

Imatinib Disrupts Lymphoma Angiogenesis by Targeting Vascular Pericytes

Jia Ruan^{1§}, Min Luo², Chunjie Wang¹, Lei Fan^{1*}, Shao Ning Yang¹, Mariano Cardenas¹, Huimin Geng^{1#}, John P. Leonard¹, Ari Melnick¹, Leandro Cerchietti^{1§}, and Katherine A. Hajjar²

Division of Hematology/Oncology, Department of Medicine¹, Department of Cell and Developmental Biology², Weill Cornell Medical College, New York, NY

§ Co-corresponding authors

* Current address: Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Current address: Department of Laboratory Medicine, University of California, San Francisco

Supported in part by an ASCO Career Development Award and NIH grant K08HL091517 to J.R.; HL090985, HL042493 to K.A.H.

Corresponding Authors

Jia Ruan, M.D., Ph.D.
Division of Hematology/Oncology
Department of Medicine
Weill Cornell Medical College
1300 York Avenue
New York, NY 10065, USA
Tel: 646-962-2064
Fax: 646-962-1605
Email: jruan@med.cornell.edu

Leandro Cerchietti, M.D.
Division of Hematology/Oncology
Department of Medicine
Weill Cornell Medical College
1300 York Avenue
New York, NY 10065, USA
Tel: 212-746-7622
Fax: 212-746-8866
Email: lcc2010@med.cornell.edu

Word Count

Abstract: 187
Words: 3998
Figures: 7
Supplemental Tables: 3
Supplemental Figures: 5

Running Title

Imatinib targets lymphoma vasculature

Conflict-of-interest Statement

None

ONLINE SUPPLEMENTAL MATERIAL

Supplemental Material and Methods

Isolation of Vascular Smooth Muscle Cells

Murine aortic vascular smooth muscle cells (VSMCs) were obtained by a modification of the explant method originally described by Ross ⁴⁷. Briefly, medial tissue was separated from segments of the thoracic aorta and incubated in dissection medium containing 165 U/mL collagenase type I (Worthington Biochemical Co, Lakewood, NJ), 15 U/mL elastase type III (Sigma-Aldrich, St. Louis, MO), and 0.375 mg/mL soybean trypsin inhibitor (Worthington) at 37°C. Partially digested tissues were placed in 6-well plates and cultured for several weeks in DMEM with 10% FBS supplemented with P/S. To isolate PDGFR β ⁺ cells, 2 - 3 million confluent primary murine VSMCs were detached with Gibco 0.02% trypsin-EDTA (Invitrogen, Calsbad, CA), rinsed with sterile PBS/2% FBS, and resuspended in 200 μ L of PBS/2%FBS. The single cell suspension was then incubated with saturating concentrations of anti-PDGFR β -PE antibody (eBioscience, San Diego, CA) for 30 mins on ice, washed in PBS/2%FBS, and sorted using the FACSVantage (Becton Dickinson, Mountain View, CA). The recovered PDGFR β ⁺ cells were cultured in DMEM with 10% FBS supplemented with penicillin/streptomycin. Cells at passages 5-10 were used for the experiments.

Isolation of Cardiac Microvascular Endothelial Cells

CMECs were isolated from neonatal day 2 murine hearts and evaluated by cell surface expression of VE-cadherin as previously described ⁴⁸. The cells were maintained in DMEM/F12 Medium with 20% FCS, endothelial cell growth supplement and P/S. Passage 2 CMECs were used for EC growth inhibition assays.

FACS sorting of lymphoma-associated CD45⁻PDGFR β ⁺ stromal cells

Mononuclear cell suspensions were prepared from OCI-Ly7 or Farage lymphoma xenografts treated with either imatinib or PBS for 72 hours. Human CD45⁺ cells were removed from the mononuclear fractions with the EasySep human CD45 depletion kit (StemCell Technologies, Vancouver, BC, Canada). The remainder of the mononuclear cell fractions was labeled with anti-human CD45-FITC, anti-mouse CD45-PerCP, anti-mouse CD140b-PE, and subjected to FACS sorting on a FACSArialIII cell sorter (Becton Dickinson, San Jose, CA). The sorted cells were immediately preserved in Trizol (Invitrogen, Grand Island, NY) reagent for RNA extraction.

ELISA for VEGF and TGF- β

Passage 2 murine VSMCs and CMECs were used for the VEGFA and TGF- β 1 secretion tests, assayed with the eBioscience VEGF and TGF- β 1 ELISA kits. Cells were cultured by phenol red free basic media with 5% BSA. All samples were triplicate.

Immunohistochemistry

VSMC cells grown in chamber slides (Nunc, Naperville, Illinois) were washed with PBS and fixed in 4% PFA for 20 minutes at RT, followed by permeabilization in 0.2% Triton x-100 for 10 minutes. The fixed slides were then subjected to a standard staining protocol using either color- or fluorescence-based detection methods.

Gene Expression Microarray Analysis

Total RNA from cells used for microarray analysis was isolated by RNeasy (Qiagen, Valencia, CA) purification. RNA quality was assessed using an Agilent Bioanalyzer (Agilent Technologies, Santa Clara, CA) and the 28S:18S rRNA ratios of all samples. cDNA was

generated from 5 μ g of total RNA using a poly(dT) oligonucleotide that contains a T7 RNA polymerase initiation site and the SuperScript III Reverse Transcriptase (Invitrogen, Carlsbad, CA). Biotinylated cDNA was generated and fragmented according to the NimbleGen protocol and hybridized to NimbleGen MM8_60mer two color mouse gene expression microarrays (Roche NimbleGen, Inc. WI, USA). Samples from imatinib-treated cells (24 h & 48 h) were labeled by Cy5 and the non-treated cells (0 h) were labeled by Cy3. After scanning (NimbleGen MS 200 scanner) of the MM8 arrays, the generated pair files were imported to NimbleScan software (version 2.5.26) and processed using the RMA algorithm (Robust Multi-array Analysis) for normalization and summarization⁴⁹. Signal intensities of probesets for the treated cells were compared to the intensities of the untreated cells using R 2.8.0 software and the probesets with ratios of two-fold or greater were exported to Ingenuity Pathway Analysis (IPA) (Ingenuity Systems, Redwood City, CA). Gene expression microarray data is available at the GEO database (accession number GSE30752).

Real time PCR

RNA was extracted from mouse VSMC at baseline and after 24 and 48 h of treatment with imatinib using RNeasy Plus kit (Qiagen) following the manufacturer's instructions. cDNA was synthesized using the High Capacity RNA-to-cDNA kit (Applied Biosystems, Carlsbad, CA). Selected genes were amplified using specific primers listed in **Supplemental Table 1** based on the Fast SYBR Green conditions (initial step of 20 sec at 95C followed by 40 cycles of 1 sec at 95C and 20 sec at 60C). The average CT values of the control gene (HPRT) were subtracted from corresponding genes of interest to derive Δ CT. The standard deviation of the difference was calculated from the standard deviation of the CT values (triplicates). Then, the Δ CT values of the imatinib-treated cells were expressed relative to their respective control-treated cells using the

$\Delta\Delta\text{CT}$ method. The fold expression for each gene in cells treated with the drug relative to control treated cells is determined by the expression: $2^{-\Delta\Delta\text{CT}}$. Results were represented as fold expression with the standard error of the mean (SEM) for three series of triplicates.

Supplemental Table 1: Real-time PCR Primer Sequences

Gene	Primer Sequence	
<i>GADD45A</i>	Forward Reverse	5'-TGAGCTGCTGCTACTGGAGA-3' 5'-TCCCGGCAAAAACAAATAAG-3'
<i>RFC5</i>	Forward Reverse	5'-TTGGGAAGGTGACAGAGGAG-3' 5'-CCAAGCCCTTCAGAGTCTTC-3'
<i>CCNE1</i>	Forward Reverse	5'-CACAACTCCAGACCCACAC-3' 5'-ACTCGGAGGAGGAGAAATCC-3'
<i>TIMP1</i>	Forward Reverse	5'-ATCAGTGCCTGCAGCTTCTT-3' 5'-TCACTCTCCAGTTTGCAAGG-3'
<i>SERPINE1</i>	Forward Reverse	5'-AGACAATGGAAGGGCAACAT-3' 5'-GCCAGGGTTGCACTAAACAT-3'
<i>KIT</i>	Forward Reverse	5'-AAAGGCCAACATTCAAGCAG-3' 5'-GAGTTGACCCTCACGGAATG-3'
<i>MMP3</i>	Forward Reverse	5'-AGATCGATGCTGCCATTTCT-3' 5'-GGCTCCATGGATTGTTTCTT-3'
<i>MMP12</i>	Forward Reverse	5'-TGATGCAGCTGTCTTTGACC-3' 5'-ATGAGCTCCTGCCTCACATC-3'
<i>MMP13</i>	Forward Reverse	5'-TTTGAGAACACGGGGGAAGAC-3' 5'-ATGAGGCGGGGATAATCTTT-3'
<i>IL6</i>	Forward Reverse	5'-CAAAGCCAGAGTCCTTCAGAG-3' 5'-GCCACTCCTTCTGTGACTCC-3'

Supplemental Table 2: Imatinib Mesylate Induces Differentially Expressed Genes in Vascular Smooth Muscle Cells

Fold Change	ID	Symbol	Entrez Gene Name	Location	Type(s)
-4.079	Il1rl1	IL1RL1	interleukin 1 receptor-like 1	Plasma Membrane	transmembrane receptor
-3.516	Adam12	ADAM12	ADAM metallopeptidase domain 12	Plasma Membrane	peptidase
-3.306	Ppil5	PPIL5	peptidylprolyl isomerase (cyclophilin)-like 5	unknown	enzyme
-3.289	Casc5	CASC5	cancer susceptibility candidate 5	Nucleus	other
-3.282	Esco2	ESCO2	establishment of cohesion 1 homolog 2 (S. cerevisiae)	Nucleus	other
-3.274	Shebp1	SHCBP1	SHC SH2-domain binding protein 1	unknown	other
-3.267	Esco2	ESCO2	establishment of cohesion 1 homolog 2 (S. cerevisiae)	Nucleus	other
-3.239	Ccne2	CCNE2	cyclin E2	Nucleus	other
-3.228	Matn3	MATN3	matrilin 3	Extracellular Space	other
-3.202	Tnfsf18	TNFSF18	tumor necrosis factor (ligand) superfamily, member 18	Extracellular Space	cytokine
-3.153	Cdca1	NUF2	NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	Nucleus	other
-3.138	Cdca1	NUF2	NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	Nucleus	other
-3.131	Fbxo5	FBXO5	F-box protein 5	Nucleus	enzyme
-3.116	Ntrk3	NTRK3	neurotrophic tyrosine kinase, receptor, type 3	Plasma Membrane	kinase
-3.115	Shebp1	SHCBP1	SHC SH2-domain binding protein 1	unknown	other
-3.074	Melk	MELK	maternal embryonic leucine zipper kinase	Cytoplasm	kinase
-3.065	Cab39l	CAB39L	calcium binding protein 39-like	unknown	other
-3.042	C79407	C14orf106	chromosome 14 open reading frame 106	Nucleus	other
-3.041	Ect2	ECT2	epithelial cell transforming sequence 2 oncogene	Nucleus	other
-3.023	Ppil5	PPIL5	peptidylprolyl isomerase (cyclophilin)-like 5	unknown	enzyme
-3.007	Slc16a4	SLC16A4	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	Plasma Membrane	transporter
-3.002	Mki67	MKI67	antigen identified by monoclonal antibody Ki-67	Nucleus	other
-2.984	Casc5	CASC5	cancer susceptibility candidate 5	Nucleus	other
-2.967	Mybl2	MYBL2	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	Nucleus	transcription regulator
-2.947	E2f7	E2F7	E2F transcription factor 7	Nucleus	transcription regulator
-2.941	Ccne2	CCNE2	cyclin E2	Nucleus	other
-2.935	Pbk	PBK	PDZ binding kinase	Cytoplasm	kinase
-2.914	Mlf1	MLF1	myeloid leukemia factor 1	Nucleus	other
-2.913	Kif15	KIF15	kinesin family member 15	Nucleus	other
-2.910	Neil3	NEIL3	nei endonuclease VIII-like 3 (E. coli)	Nucleus	enzyme
-2.897	Ect2	ECT2	epithelial cell transforming sequence 2 oncogene	Nucleus	other
-2.871	Rad51ap1	RAD51AP1	RAD51 associated protein 1	Nucleus	other
-2.861	Bub1	BUB1	budding uninhibited by benzimidazoles 1 homolog (yeast)	Nucleus	kinase
-2.860	Neil3	NEIL3	nei endonuclease VIII-like 3 (E. coli)	Nucleus	enzyme
-2.844	Aspm	ASPM	asp (abnormal spindle) homolog, microcephaly associated (Drosophila)	Nucleus	other

-2.844	Clspn	CLSPN	Claspin	Nucleus	other
-2.834	Hells	HELLS	helicase, lymphoid-specific	Nucleus	enzyme
-2.828	Klk8	KLK8	kallikrein-related peptidase 8	Extracellular Space	peptidase
-2.827	Pbk	PBK	PDZ binding kinase	Cytoplasm	kinase
-2.812	Brip1	BRIP1	BRCA1 interacting protein C-terminal helicase 1	Nucleus	enzyme
-2.810	C79407	C14orf106	chromosome 14 open reading frame 106	Nucleus	other
-2.807	C79407	C14orf106	chromosome 14 open reading frame 106	Nucleus	other
-2.802	Ttk	TTK	TTK protein kinase	Nucleus	kinase
-2.799	Ect2	ECT2	epithelial cell transforming sequence 2 oncogene	Nucleus	other
-2.784	Ccne2	CCNE2	cyclin E2	Nucleus	other
-2.779	Ect2	ECT2	epithelial cell transforming sequence 2 oncogene	Nucleus	other
-2.774	Fbxo5	FBXO5	F-box protein 5	Nucleus	enzyme
-2.766	Il18rap	IL18RAP	interleukin 18 receptor accessory protein	Plasma Membrane	transmembrane receptor
-2.750	Slurp1	SLURP1	secreted LY6/PLAUR domain containing 1	Extracellular Space	cytokine
-2.744	Ttk	TTK	TTK protein kinase	Nucleus	kinase
-2.741	Akap5	AKAP5	A kinase (PRKA) anchor protein 5	Plasma Membrane	other
-2.737	E2f7	E2F7	E2F transcription factor 7	Nucleus	transcription regulator
-2.737	Itgb6	ITGB6	integrin, beta 6	Plasma Membrane	other
-2.737	Kif11	KIF11	kinesin family member 11	Nucleus	other
-2.733	Il6	IL6	interleukin 6 (interferon, beta 2)	Extracellular Space	cytokine
-2.722	Luzp5	NCAPG2	non-SMC condensin II complex, subunit G2	Nucleus	other
-2.714	Cenpe	CENPE	centromere protein E, 312kDa	Nucleus	other
-2.707	Sprr2a	SPRR2A (includes others)	small proline-rich protein 2A	Cytoplasm	other
-2.695	Cep55	CEP55	centrosomal protein 55kDa	unknown	other
-2.671	Cep55	CEP55	centrosomal protein 55kDa	unknown	other
-2.671	Chek1	CHEK1	CHK1 checkpoint homolog (S. pombe)	Nucleus	kinase
-2.666	Cenpe	CENPE	centromere protein E, 312kDa	Nucleus	other
-2.662	Tk1	TK1	thymidine kinase 1, soluble	Cytoplasm	kinase
-2.661	Prr11	PRR11	proline rich 11	unknown	other
-2.657	E2f8	E2F8	E2F transcription factor 8	Nucleus	other
-2.654	Figl1	FIGNL1	fidgetin-like 1	unknown	enzyme
-2.653	Birc5	BIRC5	baculoviral IAP repeat-containing 5	Cytoplasm	other
-2.651	Cdca2	CDCA2	cell division cycle associated 2	Nucleus	other
-2.647	Ercc6l	ERCC6L	excision repair cross-complementing rodent repair deficiency, complementation group 6-like	Nucleus	other
-2.645	Ckap2l	CKAP2L	cytoskeleton associated protein 2-like	unknown	other
-2.640	Kntc2	NDC80	NDC80 homolog, kinetochore complex component (S. cerevisiae)	Nucleus	other

-2.640	Rad54l	RAD54L	RAD54-like (<i>S. cerevisiae</i>)	Nucleus	enzyme
-2.638	Ccna2	CCNA2	cyclin A2	Nucleus	other
-2.635	Exo1	EXO1	exonuclease 1	Nucleus	enzyme
-2.630	Prc1	PRC1	protein regulator of cytokinesis 1	Nucleus	other
-2.630	Sgol1	SGOL1	shugoshin-like 1 (<i>S. pombe</i>)	Nucleus	other
-2.627	Chek1	CHEK1	CHK1 checkpoint homolog (<i>S. pombe</i>)	Nucleus	kinase
-2.619	Stat4	STAT4	signal transducer and activator of transcription 4	Nucleus	transcription regulator
-2.617	Top2a	TOP2A	topoisomerase (DNA) II alpha 170kDa	Nucleus	enzyme
-2.614	Mlf1	MLF1	myeloid leukemia factor 1	Nucleus	other
-2.598	Kif20a	KIF20A	kinesin family member 20A	Cytoplasm	transporter
-2.598	Nusap1	NUSAP1	nucleolar and spindle associated protein 1	Nucleus	other
-2.592	Aurka	AURKA	aurora kinase A	Nucleus	kinase
-2.567	Aspm	ASPM	asp (abnormal spindle) homolog, microcephaly associated (<i>Drosophila</i>)	Nucleus	other
-2.566	Ect2	ECT2	epithelial cell transforming sequence 2 oncogene	Nucleus	other
-2.563	Birc5	BIRC5	baculoviral IAP repeat-containing 5	Cytoplasm	other
-2.562	Rad51ap1	RAD51AP1	RAD51 associated protein 1	Nucleus	other
-2.559	Il6	IL6	interleukin 6 (interferon, beta 2)	Extracellular Space	cytokine
-2.558	Ccnb1	CCNB1	cyclin B1	Nucleus	other
-2.558	Cd244	CD244	CD244 molecule, natural killer cell receptor 2B4	Plasma Membrane	other
-2.553	Ckap2l	CKAP2L	cytoskeleton associated protein 2-like	unknown	other
-2.553	Orc1l	ORC1	origin recognition complex, subunit 1	Nucleus	other
-2.551	Luzp5	NCAPG2	non-SMC condensin II complex, subunit G2	Nucleus	other
-2.543	Kntc2	NDC80	NDC80 homolog, kinetochore complex component (<i>S. cerevisiae</i>)	Nucleus	other
-2.542	Smc2l1	SMC2	structural maintenance of chromosomes 2	Nucleus	transporter
-2.534	Mphosph1	KIF20B	kinesin family member 20B	Nucleus	enzyme
-2.533	Kif23	KIF23	kinesin family member 23	Cytoplasm	other
-2.532	Melk	MELK	maternal embryonic leucine zipper kinase	Cytoplasm	kinase
-2.530	Mybl2	MYBL2	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	Nucleus	transcription regulator
-2.530	Polq	POLQ	polymerase (DNA directed), theta	Nucleus	enzyme
-2.530	Tll1	TLL1	tolloid-like 1	Extracellular Space	peptidase
-2.528	Bub1b	BUB1B	budding uninhibited by benzimidazoles 1 homolog beta (yeast)	Nucleus	kinase
-2.528	Lrrc4c	LRRC4C	leucine rich repeat containing 4C	Plasma Membrane	other
-2.527	Cep55	CEP55	centrosomal protein 55kDa	unknown	other
-2.525	Brcal	BRCA1	breast cancer 1, early onset	Nucleus	transcription regulator
-2.524	Slurp1	SLURP1	secreted LY6/PLAUR domain containing 1	Extracellular Space	cytokine
-2.520	Atp6v1c2	ATP6V1C2	ATPase, H ⁺ transporting, lysosomal 42kDa, V1 subunit C2	unknown	transporter
-2.511	Tk1	TK1	thymidine kinase 1, soluble	Cytoplasm	kinase
-2.507	Atp6v1c2	ATP6V1C2	ATPase, H ⁺ transporting, lysosomal 42kDa, V1 subunit C2	unknown	transporter

-2.507	Fancb	FANCB	Fanconi anemia, complementation group B	Nucleus	other
-2.502	Cenpf	CENPF	centromere protein F, 350/400kDa (mitosin)	Nucleus	other
-2.500	Mcm10	MCM10	minichromosome maintenance complex component 10	Nucleus	other
-2.490	Dlg7	DLGAP5	discs, large (Drosophila) homolog-associated protein 5	Nucleus	phosphatase
-2.478	Synpo	SYNPO	Synaptopodin	Cytoplasm	other
-2.476	Il1rl1	IL1RL1	interleukin 1 receptor-like 1	Plasma Membrane	transmembrane receptor
-2.473	Fancd2	FANCD2	Fanconi anemia, complementation group D2	Nucleus	other
-2.468	Anln	ANLN	anillin, actin binding protein	Cytoplasm	other
-2.467	Ccnb1	CCNB1	cyclin B1	Nucleus	other
-2.467	My17	MYL7	myosin, light chain 7, regulatory	Cytoplasm	enzyme
-2.463	Aurka	AURKA	aurora kinase A	Nucleus	kinase
-2.457	Prss35	PRSS35	protease, serine, 35	Extracellular Space	peptidase
-2.456	Mcm10	MCM10	minichromosome maintenance complex component 10	Nucleus	other
-2.456	Rad51ap1	RAD51AP1	RAD51 associated protein 1	Nucleus	other
-2.456	Sox11	SOX11	SRY (sex determining region Y)-box 11	Nucleus	transcription regulator
-2.455	Nasp	NASP	nuclear autoantigenic sperm protein (histone-binding)	Nucleus	other
-2.454	Asf1b	ASF1B	ASF1 anti-silencing function 1 homolog B (S. cerevisiae)	Nucleus	other
-2.451	Gsg2	GSG2	germ cell associated 2 (haspin)	Nucleus	kinase
-2.449	Plk1	PLK1	polo-like kinase 1	Nucleus	kinase
-2.447	Edg8	S1PR5	sphingosine-1-phosphate receptor 5	Plasma Membrane	G-protein coupled receptor
-2.441	Fshprh1	CENPI	centromere protein I	Nucleus	other
-2.436	Rrm2	RRM2	ribonucleotide reductase M2	Nucleus	enzyme
-2.433	Troap	TROAP	trophinin associated protein (tastin)	Cytoplasm	peptidase
-2.430	Orc1l	ORC1	origin recognition complex, subunit 1	Nucleus	other
-2.423	Dlg7	DLGAP5	discs, large (Drosophila) homolog-associated protein 5	Nucleus	phosphatase
-2.419	Esp1l	ESPL1	extra spindle pole bodies homolog 1 (S. cerevisiae)	Nucleus	peptidase
-2.410	Pmch	PMCH	pro-melanin-concentrating hormone	Extracellular Space	other
-2.408	Cd244	CD244	CD244 molecule, natural killer cell receptor 2B4	Plasma Membrane	other
-2.404	Col3a1	COL3A1	collagen, type III, alpha 1	Extracellular Space	other
-2.402	Upk1b	UPK1B	uropod 1B	Plasma Membrane	other
-2.396	Top2a	TOP2A	topoisomerase (DNA) II alpha 170kDa	Nucleus	enzyme
-2.395	Fancb	FANCB	Fanconi anemia, complementation group B	Nucleus	other
-2.389	Sgol1	SGOL1	shugoshin-like 1 (S. pombe)	Nucleus	other
-2.386	Upk3b	UPK3B	uropod 3B	Plasma Membrane	other
-2.384	Pmch	PMCH	pro-melanin-concentrating hormone	Extracellular Space	other
-2.383	Spr2a	SPRR2A (includes others)	small proline-rich protein 2A	Cytoplasm	other
-2.382	Msln	MSLN	Mesothelin	Extracellular Space	other

-2.382	Sgol2	SGOL2	shugoshin-like 2 (S. pombe)	Nucleus	other
-2.380	Kif2c	KIF2C	kinesin family member 2C	Nucleus	other
-2.375	Luzp5	NCAPG2	non-SMC condensin II complex, subunit G2	Nucleus	other
-2.374	Col11a1	COL11A1	collagen, type XI, alpha 1	Extracellular Space	other
-2.373	Top2a	TOP2A	topoisomerase (DNA) II alpha 170kDa	Nucleus	enzyme
-2.371	Kif22	KIF22	kinesin family member 22	Nucleus	other
-2.360	Mrgprf	MRGPRF	MAS-related GPR, member F	Plasma Membrane	G-protein coupled receptor
-2.360	Spag5	SPAG5	sperm associated antigen 5	Nucleus	peptidase
-2.358	Nusap1	NUSAP1	nucleolar and spindle associated protein 1	Nucleus	other
-2.355	Aurkb	AURKB	aurora kinase B	Nucleus	kinase
-2.341	Gjb3	GJB3	gap junction protein, beta 3, 31kDa	Plasma Membrane	transporter
-2.327	Casc5	CASC5	cancer susceptibility candidate 5	Nucleus	other
-2.322	Ccna2	CCNA2	cyclin A2	Nucleus	other
-2.322	Wdhd1	WDHD1	WD repeat and HMG-box DNA binding protein 1	Nucleus	other
-2.318	Phf19	PHF19	PHD finger protein 19	unknown	other
-2.316	Ccne1	CCNE1	cyclin E1	Nucleus	transcription regulator
-2.314	Exo1	EXO1	exonuclease 1	Nucleus	enzyme
-2.313	Iqgap3	IQGAP3	IQ motif containing GTPase activating protein 3	unknown	other
-2.311	Dtl	DTL	denticleless homolog (Drosophila)	Nucleus	other
-2.302	Gjb3	GJB3	gap junction protein, beta 3, 31kDa	Plasma Membrane	transporter
-2.302	Kif2c	KIF2C	kinesin family member 2C	Nucleus	other
-2.299	Cnot1	CNOT1	CCR4-NOT transcription complex, subunit 1	unknown	other
-2.297	Gsg2	GSG2	germ cell associated 2 (haspin)	Nucleus	kinase
-2.296	Fxyd3	FXYD3	FXYD domain containing ion transport regulator 3	Plasma Membrane	ion channel
-2.286	Ccdc99	CCDC99	coiled-coil domain containing 99	Nucleus	other
-2.286	Cdca7	CDCA7	cell division cycle associated 7	Nucleus	other
-2.278	Kif20a	KIF20A	kinesin family member 20A	Cytoplasm	transporter
-2.276	Ctsw	CTSW	cathepsin W	Cytoplasm	peptidase
-2.275	Sprr1a	SPRR1A	small proline-rich protein 1A	Cytoplasm	other
-2.274	Rad51	RAD51	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)	Nucleus	enzyme
-2.262	Polq	POLQ	polymerase (DNA directed), theta	Nucleus	enzyme
-2.258	Nid2	NID2	nidogen 2 (osteonidogen)	Extracellular Space	other
-2.254	Rrm2	RRM2	ribonucleotide reductase M2	Nucleus	enzyme
-2.244	Copg	COPG	coatomer protein complex, subunit gamma	Cytoplasm	transporter
-2.238	Stil	STIL	SCL/TAL1 interrupting locus	Nucleus	other
-2.235	Brcal	BRCA1	breast cancer 1, early onset	Nucleus	transcription regulator
-2.234	Muc15	MUC15	mucin 15, cell surface associated	Extracellular Space	other
-2.234	Srpx2	SRPX2	sushi-repeat-containing protein, X-linked 2	Cytoplasm	other

-2.230	Dna21	DNA2	DNA replication helicase 2 homolog (yeast)	Cytoplasm	other
-2.222	Cmklr1	CMKLR1	chemokine-like receptor 1	Plasma Membrane	G-protein coupled receptor
-2.220	Pole	POLE	polymerase (DNA directed), epsilon	Nucleus	enzyme
-2.218	Col11a1	COL11A1	collagen, type XI, alpha 1	Extracellular Space	other
-2.217	Gcnt3	GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type	Plasma Membrane	enzyme
-2.216	Mal	MAL	mal, T-cell differentiation protein	Plasma Membrane	transporter
-2.209	Cdc6	CDC6	cell division cycle 6 homolog (<i>S. cerevisiae</i>)	Nucleus	other
-2.204	Cdca7	CDCA7	cell division cycle associated 7	Nucleus	other
-2.200	Sass6	SASS6	spindle assembly 6 homolog (<i>C. elegans</i>)	Cytoplasm	other
-2.197	Cdca5	CDCA5	cell division cycle associated 5	Cytoplasm	other
-2.196	Uhrf1	UHRF1	ubiquitin-like with PHD and ring finger domains 1	Nucleus	transcription regulator
-2.191	Phf19	PHF19	PHD finger protein 19	unknown	other
-2.190	Kif18a	KIF18A	kinesin family member 18A	Cytoplasm	other
-2.188	Tcf19	TCF19	transcription factor 19	Nucleus	transcription regulator
-2.177	Mcm5	MCM5	minichromosome maintenance complex component 5	Nucleus	enzyme
-2.176	Brip1	BRIP1	BRCA1 interacting protein C-terminal helicase 1	Nucleus	enzyme
-2.173	Mal2	MAL2	mal, T-cell differentiation protein 2	Plasma Membrane	transporter
-2.170	Cdc25c	CDC25C	cell division cycle 25 homolog C (<i>S. pombe</i>)	Nucleus	phosphatase
-2.167	Eme1	EME1	essential meiotic endonuclease 1 homolog 1 (<i>S. pombe</i>)	Nucleus	other
-2.164	Foxm1	FOXM1	forkhead box M1	Nucleus	transcription regulator
-2.157	Chtf18	CHTF18	CTF18, chromosome transmission fidelity factor 18 homolog (<i>S. cerevisiae</i>)	unknown	other
-2.157	Iqgap3	IQGAP3	IQ motif containing GTPase activating protein 3	unknown	other
-2.152	Plk4	PLK4	polo-like kinase 4	Cytoplasm	kinase
-2.151	Sprr2b	SPRR2A (includes others)	small proline-rich protein 2A	Cytoplasm	other
-2.150	Cdc20	CDC20	cell division cycle 20 homolog (<i>S. cerevisiae</i>)	Nucleus	other
-2.147	Casc5	CASC5	cancer susceptibility candidate 5	Nucleus	other
-2.145	Mcm5	MCM5	minichromosome maintenance complex component 5	Nucleus	enzyme
-2.144	Lin9	LIN9	lin-9 homolog (<i>C. elegans</i>)	Nucleus	other
-2.141	Cdc45l	CDC45	cell division cycle 45 homolog (<i>S. cerevisiae</i>)	Nucleus	other
-2.136	F2r1l	F2RL1	coagulation factor II (thrombin) receptor-like 1	Plasma Membrane	G-protein coupled receptor
-2.135	Mfap5	MFAP5	microfibrillar associated protein 5	Extracellular Space	other
-2.135	Sprr2e	SPRR2A (includes others)	small proline-rich protein 2A	Cytoplasm	other
-2.133	Nrip3	NRIP3	nuclear receptor interacting protein 3	unknown	other
-2.132	Mcm6	MCM6	minichromosome maintenance complex component 6	Nucleus	enzyme
-2.132	Upk1b	UPK1B	uropod protein 1B	Plasma Membrane	other

-2.129	Kif18a	KIF18A	kinesin family member 18A	Cytoplasm	other
-2.118	Mxd3	MXD3	MAX dimerization protein 3	Nucleus	transcription regulator
-2.116	Kntc1	KNTC1	kinetochore associated 1	Nucleus	other
-2.112	Cmah	CMAH	cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMP-N-acetylneuraminate monooxygenase) pseudogene	Cytoplasm	enzyme
-2.110	Edn2	EDN2	endothelin 2	Extracellular Space	growth factor
-2.106	Mad211	MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	Nucleus	other
-2.102	Gpm6a	GPM6A	glycoprotein M6A	Plasma Membrane	ion channel
-2.102	Slc16a4	SLC16A4	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	Plasma Membrane	transporter
-2.100	Mal	MAL	mal, T-cell differentiation protein	Plasma Membrane	transporter
-2.099	Timeless	TIMELESS	timeless homolog (Drosophila)	Nucleus	other
-2.098	Tpx2	TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	Nucleus	other
-2.095	Pdss1	PDSS1	prenyl (decaprenyl) diphosphate synthase, subunit 1	unknown	enzyme
-2.095	Timp1	TIMP1	TIMP metalloproteinase inhibitor 1	Extracellular Space	other
-2.093	Cd244	CD244	CD244 molecule, natural killer cell receptor 2B4	Plasma Membrane	other
-2.092	Mfap5	MFAP5	microfibrillar associated protein 5	Extracellular Space	other
-2.085	Als2cr12	ALS2CR12	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 12	unknown	other
-2.083	Tns4	TNS4	tensin 4	Cytoplasm	other
-2.080	Spbc24	SPC24	SPC24, NDC80 kinetochore complex component, homolog (S. cerevisiae)	unknown	other
-2.079	AI449441	PIF1	PIF1 5'-to-3' DNA helicase homolog (S. cerevisiae)	Nucleus	enzyme
-2.079	Stat4	STAT4	signal transducer and activator of transcription 4	Nucleus	transcription regulator
-2.078	Mal2	MAL2	mal, T-cell differentiation protein 2	Plasma Membrane	transporter
-2.073	Uhrf1	UHRF1	ubiquitin-like with PHD and ring finger domains 1	Nucleus	transcription regulator
-2.069	Dpcr1	DPCR1	diffuse panbronchiolitis critical region 1	unknown	other
-2.069	Prim1	PRIM1	primase, DNA, polypeptide 1 (49kDa)	Nucleus	enzyme
-2.066	Kif14	KIF14	kinesin family member 14	Cytoplasm	other
-2.065	Asb15	ASB15	ankyrin repeat and SOCS box-containing 15	Nucleus	transcription regulator
-2.063	Gins4	GINS4	GINS complex subunit 4 (Sld5 homolog)	unknown	other
-2.063	Timp1	TIMP1	TIMP metalloproteinase inhibitor 1	Extracellular Space	other
-2.061	Bard1	BARD1	BRCA1 associated RING domain 1	Nucleus	transcription regulator
-2.060	Racgap1	RACGAP1	Rac GTPase activating protein 1	Cytoplasm	transporter
-2.059	Smyd1	SMYD1	SET and MYND domain containing 1	Nucleus	transcription regulator
-2.059	Tacc3	TACC3	transforming, acidic coiled-coil containing protein 3	Nucleus	other
-2.056	Timeless	TIMELESS	timeless homolog (Drosophila)	Nucleus	other
-2.056	Timeless	TIMELESS	timeless homolog (Drosophila)	Nucleus	other
-2.053	Elmod1	ELMOD1	ELMO/CED-12 domain containing 1	unknown	other
-2.052	Depdc1b	DEPDC1B	DEP domain containing 1B	unknown	other
-2.047	Cdh3	CDH3	cadherin 3, type 1, P-cadherin (placental)	Plasma Membrane	other
-2.046	Cdc6	CDC6	cell division cycle 6 homolog (S. cerevisiae)	Nucleus	other

-2.045	Cdca3	CDCA3	cell division cycle associated 3	Cytoplasm	other
-2.045	Plk4	PLK4	polo-like kinase 4	Cytoplasm	kinase
-2.043	Plk4	PLK4	polo-like kinase 4	Cytoplasm	kinase
-2.040	Lin9	LIN9	lin-9 homolog (C. elegans)	Nucleus	other
-2.039	Epn3	EPN3	epsin 3	Cytoplasm	other
-2.039	Hmgb2	HMGB2	high-mobility group box 2	Nucleus	transcription regulator
-2.037	Nek2	NEK2	NIMA (never in mitosis gene a)-related kinase 2	Cytoplasm	kinase
-2.037	Tacc3	TACC3	transforming, acidic coiled-coil containing protein 3	Nucleus	other
-2.037	Timp1	TIMP1	TIMP metalloproteinase inhibitor 1	Extracellular Space	other
-2.030	Tacc3	TACC3	transforming, acidic coiled-coil containing protein 3	Nucleus	other
-2.029	Mfap5	MFAP5	microfibrillar associated protein 5	Extracellular Space	other
-2.023	Snail	SNAIL	snail homolog 1 (Drosophila)	Nucleus	other
-2.017	Mbnl3	MBNL3	muscleblind-like 3 (Drosophila)	Nucleus	other
-2.016	Serpine1	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	Extracellular Space	other
-2.011	Acsm3	ACSM3	acyl-CoA synthetase medium-chain family member 3	Cytoplasm	enzyme
-2.011	Rfc5	RFC5	replication factor C (activator 1) 5, 36.5kDa	Nucleus	enzyme
-2.009	Spbc24	SPC24	SPC24, NDC80 kinetochore complex component, homolog (S. cerevisiae)	unknown	other
-2.003	Serpine1	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	Extracellular Space	other
-2.002	Blm	BLM	Bloom syndrome, RecQ helicase-like	Nucleus	enzyme
3.681	Mmp12	MMP12	matrix metalloproteinase 12 (macrophage elastase)	Extracellular Space	peptidase
3.068	Kit	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Plasma Membrane	kinase
3.024	Grm7	GRM7	glutamate receptor, metabotropic 7	Plasma Membrane	G-protein coupled receptor
3.015	Kit	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Plasma Membrane	kinase
2.957	Mmp3	MMP3	matrix metalloproteinase 3 (stromelysin 1, progelatinase)	Extracellular Space	peptidase
2.938	Kit	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Plasma Membrane	kinase
2.847	Ccdc3	CCDC3	coiled-coil domain containing 3	Cytoplasm	other
2.719	AI317395	AI317395	expressed sequence AI317395	unknown	peptidase
2.67	Ces3	CES3	carboxylesterase 3	Cytoplasm	enzyme
2.509	Kcnj2	KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2	Plasma Membrane	ion channel
2.474	Ces3	CES3	carboxylesterase 3	Cytoplasm	enzyme
2.378	Mmp13	MMP13	matrix metalloproteinase 13 (collagenase 3)	Extracellular Space	peptidase
2.368	Mamdc2	MAMDC2	MAM domain containing 2	Extracellular Space	other
2.316	Pappa2	PAPPA2	pappalysin 2	Extracellular Space	peptidase
2.304	Saa3	saa3p	serum amyloid A3 pseudogene	unknown	other
2.3	Slc40a1	SLC40A1	solute carrier family 40 (iron-regulated transporter), member 1	Plasma Membrane	transporter
2.281	Tmod1	TMOD1	tropomodulin 1	Cytoplasm	enzyme
2.254	Cfh	CFH	complement factor H	Extracellular Space	other

2.249	Slc40a1	SLC40A1	solute carrier family 40 (iron-regulated transporter), member 1	Plasma Membrane	transporter
2.241	Gadd45a	GADD45A	growth arrest and DNA-damage-inducible, alpha	Nucleus	other
2.212	BC026782	CFHR2	complement factor H-related 2	Extracellular Space	other
2.206	Cfh	CFH	complement factor H	Extracellular Space	other
2.179	Rgs7	RGS7	regulator of G-protein signaling 7	Cytoplasm	enzyme
2.174	Mamdc2	MAMDC2	MAM domain containing 2	Extracellular Space	other
2.152	Svep1	SVEP1	sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1	Cytoplasm	other
2.115	C4b	C4A/C4B	complement component 4B (Chido blood group)	Extracellular Space	other
2.112	C4b	C4A/C4B	complement component 4B (Chido blood group)	Extracellular Space	other
2.1	BC005764	LPPR3	lipid phosphate phosphatase-related protein type 3	unknown	other
2.098	Colec12	COLEC12	collectin sub-family member 12	Plasma Membrane	transmembrane receptor
2.096	Nyx	NYX	Nyctalopin	Extracellular Space	other
2.079	Xpa	XPA	xeroderma pigmentosum, complementation group A	Nucleus	other
2.07	Opcml	OPCML	opioid binding protein/cell adhesion molecule-like	Plasma Membrane	transmembrane receptor
2.067	Vwf	VWF	von Willebrand factor	Extracellular Space	other
2.008	Gpnmb	GPNMB	glycoprotein (transmembrane) nmb	Plasma Membrane	enzyme
2.005	Plxdc1	PLXDC1	plexin domain containing 1	Plasma Membrane	other
2.002	Kif21b	KIF21B	kinesin family member 21B	Cytoplasm	other

Supplemental Table 3: Imatinib Mesylate Alters Gene Expression Patterns in Multiple Networks in Vascular Smooth Muscle Cells

ID	Score	Focus Molecules	Top Functions	Molecules in Network
1	56	30	Cell Cycle, DNA Replication, Recombination, and Repair, Cellular Assembly and Organization	Akt, ATPase, AURKA, BARD1, BIRC5, BLM, BRCA1, BRCA1-BRCA2-FANCD2-FANCN-RAD51, CCNE2, CENPF, EXO1, FANCB, FANCD2, FXYD3, HELLS, Ige, KIF15, KIF22, KIF20B, KIF2C, LIN9, MELK, MKI67, NCAPG2, NID2, PMCH, RAD51, RAD51AP1, RAD54L, RRM2, SMC2, SPAG5, STIL, TPX2, Vegf
2	48	28	Cell Cycle, Cellular Assembly and Organization, DNA Replication, Recombination, and Repair	alcohol group acceptor phosphotransferase, APC, AURKB, BUB1, BUB1B, CASC5, CCNA2, CCNB1, Cdc2, CDC20, Cdc25B/C, CDC25C, CENPE, CHEK1, CLSPN, Cyclin B, ERCC6L, ERK1/2, ESPL1, FBXO5, FOXM1, KIF11, MAD2L1, Mpf, NDC80, NEK2, NUF2, PLK1, PRC1, SGOL1, SGOL2, SPC24, TIMELESS, TK1, TTK
3	40	23	Cell Cycle, Cellular Movement, Cancer	14-3-3, ADAM12, BRIP1, CD244, CDC6, CDC45, Cyclin A, Cyclin E, E2f, ECT2, Gamma tubulin, KIF23, KIT, MAP2K1/2, Mcm, MCM5, MCM6, MCM10, MSLN, MYBL2, NTRK3, NUSAP1, ORC1, p85 (pik3r), PI3K (complex), PLK4, PRR11, RACGAP1, Raf, Rb, RGS7, RPA, SHCBP1, SNAI1, TOP2A
4	39	23	Cell Cycle, Cellular Movement, DNA Replication, Recombination, and Repair	ANLN, ASB15, ASPM, BAG6, C14orf106, CAB39L, CCDC99, CDCA3, CDKN1A, CEP55, CES2, CTSW, DLGAP5, EXO1, FIGNL1, HJURP, HNF4A, KIAA0101, KIF20A, KNTC1, LPPR3, MAL2, NCAPD3, NUSAP1, PCBD1, PERP, SHOX, SLC16A4, SMC2, STK11, TCF19, TP53, TPX2, TTK, WDHD1
5	31	19	Immunological Disease, Inflammatory Disease, Renal Nephritis	Ap1, ASF1B, C4A/C4B, CCNE1, CFH, CHTF18, COPG, DNA-directed DNA polymerase, EME1, GADD45A, GPNMB, GSG2, HISTONE, Histone H1, Histone h3, Histone h4, Hsp90, IgG, IL6, IL12 (complex), IL12 (family), Interferon alpha, Jnk, KLK8, LDL, P38 MAPK, PDGF BB, POLE, POLQ, PRIM1, PRSS35, RFC5, STAT4, STAT5a/b, UHRF1
6	29	18	Connective Tissue Disorders, Genetic Disorder, Tissue Morphology	Casein, COL11A1, COL3A1, collagen, Collagen type I, Collagen type III, Collagen type IV, Collagen(s), E2F7, E2F8, Elastase, ETS, Fibrinogen, IL1, IL-1R, IL18RAP, IL1RL1, ITGB6, Laminin, MFAP5, MMP3, MMP12, MMP13, Nfkb (complex), Nfkb1-RelA, PBK, Pdgf (complex), SAA, saa3p, SERPINE1, Tgf beta, TIMP1, TLL1, TNFSF18, VWF
7	24	16	Cancer, Tissue Morphology, Cell Cycle	ACSM3, ANLN, beta-estradiol, Cadherin (E,N,P,VE), CDH3, CDH4, COLEC12, CTNNB1, DDIT4, ERCC4, FOXO1, HLA-DQA1, HTRA1, KIF18A, LEFTY2, MCM5, MYH2, MYH4, MYH6, MYL7, MYL12B, NRIP3, PLXDC1, PPIL5, PRC1, PRSS23, PTPRK, RRM2, Sox, SOX11, TACC3, TCF/LEF, TERT, TK1, XPA
8	21	14	Cell-To-Cell Signaling and Interaction, Tissue Development, Cellular Movement	ADAM12, ADAMTS4, ALS2CR12, ANXA11, ASPM, BCAN, BYSL, C13orf15, CD97, CES3, CMA1, DDR2, EGFR, FN1, GCNT3, GJB3, HNF1A, HTRA1, KCNQ3, KIF20A, KIF21B, KRT18, MIA2, MKI67, MXD3, PTGER1, SHC2, SPRR2A (includes others), SRC, SVEP1, TGFB1, TNFSF13B, TNS4, TRO, TROP
9	19	13	Organ Morphology, Organismal Injury and Abnormalities, Connective Tissue Disorders	ACADL, ADAMTS5, ALDOC, CENPB, CMAH, COL9A1, DECR1, EIF3G, ELMOD1, ESR1, ethanol, GPM6A, HDAC1, HMGB2, HTT, IL4, KCNAB1, KCNAB2, KIF14, MAL, MATN3, MLF1, NR3C1, Nuclear factor 1, OPCML, POU3F1, RIPK2, SLC40A1, SMYD1, SPRR1A, TFF3, Thymidine Kinase, TMOD1, Trim30a/Trim30d
10	15	11	Cellular Movement, Inflammatory Disease, Cellular Development	26s Proteasome, AKAP5, Alpha tubulin, Caspase, CDCA5, CENPI, Ck2, CMKLR1, DLGAP5, DTL, EDN2, ERK, F2RL1, FFAR2, Focal adhesion kinase, FSH, Gpcr, GPR77, GPR172B, GRM7, Gα12/13, hCG, Insulin, KCNJ2, Lh, LPAR3, Mapk, Mmp, Pka, Pkc(s), PP2A, RNA polymerase II, S1PR5, STAT, Ubiquitin
11	15	11	Cell Cycle, Cellular Growth and Proliferation, Carbohydrate Metabolism	ALDH9A1, ASXL1, CCDC99, CD53, CDCA2, CDCA7, CDK1, CDKN3, CKS2, CNOT1, CORO1C, ENPP2, EPN3, Epsin, HIST1H1A, HIST1H1B, HSPA2, ICAM3, ITGB1, KNTC1, LATS2, MIR124 (human), MPRIP, NASP, NDUFA13, PAPP2, PHF19, PLS3, PPPICC, SASS6, SYNPO, TOP2B, tretinoin, ZW10, ZWILCH

Supplemental Figure Legends

Supplemental Figure 1. Imatinib impaired lymphoma growth by inducing apoptosis. A-C:

TUNEL assay of Farage (A), OCI-Ly7 (B), and Karpas422 (C) tumors treated with either PBS (1) or imatinib (2), and then quantified as apoptosis index estimated as percent of tumor areas positive for TUNEL staining (3). Scale bar = 100 μ m.

Supplemental Figure 2. FACS analysis of day 14 EL4 tumor vascular cell populations. A:

Percentage of CD45⁺ and CD45⁻ cells. B: Percentage of CD45⁺CD11b⁺ inflammatory cells. C: Quad-gate analysis of percentage of CD45⁻CD11b⁻ cells. Q1 group represents CD45⁻CD11b⁻CD31⁺PDGFR β ⁻ endothelial cells, Q2 group represents CD45⁻CD11b⁻CD31⁺PDGFR β ⁺ endothelial cells, Q3 group represents CD45⁻CD11b⁻CD31⁻PDGFR β ⁻ stromal cells, while Q4 group represents CD45⁻CD11b⁻CD31⁻PDGFR β ⁺ pericytes. The PDGFR β -PE relative mean fluorescence values for the CD45⁻CD11b⁻ cells were: 281.39 for Q1, 4243.75 for Q2, 137.37 for Q3, and 5579.45 for Q4.

Supplemental Figure 3. FACS analysis of lymphoma vascular cell populations. A:

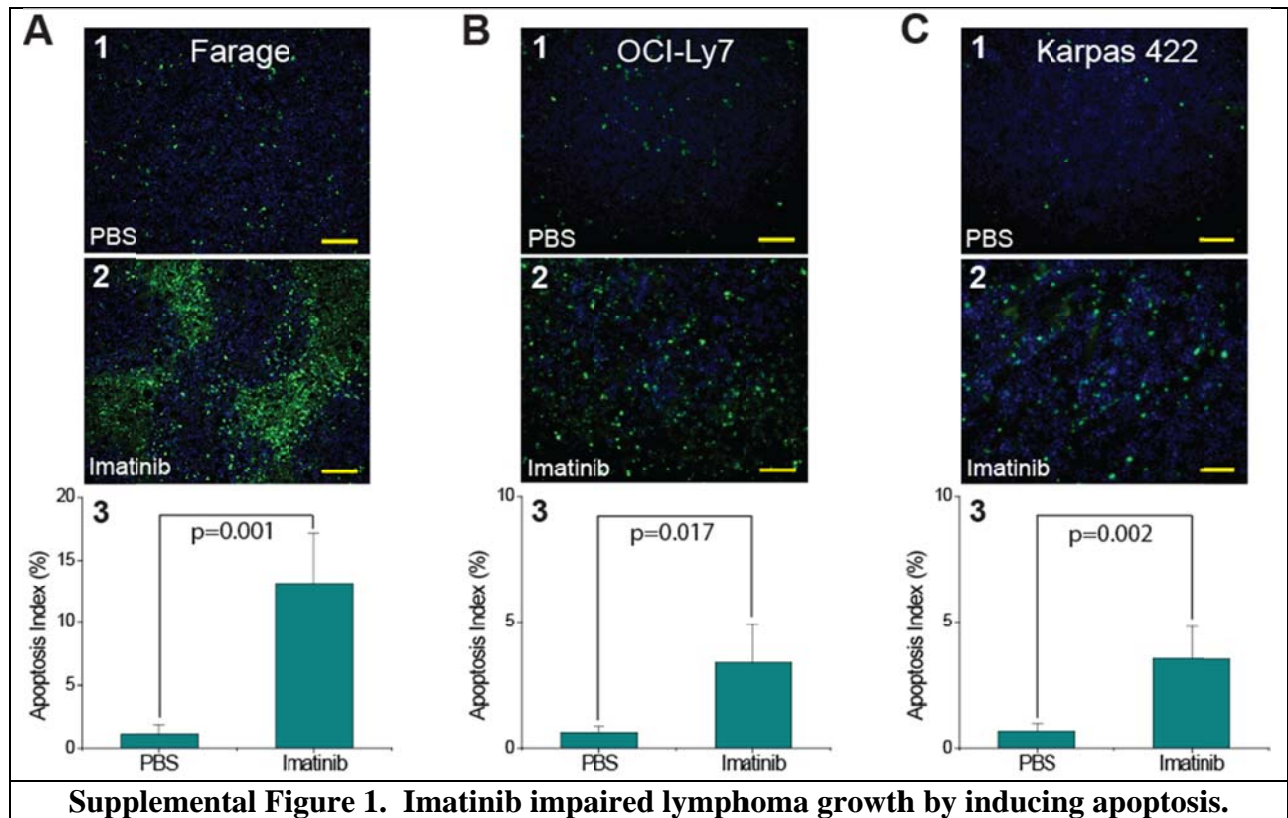
Quad-gate analysis of the OCI-Ly7 model. Murine EPC as hCD45⁻mCD45⁻VEGFR2⁺CD117⁺, mature EC as hCD45⁻mCD45⁻VEGFR2⁺CD31⁺, murine PPC as hCD45⁻mCD45⁻CD140b⁺CD117⁺, and mature PC as hCD45⁻mCD45⁻CD140b⁺. Blue-dotted squares outline individual quad-gates for EPC, PPC, EC and PC. B: Quantification of stromal cell populations in OCI-Ly7 tumors treated with imatinib vs. PBS. “*” denotes p<0.05, compared with control.

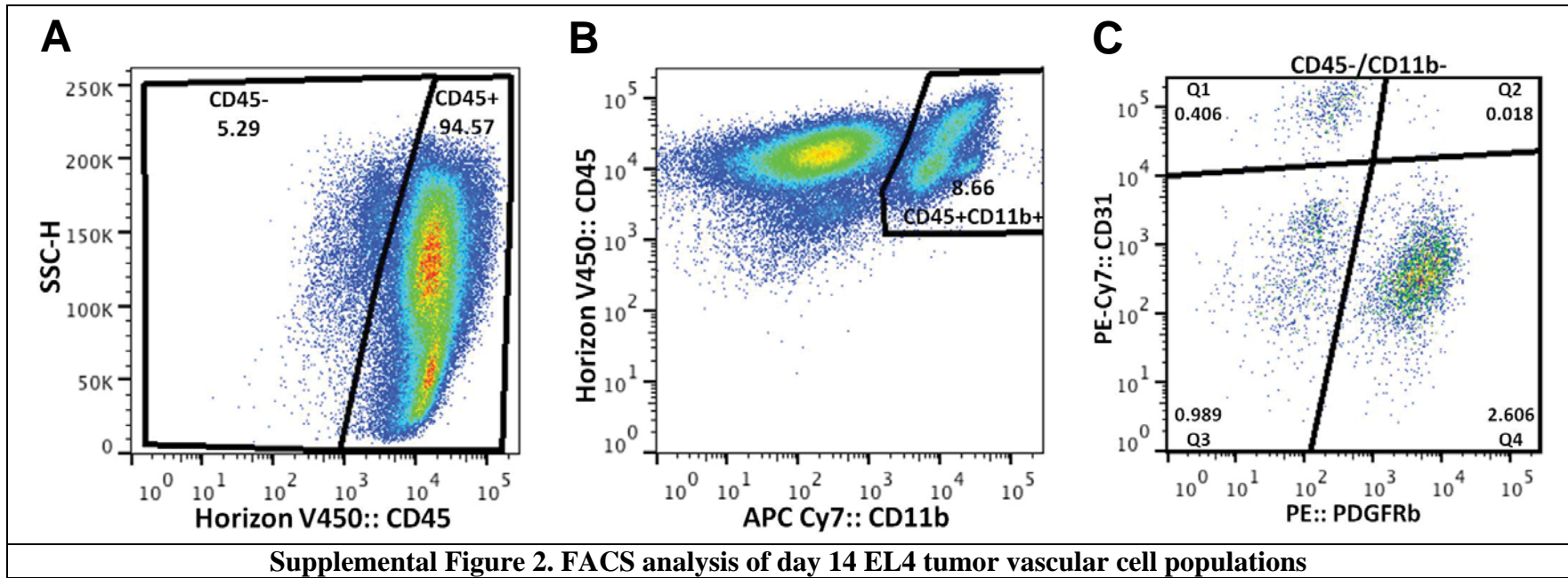
Supplemental Figure 4. Imatinib induced apoptosis of PDGFR β ⁺ VSMC *in vitro*.

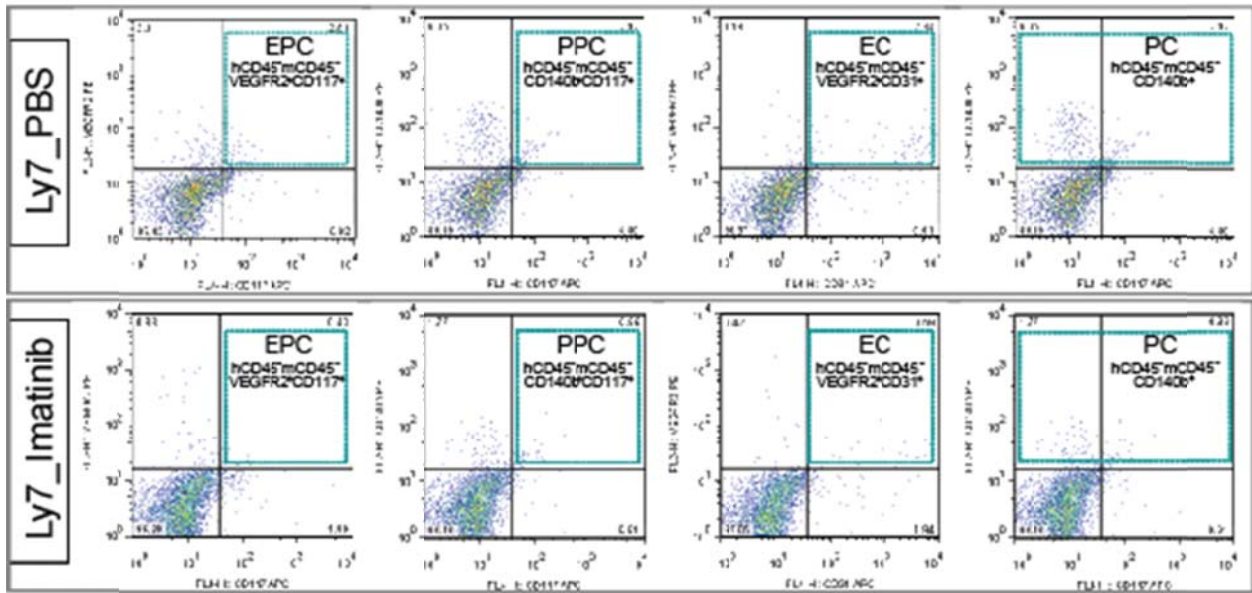
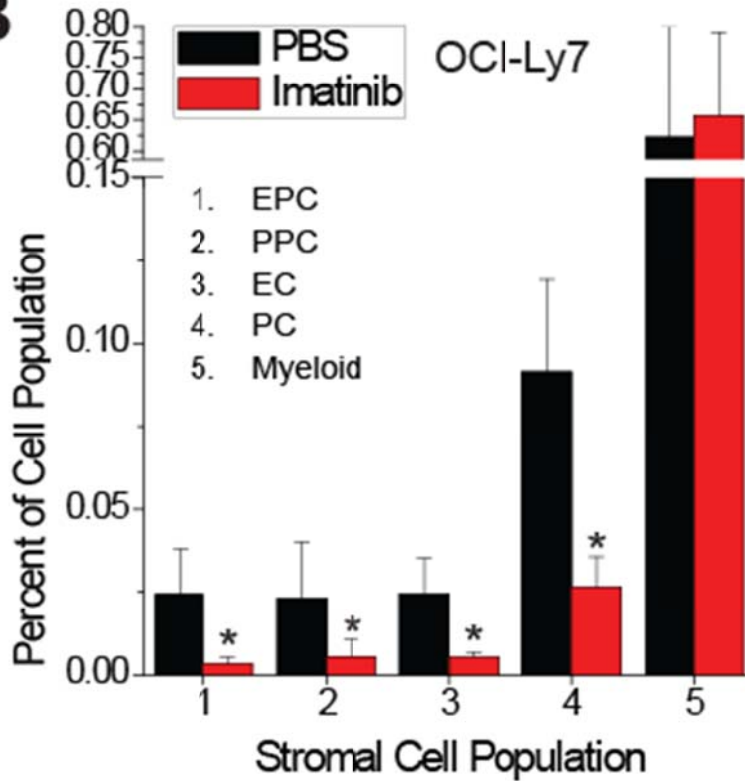
PDGFR β ⁺ VSMCs cultured in the absence (1-3) and presence (4-6) of imatinib. 1&4: Morphology by phase contrast light microscopy. 2&5: Detection of PDGFR β (2), and cleaved

caspase 3 following imatinib (**5**, white arrow). **3&6**: Detection of α -SMA (**3**), and cleaved caspase 3 following imatinib treatment (**6**).

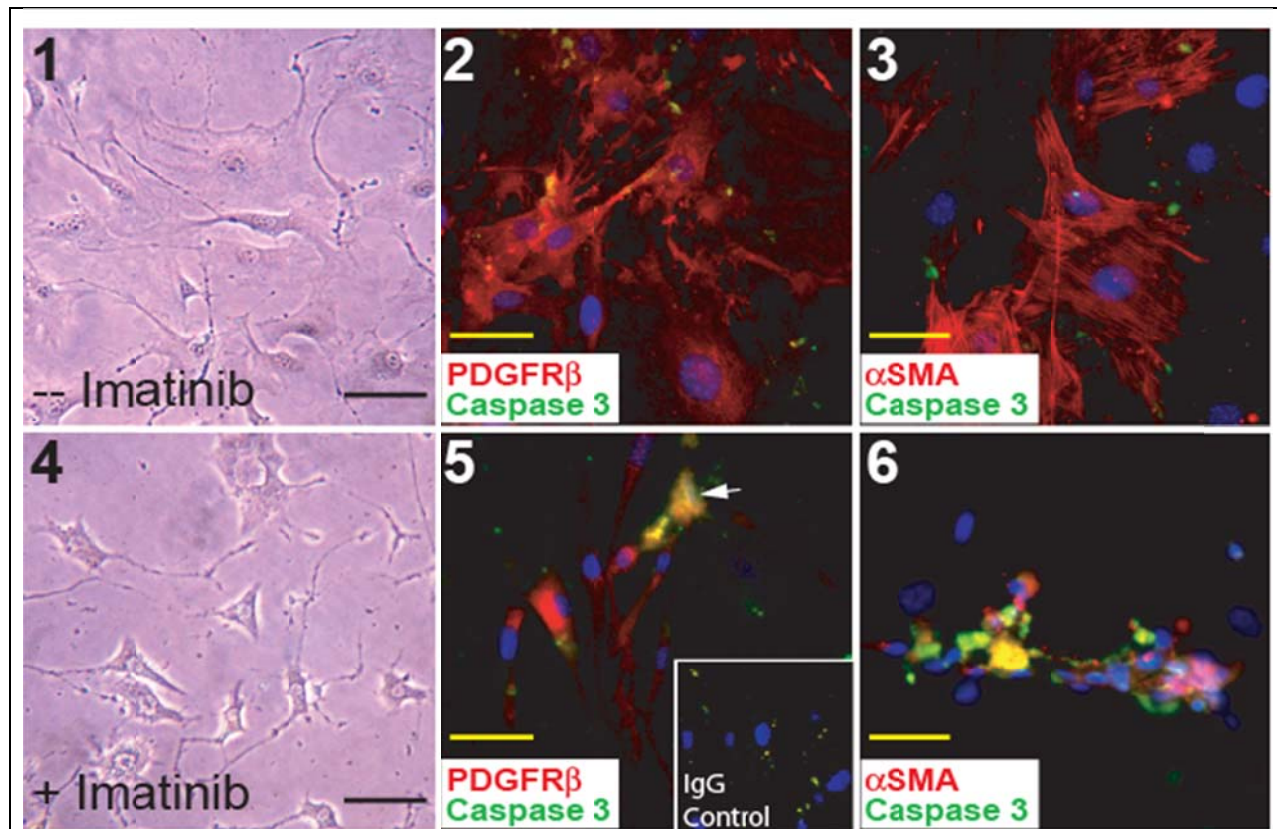
Supplemental Figure 5. Imatinib induced a PDGF-BB-specific anti-proliferative gene expression signature in vascular mural cells. **A, B**: Ingenuity Pathway analysis of networks of differentially expressed genes. VEGF target genes were highlighted in **A**, while TGF- β target genes were highlighted in **B**. Green color denotes down-regulated genes, while red color indicates up-regulated genes. **C**: qPCR analysis of representative differentially expressed genes related to PDGF-BB and PDGFR β pathways in cultured primary murine vascular smooth muscle cells at 24h and 48h following imatinib treatment (**1**), or in FACS-sorted CD45⁻PDGFR β ⁺ lymphoma-associated stromal cells, harvested 72h following imatinib treatment (**2**). Results are expressed as “fold change” relative to baseline levels.



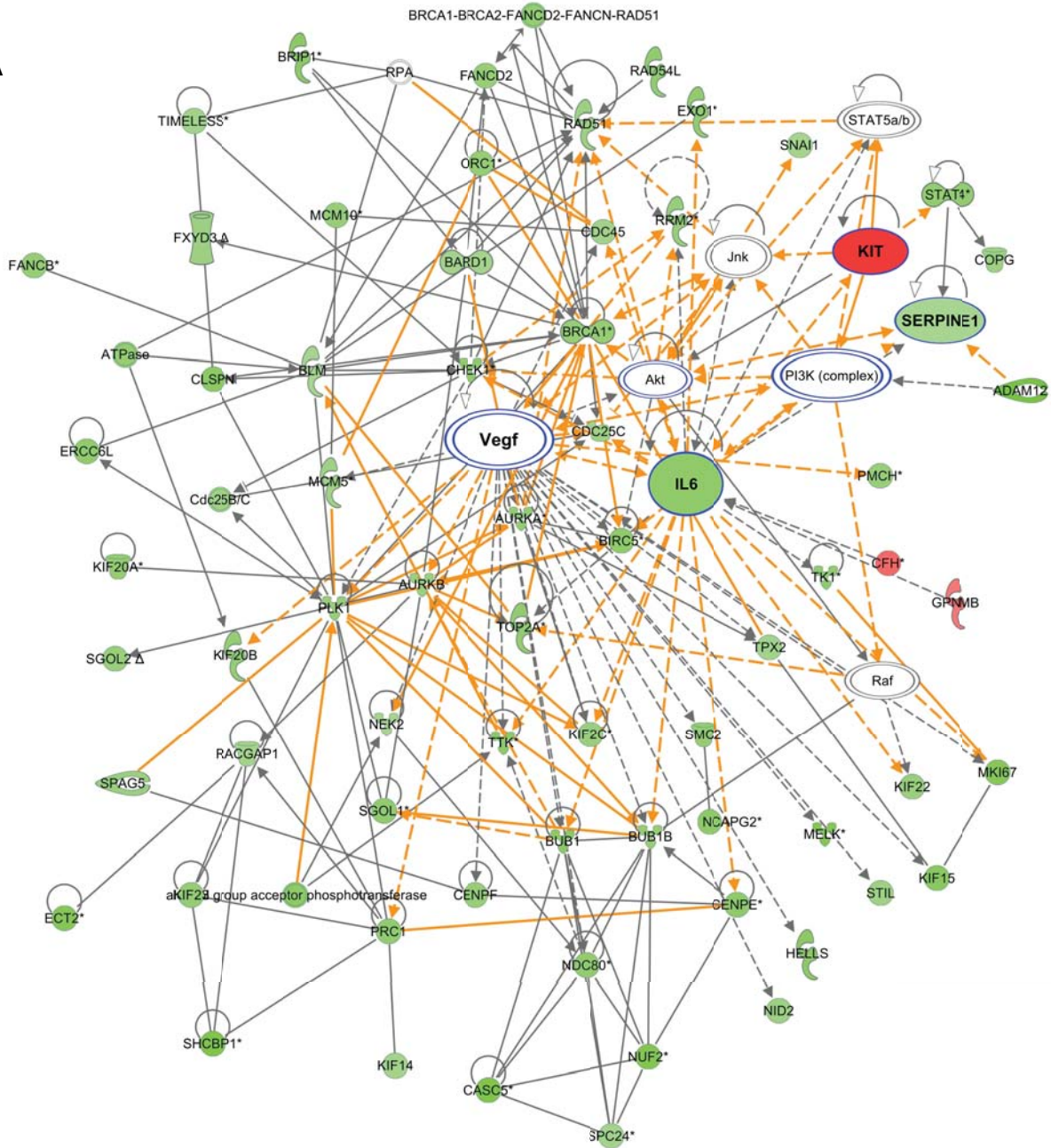


A**B**

Supplemental Figure 3. FACS analysis of lymphoma vascular cell populations

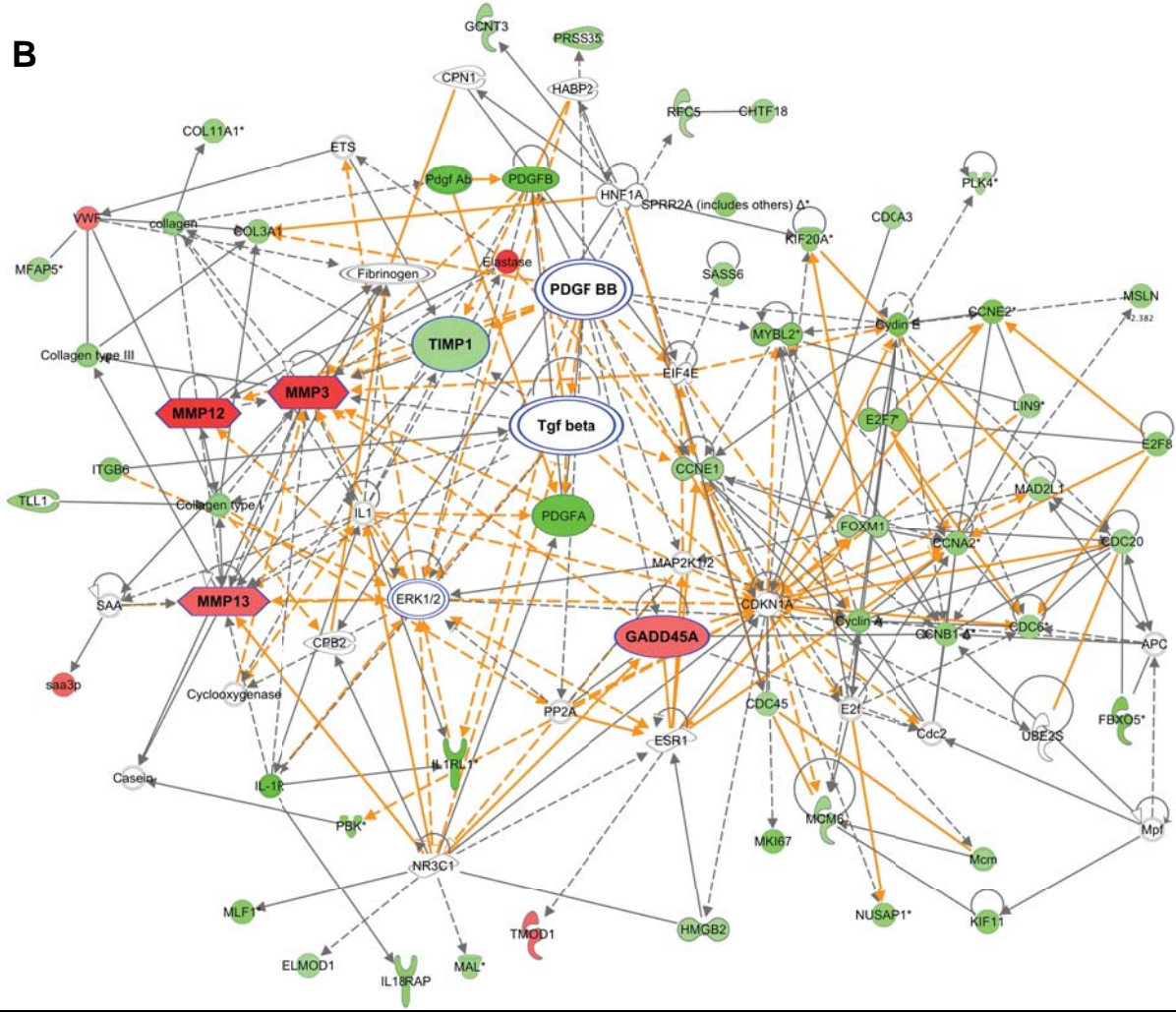


Supplemental Figure 4. Imatinib induced apoptosis of PDGFR β^+ VSMC *in vitro*.

A

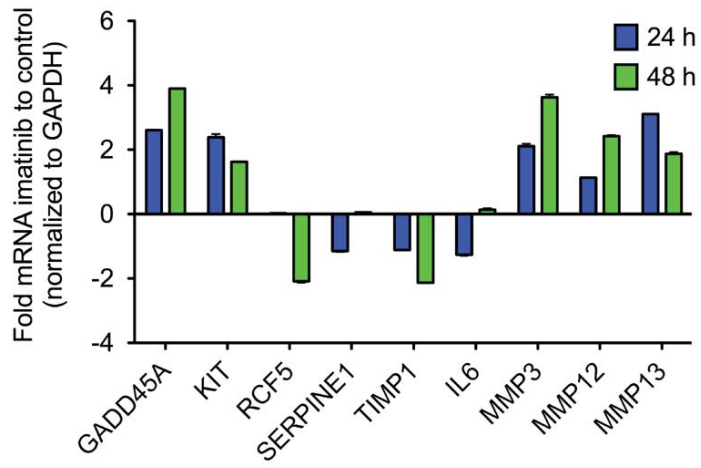
Supplemental Figure 5. Imatinib induced an anti-proliferative gene expression signature in vascular mural cells.

B

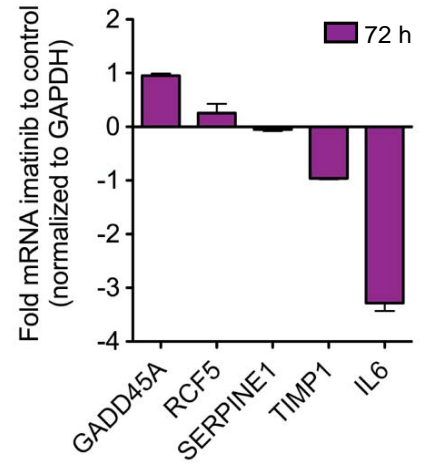


Supplemental Figure 5 (cont). Imatinib induced an anti-proliferative gene expression signature in vascular mural cells.

C 1



2



Supplemental Figure 5 (cont). Imatinib induced an anti-proliferative gene expression signature in vascular mural cells.