04</td>
<td>3.102</td>
<td>CD151,CLU,CTTN,DAB2,EGF,FOLR1,ITGB3,LCN2,MAP1B,MYLK,PEAR1,PF4,PORSI,STON2,THBS1,TM4SF1</td>
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<td><strong>Metastasis of cells</strong></td>
<td>1.59E-04</td>
<td>2.238</td>
<td>CD151,CNN1,CTTN,CXCL5,EGF,EGFL7,KCNN3,NCKAP1,PDLIM1,SELP,THBS1</td>
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<td><strong>Viral Infection</strong></td>
<td>1.70E-04</td>
<td>4.575</td>
<td>ABLIM3,ALOX12,ANKRD9,CALD1,CDC42BPA,CEL,CLU,EGF,F13A1,FOLR1,HB E1,ITGA29,ITGB3,ITGB5,LCN2,MAP1A,MGLL,NCKAP1,NDUFAF3,NECAB3,PAR V8,PCSK6,PDSE5A,PF4,PPBP,PRSS27,PTGS1,PTPRN,VALB,RAB6B,S EC14L2,SPARC,SPHK1,TUBA8,TUBB1,WASF1</td>
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<td><strong>Adhesion of blood cells</strong></td>
<td>1.79E-04</td>
<td>2.506</td>
<td>ABC4,ALOX12,CD151,CTTN,GP1BA,ITGA25,ITGB3,JAM3,MIF,PF4,PPBP,SE LP,THBS1</td>
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<td><strong>Chemotaxis of leukocytes</strong></td>
<td>2.14E-04</td>
<td>3.072</td>
<td>CD151,CDKN1A,CXCL5,ITGB3,JAM3,LCN2,MYLK,PF4,PF4V1,PPBP,SELP,SPH K1,THBS1</td>
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<td><strong>Chemotaxis</strong></td>
<td>2.35E-04</td>
<td>3.494</td>
<td>CD151,CDKN1A,CXCL5,EGF,ITGB3,JAM3,LCN2,MYLK,PDGFA,PF4,PF4V1,PLX NB3,PPBP,SCN1B,SELP,SPHK1,THBS1</td>
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<tr>
<td><strong>Neoplasia of tumor cell lines</strong></td>
<td>2.61E-04</td>
<td>2.101</td>
<td>CD151,CDKN1A,CNN1,CTTN,CXCL5,EGF,EGFL7,IGFBP2,KCNN3,NCKAP1,N DUFAF3,PDLIM1,SELP,THBS1</td>
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<td><strong>Adhesion of phagocytes</strong></td>
<td>2.86E-04</td>
<td>2.137</td>
<td>ALOX12,CTTN,JAM3,MIF,PF4,PPBP,SELP</td>
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<td><strong>Inflammatory response</strong></td>
<td>3.92E-04</td>
<td>3.358</td>
<td>CD151,CDKN1A,CXCL5,ECM1,ITGB3,JAM3,LCN2,MGLL,MYLK,PDE2A,PF4,PF4 V1,PPBP,PRKAR1B,PROS1,PTGS1,SELP,SPHK1,THBS1,TUBA8,TUBB1</td>
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<tr>
<td><strong>Binding of professional phagocytic cells</strong></td>
<td>5.13E-04</td>
<td>2.342</td>
<td>ALOX12,CTTN,ITGB3,JAM3,MIF,PF4,PPBP,SELP</td>
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<tr>
<td><strong>Adhesion of granulocytes</strong></td>
<td>5.95E-04</td>
<td>2.142</td>
<td>CTTN,ITGB3,JAM3,PF4,PPBP,SELP</td>
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<tr>
<td><strong>Cell movement of neutrophils</strong></td>
<td>6.74E-04</td>
<td>2.562</td>
<td>CD151,CTTN,CXCL5,ITGB3,JAM3,LCN2,MYLK,PF4,PFBP,SELP,SPHK1</td>
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<tr>
<td><strong>Adhesion of breast cancer cell lines</strong></td>
<td>7.90E-04</td>
<td>2.2</td>
<td>EGF,ITGB3,PARV8,TGFBI1,THBS1</td>
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<tr>
<td><strong>Formation of cellular protrusions</strong></td>
<td>8.43E-04</td>
<td>2.129</td>
<td>ABC4,ABLIM3,ATL1,BACE1,CALD1,CLU,CTTN,EGF,ITGB3,LCN2,MAP1B,NCK AP1,NTRK1,PARV8,PCYT1B,PDGFA,PLXNB3,PVALB,RET,SPARC,SPHK1,THBS 1,TM4SF1,WASF1</td>
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<tr>
<td><strong>Cell viability of breast cancer cell lines</strong></td>
<td>1.09E-03</td>
<td>2.597</td>
<td>CD151,CDKN1A,CLU,ECM1,EGF,ITGB3,PGRMC1,RET,SPHK1</td>
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<tr>
<td><strong>Leukocyte migration</strong></td>
<td>1.22E-03</td>
<td>3.693</td>
<td>CD151,CDKN1A,CTTN,CXCL5,ESAM,F13A1,GFAP,GP1BA,ITGA2B,ITGB3,JAM3 LCN2,MYLK,PF4,PF4V1,PPBP,SELP,SPARC,SPHK1,TFPI,THBS1</td>
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<td><strong>Cell movement of granulocytes</strong></td>
<td>1.32E-03</td>
<td>2.851</td>
<td>CD151,CTTN,CXCL5,ITGB3,JAM3,LCN2,MYLK,PF4,PPBP,PGTR,SELP,SPHK1</td>
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<tr>
<td><strong>Cell survival</strong></td>
<td>1.41E-03</td>
<td>3.222</td>
<td>ABC3,ALOX12,CD151,CDC42BPA,CDKN1A,CEL,CLU,CTDSPL,CTTN,DAB2,EG F1,ECM1,EGF,HSPB6,IGFBP2,ITGB3,LCN2,MCUR1,NTRK1,PCSK6,PDGFA,P F4,PGRMC1,PPBP,PTPRN,RET,SPARC,SPHK1,STX1A,TFPI,THBS1</td>
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<tr>
<td><strong>Cell movement of fibrosarcoma cell lines</strong></td>
<td>1.43E-03</td>
<td>2</td>
<td>CTTN,DAB2,PARV8,WASF1</td>
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<tr>
<td><strong>Cell viability</strong></td>
<td>1.49E-03</td>
<td>3.173</td>
<td>ABC3,ALOX12,CD151,CDC42BPA,CDKN1A,CEL,CLU,CTDSPL,CTTN,DAB2,EG F1,ECM1,EGF,HSPB6,IGFBP2,ITGB3,LCN2,MCUR1,NTRK1,PCSK6,PDGFA,P F4,PGRMC1,PPBP,PTPRN,RET,SPARC,SPHK1,STX1A,TFPI,THBS1</td>
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<tr>
<td><strong>Chemotaxis of myeloid cells</strong></td>
<td>1.50E-03</td>
<td>2.586</td>
<td>CD151,CDKN1A,CXCL5,ITGB3,JAM3,LCN2,PPBP,SELP,SPHK1,THBS1</td>
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<tr>
<td><strong>Cell-cell contact</strong></td>
<td>1.53E-03</td>
<td>2.546</td>
<td>BACE1,CD151,CLDN5,CTTN,DAB2,EGF,ESAM,GFAP,JAM3,MYLK,NTRK1,OXT R,PTGIR,RET,SELP,STX1A,THBS1</td>
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# Supplemental Table S5. Canonical pathways that have significant gene enrichment in these eltrombopag-induced genes

<table>
<thead>
<tr>
<th>Ingenuity Canonical Pathways</th>
<th>-log(p-value)</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular Effects of Sildenafil (Viagra)</td>
<td>3.72E+00</td>
<td>MYL9,PDE2A, KCNN3, SLC4A11, PRKAR1B, PDE5A, MYLK</td>
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<tr>
<td>Extrinsic Prothrombin Activation Pathway</td>
<td>3.43E+00</td>
<td>PROS1, F13A1, TFPI</td>
</tr>
<tr>
<td>Clathrin-mediated Endocytosis Signaling</td>
<td>3.22E+00</td>
<td>STON2, PDEGA, DAB2, EGFR, CTTN, CLU, ITGB5, ITGB3</td>
</tr>
<tr>
<td>Integrin Signaling</td>
<td>3.06E+00</td>
<td>MYL9, PARVB, ITGA2B, CAPN11, MYLK, CTTN, ITGB5, ITGB3</td>
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<tr>
<td>Granulocyte Adhesion and Diapedesis</td>
<td>2.88E+00</td>
<td>CLDN5, SELP, JAM3, PPBP, PF4, CXCL5, ITGB3</td>
</tr>
<tr>
<td>Cardiac β-adrenergic Signaling</td>
<td>2.75E+00</td>
<td>PDE2A, GNG11, PRKAR1B, SLC8A3, PDE5A, PPP1R14A</td>
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<tr>
<td>Agranulocyte Adhesion and Diapedesis</td>
<td>2.72E+00</td>
<td>MYL9, CLDN5, SELP, JAM3, PPBP, PF4, CXCL5</td>
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<tr>
<td>Breast Cancer Regulation by Stathmin1</td>
<td>2.58E+00</td>
<td>TUBB1, GNG11, TUBA8, E2F1, CDKN1A, PRKAR1B, PPP1R14A</td>
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<tr>
<td>Coagulation System</td>
<td>2.42E+00</td>
<td>PROS1, F13A1, TFPI</td>
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<td>Caveolar-mediated Endocytosis Signaling</td>
<td>2.41E+00</td>
<td>ITGA2B, EGFR, ITGB5, ITGB3</td>
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<tr>
<td>Acyl-CoA Hydrolysis</td>
<td>2.30E+00</td>
<td>THEM5, ACO7</td>
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<td>RhoA Signaling</td>
<td>2.27E+00</td>
<td>MYL9, SEPT5, ARHGP6, WASF1, MYLK</td>
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<tr>
<td>Atherosclerosis Signaling</td>
<td>2.23E+00</td>
<td>SELP, PDGFA, COL10A, ALOX12, CLU</td>
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<tr>
<td>Macropinocytosis Signaling</td>
<td>2.21E+00</td>
<td>PDGFA, EGFR, ITGB5, ITGB3</td>
</tr>
<tr>
<td>Intrinsic Prothrombin Activation Pathway</td>
<td>2.19E+00</td>
<td>PROS1, F13A1, COL10A</td>
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<tr>
<td>Axonal Guidance Signaling</td>
<td>2.06E+00</td>
<td>MYL9, TUBB1, GNG11, TUBA8, PDGFA, NTRK1, ABLIM3, PRKAR1B, EGF, PLXNB3</td>
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<tr>
<td>Bladder Cancer Signaling</td>
<td>2.06E+00</td>
<td>THBS1, E2F1, CDKN1A, EGFR</td>
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<tr>
<td>HER-2 Signaling in Breast Cancer</td>
<td>2.08E+00</td>
<td>CDKN1A, EGFR, ITGB5, ITGB3</td>
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<td>Epithelial Adherens Junction Signaling</td>
<td>1.98E+00</td>
<td>MYL9, TUBB1, TUBA8, EGFR, WASF1</td>
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<tr>
<td>Protein Kinase A Signaling</td>
<td>1.96E+00</td>
<td>MYL9, PDE2A, GNG11, CDC14B, PRKAR1B, PDE5A, PPP1R14A, MYLK, PTPRN</td>
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<tr>
<td>Amyloid Processing</td>
<td>1.96E+00</td>
<td>CAPN11, PRKAR1B, BACE1</td>
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<tr>
<td>Melanoma Signaling</td>
<td>1.87E+00</td>
<td>MITF, E2F1, CDKN1A</td>
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<tr>
<td>Actin Cytoskeleton Signaling</td>
<td>1.76E+00</td>
<td>MYL9, PDGFA, EGFR, WASF1, MYLK, NCKAP1</td>
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<tr>
<td>Tight Junction Signaling</td>
<td>1.75E+00</td>
<td>MYL9, CLDN5, JAM3, PRKAR1B, MYLK</td>
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<tr>
<td>Glioma Signaling</td>
<td>1.70E+00</td>
<td>PDGFA, E2F1, CDKN1A, EGFR</td>
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<tr>
<td>Neuroprotective Role of THOP1 in Alzheimer's Disease</td>
<td>1.64E+00</td>
<td>PRSS50, PRKAR1B, HPN, PRSS27</td>
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<td>Eicosanoid Signaling</td>
<td>1.64E+00</td>
<td>PTGIR, PTGS1, ALOX12</td>
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<tr>
<td>Estrogen-mediated S-phase Entry</td>
<td>1.64E+00</td>
<td>E2F1, CDKN1A</td>
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<td>Sertoli Cell-Sertoli Cell Junction Signaling</td>
<td>1.64E+00</td>
<td>TUBB1, CLDN5, TUBA8, JAM3, PRKAR1B</td>
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<tr>
<td>Signaling by Rho Family GTPases</td>
<td>1.57E+00</td>
<td>MYL9, SEPT5, GNG11, WASF1, GFAP, MYLK</td>
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<td>Glutathione-mediated Detoxification</td>
<td>1.50E+00</td>
<td>GSTM5, GSTM4</td>
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<td>Dopamine Receptor Signaling</td>
<td>1.49E+00</td>
<td>PRKAR1B, PPP1R14A, SLC18A2</td>
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<td>IL-8 Signaling</td>
<td>1.48E+00</td>
<td>MYL9, GNG11, EGFR, ITGB5, ITGB3</td>
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<tr>
<td>P2Y Purigenic Receptor Signaling Pathway</td>
<td>1.48E+00</td>
<td>ITGA2B, GNG11, PRKAR1B, ITGB3</td>
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<td>ILK Signaling</td>
<td>1.48E+00</td>
<td>MYL9, PARVB, TGFB11, ITGB5, ITGB3</td>
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<td>Aryl Hydrocarbon Receptor Signaling</td>
<td>1.41E+00</td>
<td>GSTM5, E2F1, CDKN1A, GSTM4</td>
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<tr>
<td>IL-17A Signaling in Fibroblasts</td>
<td>1.40E+00</td>
<td>LCN2, CXCL5</td>
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<td>Ovarian Cancer Signaling</td>
<td>1.38E+00</td>
<td>PTGS1, E2F1, PRKAR1B, EGFR</td>
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<tr>
<td>Leukocyte Extravasation Signaling</td>
<td>1.37E+00</td>
<td>ARHGP6, CLDN5, JAM3, CTTN, ITGB3</td>
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<td>α-Adrenergic Signaling</td>
<td>1.35E+00</td>
<td>GNG11, PRKAR1B, SLC8A3</td>
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<td>Tyrosine Degradation I</td>
<td>1.35E+00</td>
<td>FAH</td>
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<tr>
<td>Regulation of Actin-based Motility by Rho</td>
<td>1.32E+00</td>
<td>MYL9, WASF1, MYLK</td>
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* Canonical pathway analysis was performed by using Ingenuity Pathways Analysis (IPA). The listed pathways have significant gene enrichment in these eltrombopag-induced genes, p < 0.05, which is –log (p-value) > 1.30.
Supplemental Table S6. Potential upstream regulators that may cause the expression changes of the eltrombopag-induced genes at 1-week time point

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<tr>
<th>Upstream Regulator</th>
<th>Molecule Type</th>
<th>Predicted Activation State</th>
<th>Activation z-score</th>
<th>p-value of overlap</th>
<th>Target molecules in dataset</th>
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<tr>
<td>VIPAS39</td>
<td>other</td>
<td>Activated</td>
<td>2.236</td>
<td>4.07E-10</td>
<td>PF4,PPBP,SELP,SPARC,THBS1</td>
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<td>GATA1</td>
<td>transcription regulator</td>
<td>Activated</td>
<td>2.942</td>
<td>9.54E-10</td>
<td>ABCC4,ALOX12,FHL1,GP1BA,GP1BB,GP9,HBE1,ITGA2B,ITGB3,PF4,THBS1</td>
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<td>THPO</td>
<td>cytokine</td>
<td>Activated</td>
<td>2.4</td>
<td>2.17E-08</td>
<td>CTTN,GP1BA,ITGA2B,ITGB1</td>
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<td>TGFB1</td>
<td>growth factor</td>
<td>Activated</td>
<td>2.351</td>
<td>1.45E-05</td>
<td>BACE1,CDKN1A,CMX5,E2F1,EGF,GFAP,IGFBP2,ITGB3,LCN2,PDGFA,PTGS1,SMN,SELP,SPARC,SPHK1,THBS1,TPM1,TSC22D1</td>
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<td>ZFPM1</td>
<td>transcription regulator</td>
<td>Activated</td>
<td>2</td>
<td>2.05E-05</td>
<td>GP1BA,GP9,ITGA2B,MMD,PF4,SELP</td>
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<td>MYOCD</td>
<td>transcription regulator</td>
<td>Activated</td>
<td>2.226</td>
<td>4.72E-04</td>
<td>CALD1,CDKN1A,CMX5,MYLK,TPM1</td>
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<td>IL10RA</td>
<td>transmembrane receptor</td>
<td>Activated</td>
<td>2.53</td>
<td>5.38E-04</td>
<td>CYP2F1,ECM1,F13A1,FHL1,GSTM5,LCN2,PDE2A,PF4,SELP,SPARC,VSIG2</td>
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<td>ERG</td>
<td>transcription regulator</td>
<td>Activated</td>
<td>2.449</td>
<td>8.82E-04</td>
<td>ABCC4,ALOX12,EGF7,FHL1,GFRA3,RHOBTB1,THBS1</td>
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<td>NR1I3</td>
<td>ligand-dependent nuclear receptor</td>
<td>Activated</td>
<td>2.2</td>
<td>1.50E-03</td>
<td>ABCC3,CDKN1A,CYP2F1,GSTM4,GSTM5</td>
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<td>HIF1A</td>
<td>transcription regulator</td>
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<td>2.242</td>
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<td>BACE1,CDKN1A,FHL1,ITGB3,MITF,PDGFA,RET,SPHK1,THBS1</td>
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<td>MKNK1</td>
<td>kinase</td>
<td>Activated</td>
<td>2.236</td>
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<td>ACOT7,LCN2,MAP1B,PRKAR1B,SPARC</td>
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<td>SYVN1</td>
<td>transporter</td>
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<td>9.16E-03</td>
<td>ABCC3,ABCC4,CD151,DAB2,FOLR1</td>
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<td>SMARCA4</td>
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<td>2.433</td>
<td>9.84E-03</td>
<td>ABLIM3,C19orf33,CDKN1A,E2F1,FOLR1,HBE1,MAP1B,MYLK,SPHK1,TPM1</td>
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<tr>
<td>PI3K (complex)</td>
<td>complex</td>
<td>Activated</td>
<td>2.236</td>
<td>1.66E-02</td>
<td>ABCC4,GSTM5,IGFBP2,LCN2,MITF</td>
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<tr>
<td>IK8KB</td>
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<td>1.77E-02</td>
<td>CDKN1A,CLU,IGFBP2,ITGB3,ITGB5,LCN2</td>
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<tr>
<td>TET2</td>
<td>enzyme</td>
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<td>2</td>
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<td>LHFP,NCKAP1,PXDC1,SLC4A11</td>
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<tr>
<td>IKZF1</td>
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<td>5.41E-04</td>
<td>GP1BA,GP9,HBE1,ITGA2B,LHFP,PTCRA</td>
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<td>CBX5</td>
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<td>4.24E-03</td>
<td>CDKN1A,CXCL5,LCN2,LY6G6D,TM4SF1</td>
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Supplemental Table S7. Sequences of primers used for 3SEQ library construction

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<tr>
<th>Primer name</th>
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<tr>
<td>oligoT-R2SP</td>
<td>5'-GTG ACT GGA GTT CAG ACG TGT CTT CCG ATC TTT TTT TTT TTT TTT TTT TTT TTT TVN-3'</td>
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<tr>
<td>P5-Rd1SP</td>
<td>5'-AAT GAT ACG GCG ACC ACC GAG ATC TAC ACT CTT TCC CTA CAC GAC GCT CTT CCG ATC T-3'</td>
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<tr>
<td>P7-Index1-Rd2SP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5'-CAA GCA GAA GAC GGC ATA CGA GAT CGT GAT GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC-3'</td>
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<tr>
<td>P7-Index2-Rd2SP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5'-CAA GCA GAA GAC GGC ATA CGA GAT ACA TCG GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC-3'</td>
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<tr>
<td>P7-Index3-Rd2SP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5'-CAA GCA GAA GAC GGC ATA CGA GAT GCC TAA GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC-3'</td>
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<tr>
<td>P7-Index4-Rd2SP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5'-CAA GCA GAA GAC GGC ATA CGA GAT TGG TCA GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC-3'</td>
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<tr>
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<td>5'-CAA GCA GAA GAC GGC ATA CGA GAT CAC TGT GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC-3'</td>
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<tr>
<td>P7-Index7-Rd2SP&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>P5</td>
<td>5'-AAT GAT ACG GCG ACC ACC GAG ATC T-3'</td>
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<td>P7</td>
<td>5'-CAA GCA GAA GGC ATA CGA GAT-3'</td>
</tr>
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</table>

<sup>a</sup>Corresponding index sequence in the primer was underlined.
Supplemental Figure S1. Longitudinal effects of eltrombopag on platelet count normalized expression of platelet-specific genes in responding patients. Responders (R) who had all three time points available without confounding pretreatment platelet count were analyzed. The platelet-specific genes listed in the figure were the overlapping platelet-specific genes identified in three separate platelet-microarray studies.\textsuperscript{12-14} Of these 11 genes, 8 (in black) were identified as eltrombopag-induced genes in this study, and 3 (in grey) were not. Median expression levels of the 11 genes were normalized to corresponding platelet counts. Then platelet count normalized gene expression at 1-week (1wk) and 1-month (1mo) time points were calculated as fold changes over the pretreatment (pre) values of individual patients. Fold changes of the platelet count normalized platelet-specific gene expression levels at various time points were plotted as median with interquartile range. Differences between time points were assessed by paired student t test.
References