ESC Summer School Cardiovascular Sciences June 15, 2011

GENOMICS IN VASCULAR BIOLOGY

special look on biomechanics

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http://genomebiology.com/2001/2/11/comment/2008.1

Opinion

What does a worm want with 20,000 genes?

Jonathan Hodgkin

Image source: Juergen Berger & Ralph Sommer, Max-Planck Institute for Developmental Biology

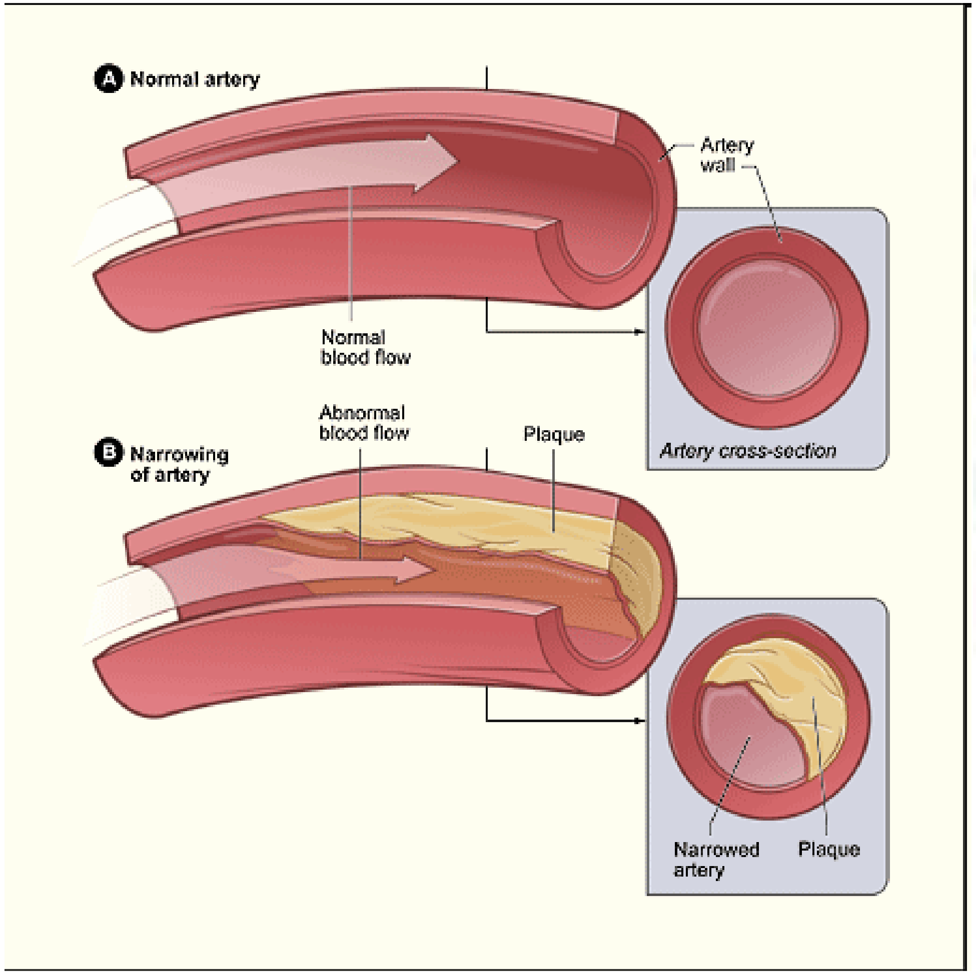
Sentrix® Human-6 Expression BeadChip

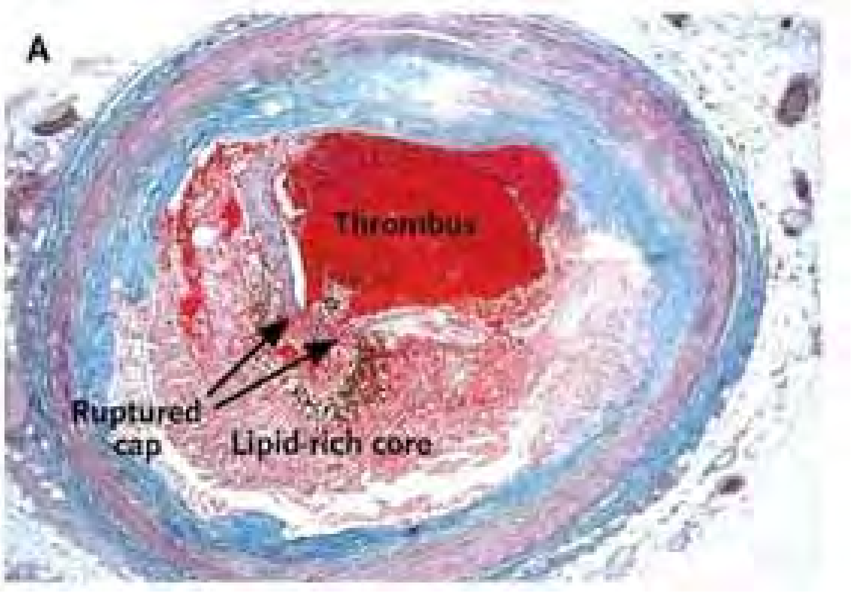
FIGURE 1: SENTRIX HUMAN-6 EXPRESSION BEADCHIP

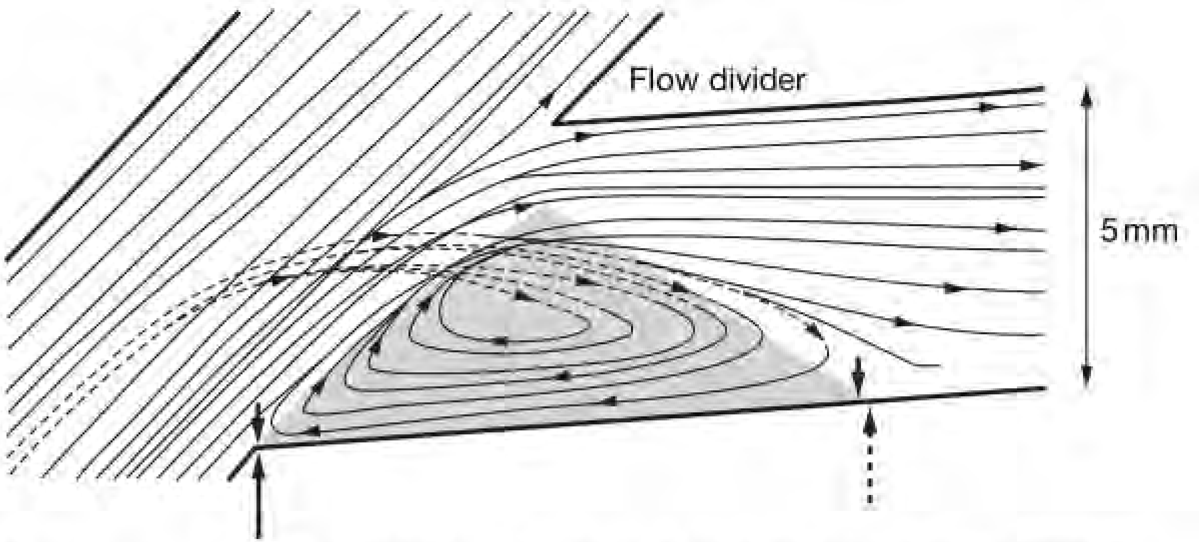
Profile six individual samples in parallel, >46,000 transcripts apiece, on the Sentrix Human-6 Expression BeadChip.

illumina®
making sense out of life

Atherosclerosis is focal inflammation







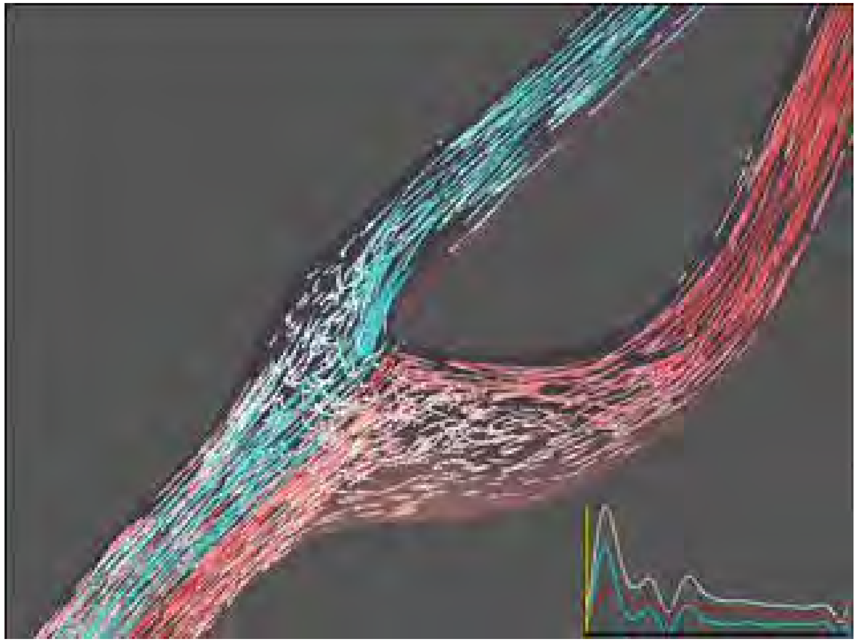
Key

⇢ → **Two-dimensional flow trajectories:** all regions are at relatively high flow velocity and high shear stress except the flow separation region (shaded)

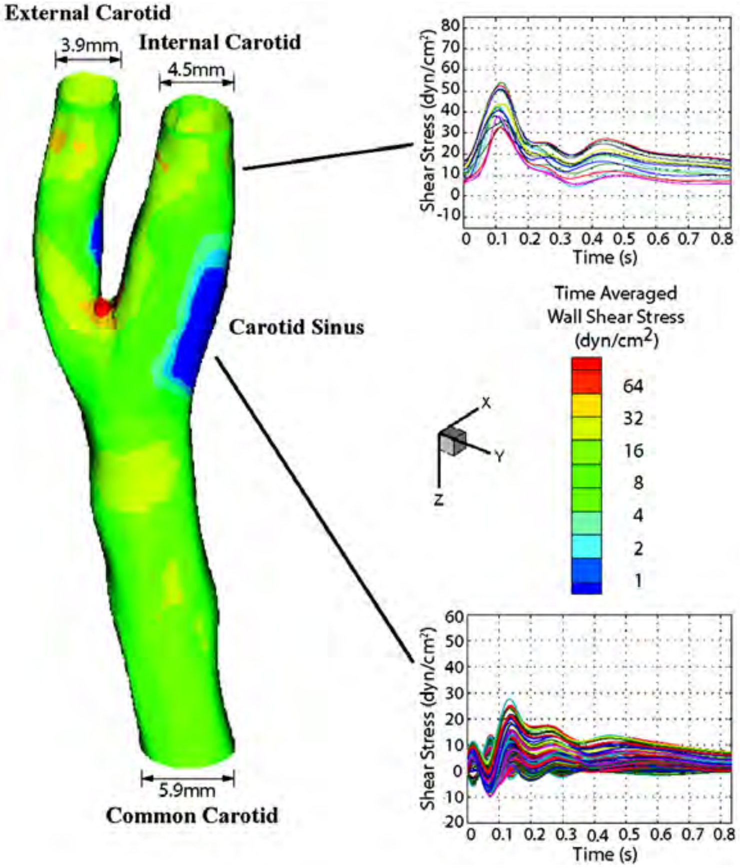
▲ **Region of flow separation:** region of disturbed flow, low shear stress and flow reversal with oscillatory shear index that is highly susceptible to atherosclerosis

↑ ⇡ Arrows mark the flow-separation boundaries, the distal arrow (dashed) indicates where the flow disturbance and flow reversal end; here flow connects with the artery wall to continue its unidirectional downstream trajectory

Focality of lesions correlates with flow patterns: Turbulence result in low shear stress and NFkB activation



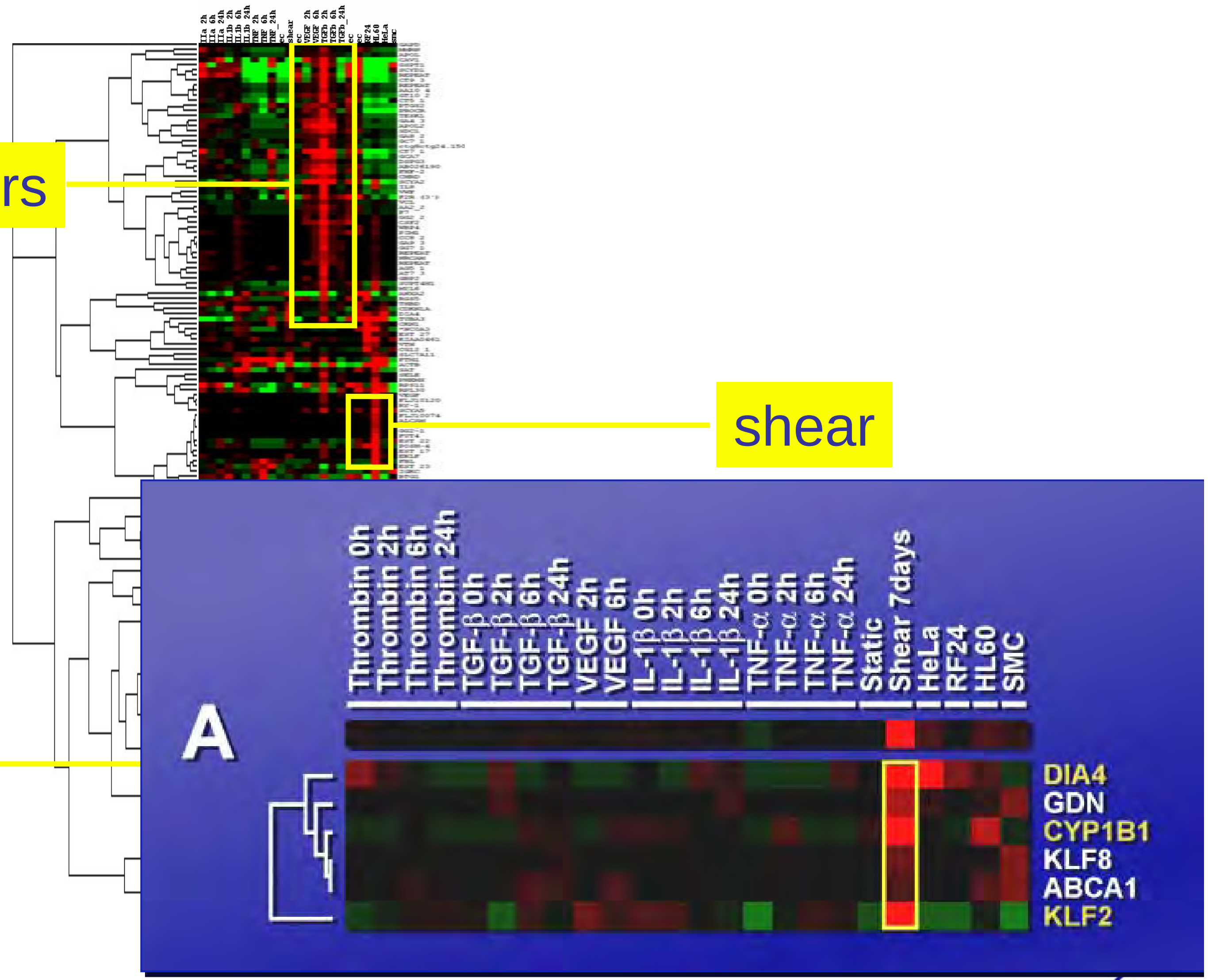
Flow imaging and computing: large artery hemodynamics.
Steinman DA Ann Biomed Eng. 2005;33:1704-9.



Dai, G PNAS 2004;101, 14871-14876

SOM & hierarchical clustering of genes: digitized cellular phenotypes

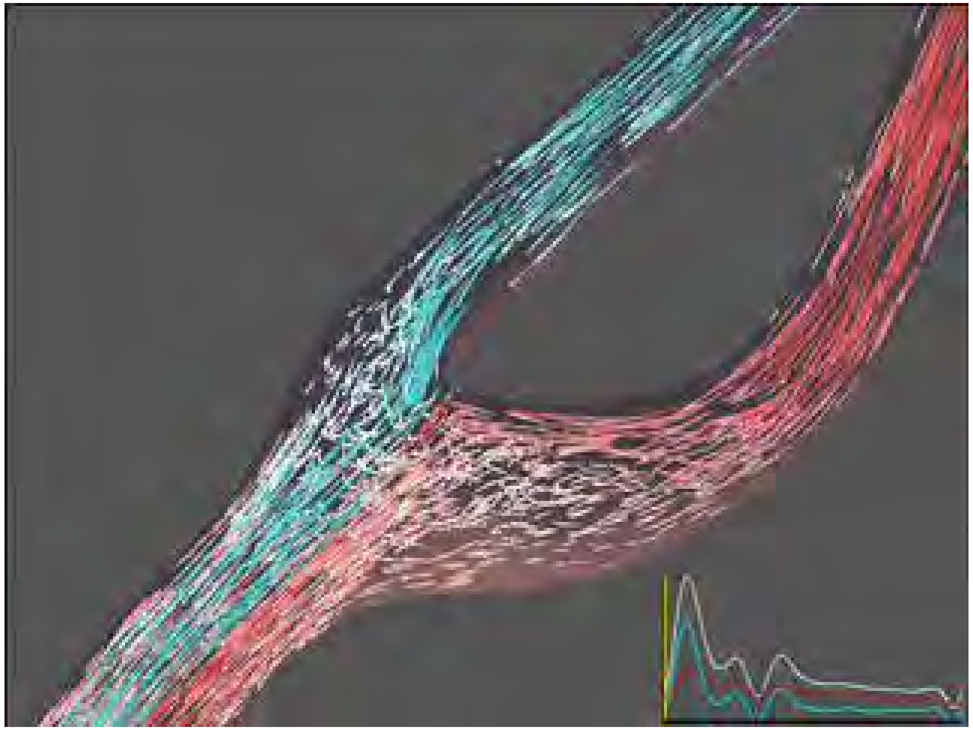
TGF-β
VEGF
b-FGF
Shear stress
NO
Thrombin
TNF-α
IL-1α



Dekker et al, Blood 2002

Transcription factor *KLF2* drives atheroprotective effects shear stress

Specific expression in the protected parts of vascular tree, EC quiescence



Flow imaging and computing: large artery hemodynamics.
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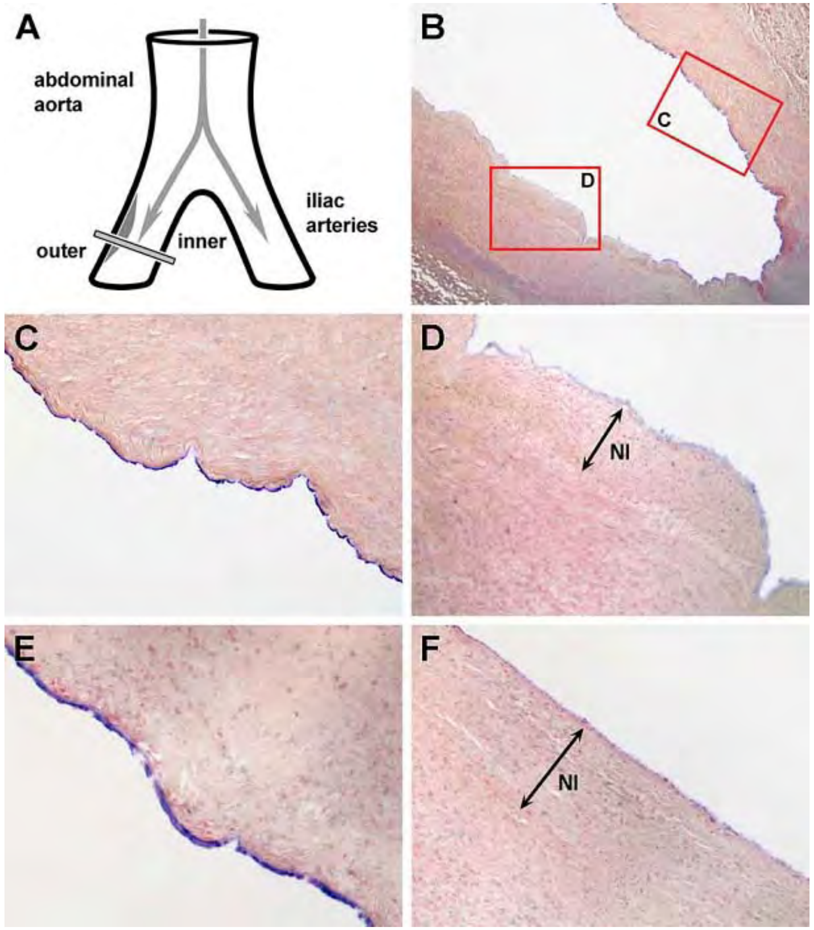
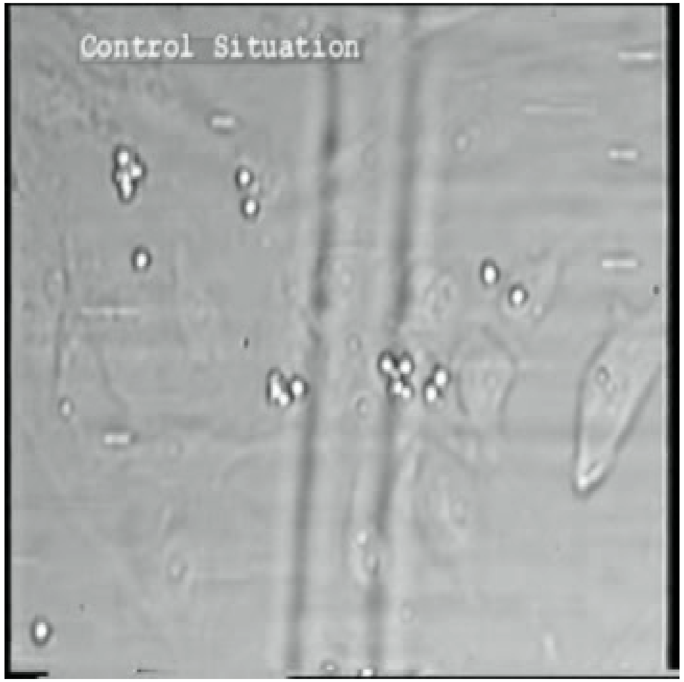
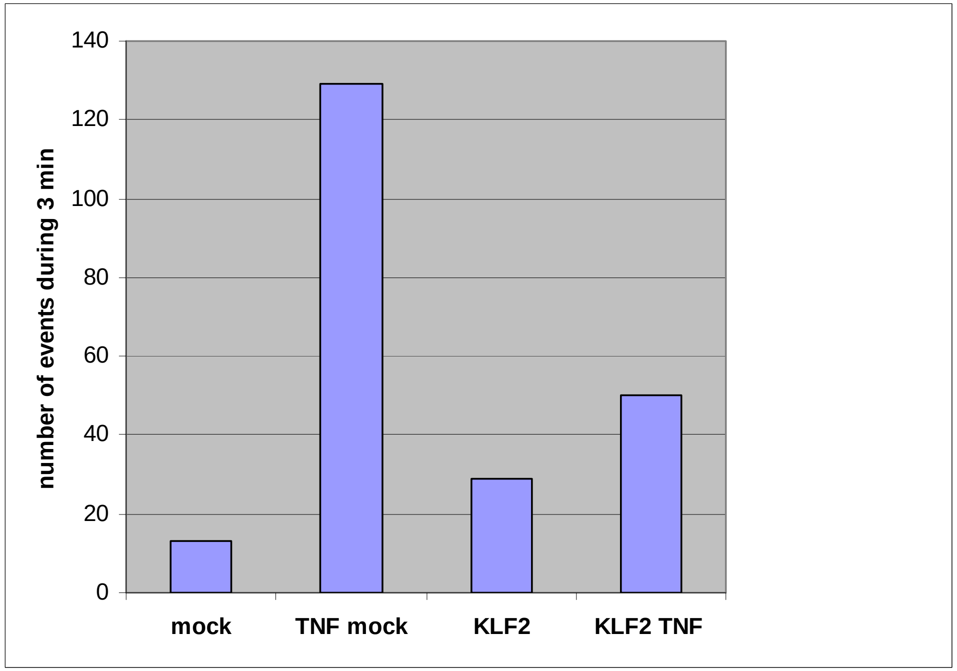


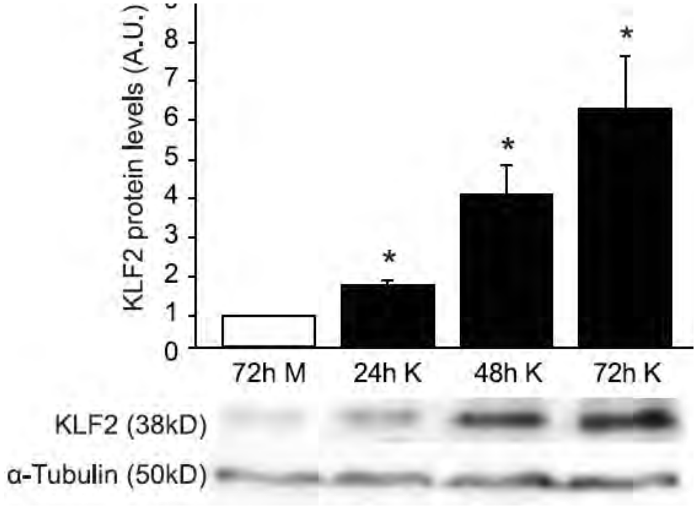
Dekker et al Blood 2002, Am J Pathol 2005, Blood 2006

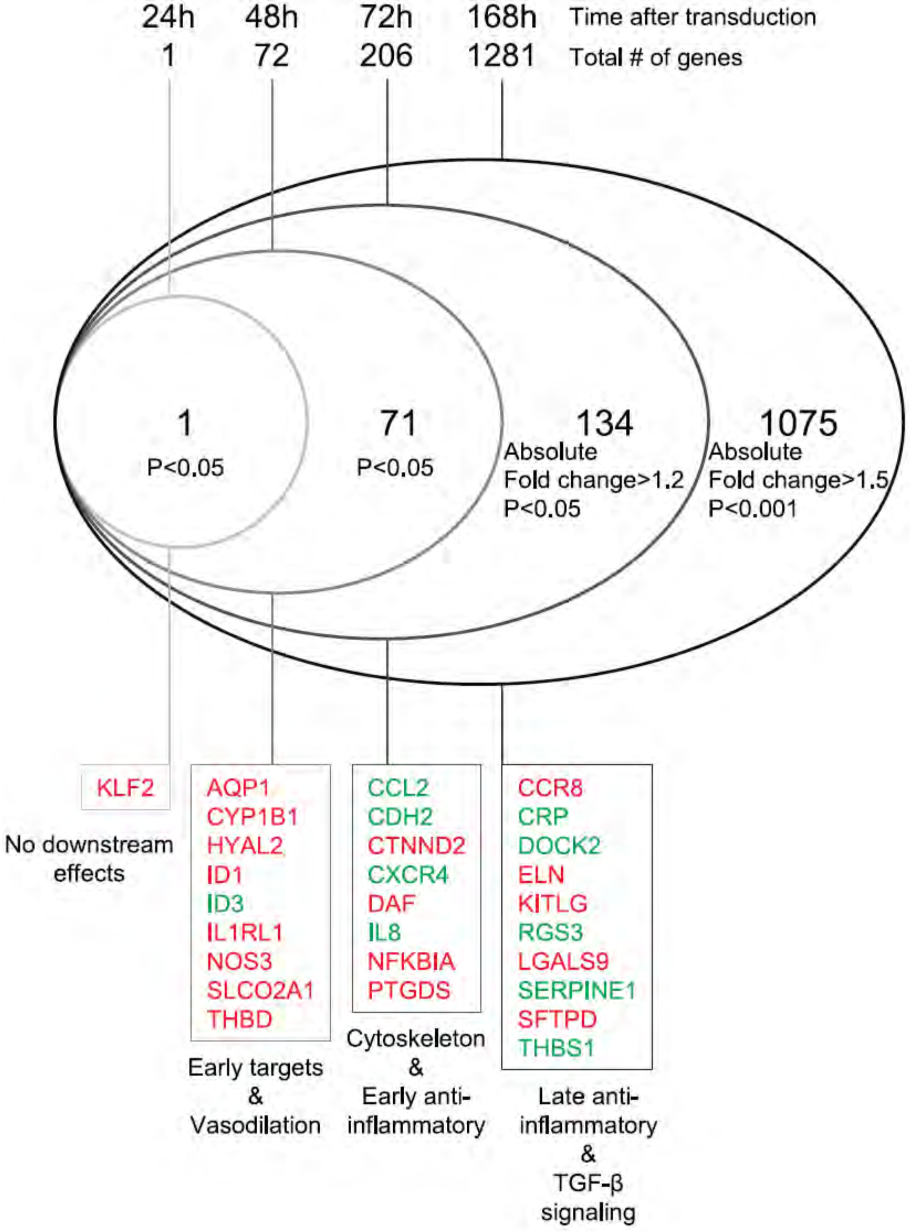
KLF2 suppresses monocyte adhesion in presence TNFa





Effects of KLF2: >1000 genes regulated





24h 48h 72h 168h Time after transduction

1 72 206 1281 Total # of genes

1 P<0.05

71 P<0.05

134 Absolute Fold change>1.2 P<0.05

1075 Absolute Fold change>1.5 P<0.001

KLF2

No downstream effects

AQP1
CYP1B1
HYAL2
ID1
ID3
IL1RL1
NOS3
SLCO2A1
THBD

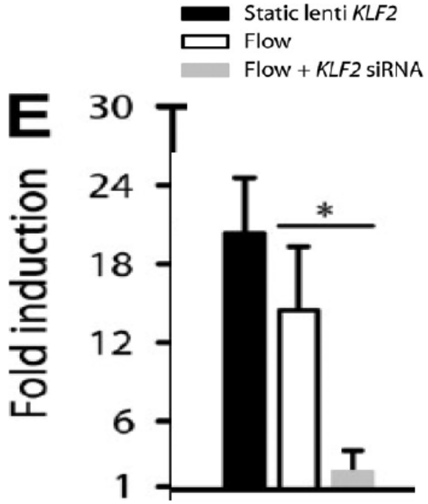
Early targets & Vasodilation

CCL2
CDH2
CTNND2
CXCR4
DAF
IL8
NFKBIA
PTGDS

Cytoskeleton & Early anti-inflammatory

CCR8
CRP
DOCK2
ELN
KITLG
RGS3
LGALS9
SERPINE1
SFTPD
THBS1

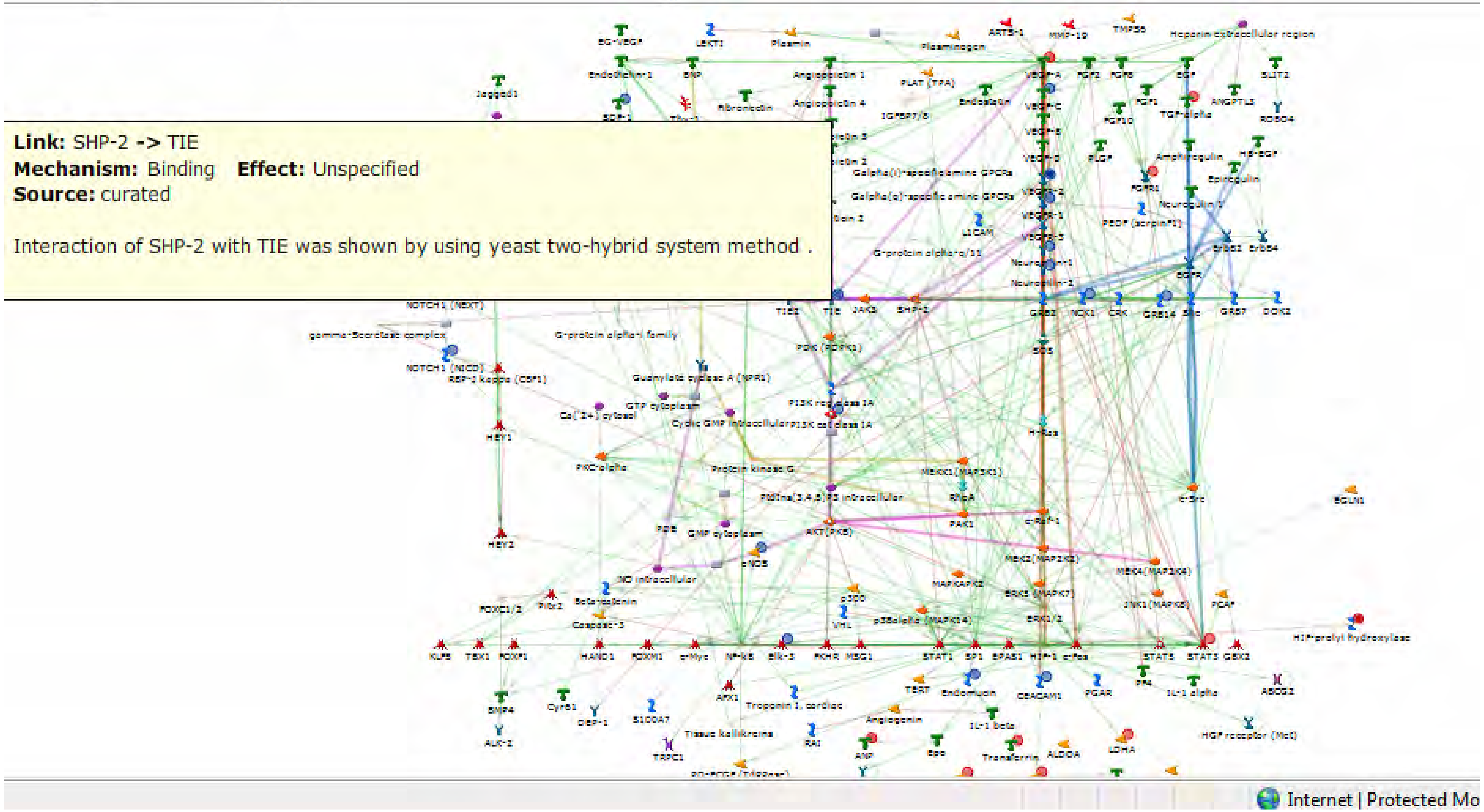
Late anti-inflammatory & TGF-β signaling



Ingenuity or Metacore Knowledge Base for computation (multiple genes to function)

- **Expert Extraction (EE) from the full text of top journals**
  - Current coverage of 32 top journals and review articles and textbooks
  - Manually extracted by trained Ph.D. scientists
  - Over 1.2 million EE findings to date
- **Automated Extraction (AE) from abstracts**
  - Automated text mining methods across Medline abstracts from 1980 (685 journals)
  - Manually checked for accuracy
  - Approximately 200,000 AE findings
- **All findings structured for computation**

A PubMed network is not a gene network

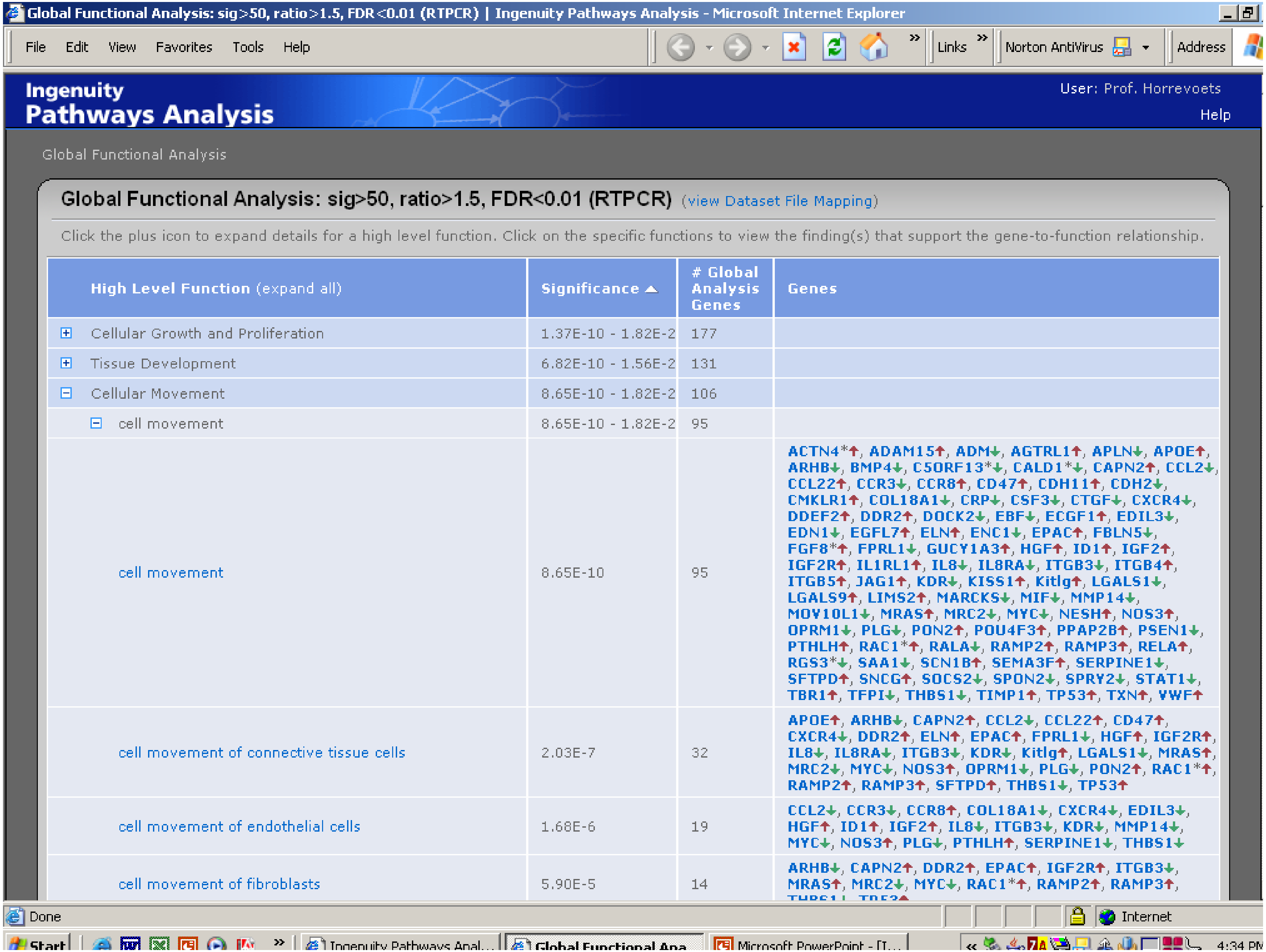


Link: SHP-2 **->** TIE
Mechanism: Binding **Effect:** Unspecified
Source: curated

Interaction of SHP-2 with TIE was shown by using yeast two-hybrid system method .

GO processes

#	Check ☑ ▨ ☐	Process	ratio	p-value
1	☐	anatomical structure development	330/3603	1.7130e-37
2	☐	system development	316/3396	5.9542e-37
3	☐	developmental process	374/4404	4.1936e-36
4	☐	organ development	263/2634	5.8220e-35
5	☐	multicellular organismal development	349/4054	2.5364e-34
6	☐	regulation of biological quality	228/2234	3.1645e-31
7	☐	vasculature development	83/401	4.5732e-31
8	☐	anatomical structure morphogenesis	195/1771	1.1929e-30
9	☐	response to stress	243/2487	1.6010e-30
10	☐	response to organic substance	176/1510	1.6300e-30
11	☐	blood vessel development	80/390	1.0941e-29
12	☐	cellular response to chemical stimulus	100/628	1.6341e-27
13	☐	cellular process	741/12491	1.8472e-26
14	☐	regulation of cellular component movement	69/335	7.7230e-26
15	☐	regulation of localization	129/1033	5.8316e-25



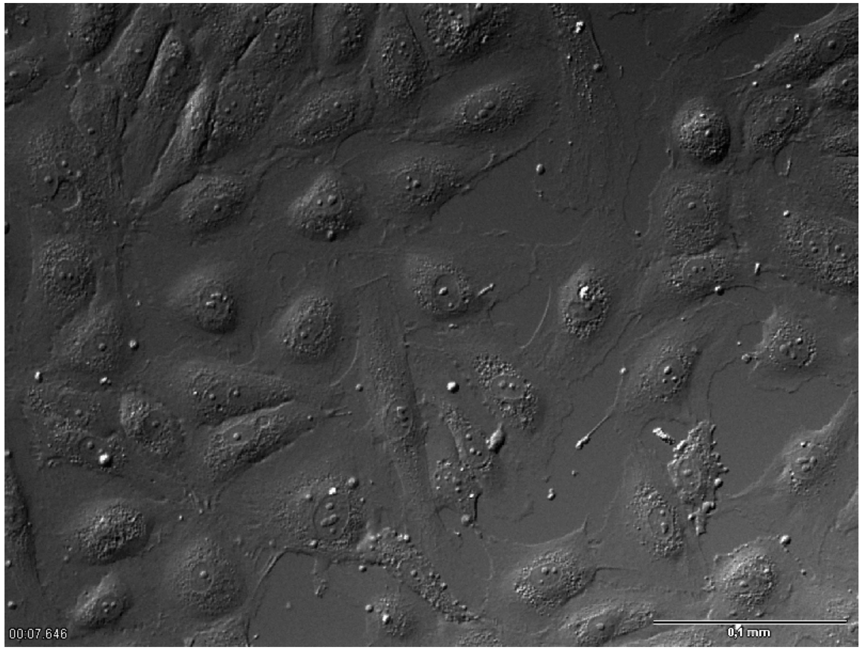
Global Functional Analysis: sig>50, ratio>1.5, FDR<0.01 (RTPCR) (view Dataset File Mapping)

Click the plus icon to expand details for a high level function. Click on the specific functions to view the finding(s) that support the gene-to-function relationship.

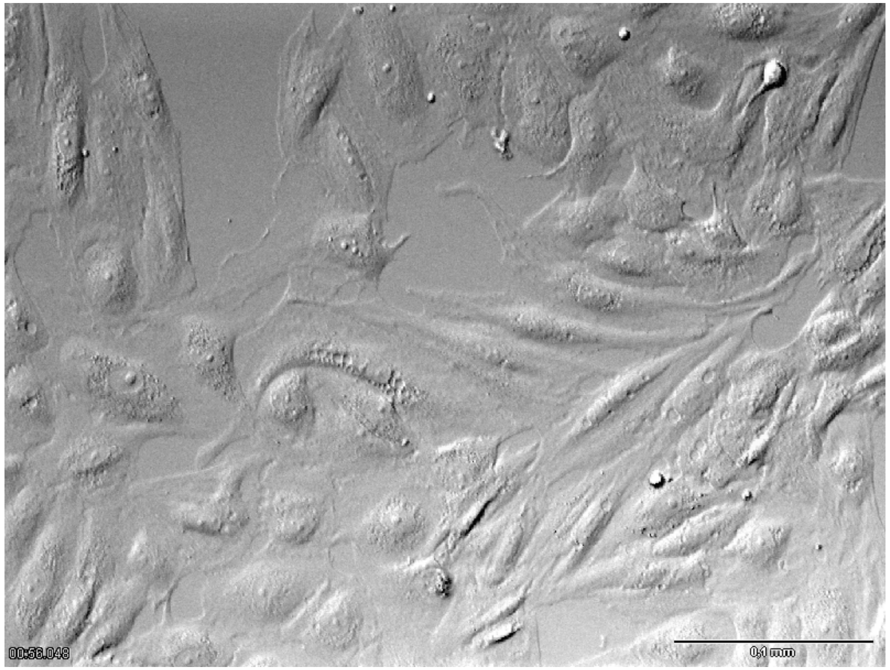
High Level Function (expand all)	**Significance ▲**	**# Global Analysis Genes**	**Genes**
⊞ Cellular Growth and Proliferation	1.37E-10 - 1.82E-2	177	
⊞ Tissue Development	6.82E-10 - 1.56E-2	131	
⊟ Cellular Movement	8.65E-10 - 1.82E-2	106	
⊟ cell movement	8.65E-10 - 1.82E-2	95	
cell movement	8.65E-10	95	ACTN4*↑, ADAM15↑, ADM↓, AGTRL1↑, APLN↓, APOE↑, ARHB↓, BMP4↓, C5ORF13*↓, CALD1*↓, CAPN2↑, CCL2↓, CCL22↑, CCR3↓, CCR8↑, CD47↑, CDH11↑, CDH2↓, CMKLR1↑, COL18A1↓, CRP↓, CSF3↓, CTGF↓, CXCR4↓, DDEF2↑, DDR2↑, DOCK2↓, EBF↓, ECGF1↑, EDIL3↓, EDN1↓, EGFL7↑, ELN↑, ENC1↓, EPAC↑, FBLN5↓, FGF8*↑, FPRL1↓, GUCY1A3↑, HGF↑, ID1↑, IGF2↑, IGF2R↑, IL1RL1↑, IL8↓, IL8RA↓, ITGB3↓, ITGB4↑, ITGB5↑, JAG1↑, KDR↓, KISS1↑, Kitlg↑, LGALS1↓, LGALS9↑, LIMS2↑, MARCKS↓, MIF↓, MMP14↓, MOV10L1↓, MRAS↑, MRC2↓, MYC↓, NESH↑, NOS3↑, OPRM1↓, PLG↓, PON2↑, POU4F3↑, PPAP2B↑, PSEN1↓, PTHLH↑, RAC1*↑, RALA↓, RAMP2↑, RAMP3↑, RELA↑, RGS3*↓, SAA1↓, SCN1B↑, SEMA3F↑, SERPINE1↓, SFTPD↑, SNCG↑, SOCS2↓, SPON2↓, SPRY2↓, STAT1↓, TBR1↑, TFPI↓, THBS1↓, TIMP1↑, TP53↑, TXN↑, VWF↑
cell movement of connective tissue cells	2.03E-7	32	APOE↑, ARHB↓, CAPN2↑, CCL2↓, CCL22↑, CD47↑, CXCR4↓, DDR2↑, ELN↑, EPAC↑, FPRL1↓, HGF↑, IGF2R↑, IL8↓, IL8RA↓, ITGB3↓, KDR↓, Kitlg↑, LGALS1↓, MRAS↑, MRC2↓, MYC↓, NOS3↑, OPRM1↓, PLG↓, PON2↑, RAC1*↑, RAMP2↑, RAMP3↑, SFTPD↑, THBS1↓, TP53↑
cell movement of endothelial cells	1.68E-6	19	CCL2↓, CCR3↓, CCR8↑, COL18A1↓, CXCR4↓, EDIL3↓, HGF↑, ID1↑, IGF2↑, IL8↓, ITGB3↓, KDR↓, MMP14↓, MYC↓, NOS3↑, PLG↓, PTHLH↑, SERPINE1↓, THBS1↓
cell movement of fibroblasts	5.90E-5	14	ARHB↓, CAPN2↑, DDR2↑, EPAC↑, IGF2R↑, ITGB3↓, MRAS↑, MRC2↓, MYC↓, RAC1*↑, RAMP2↑, RAMP3↑, THBS1↓, TP53↑

KLF2 suppresses cellular movement

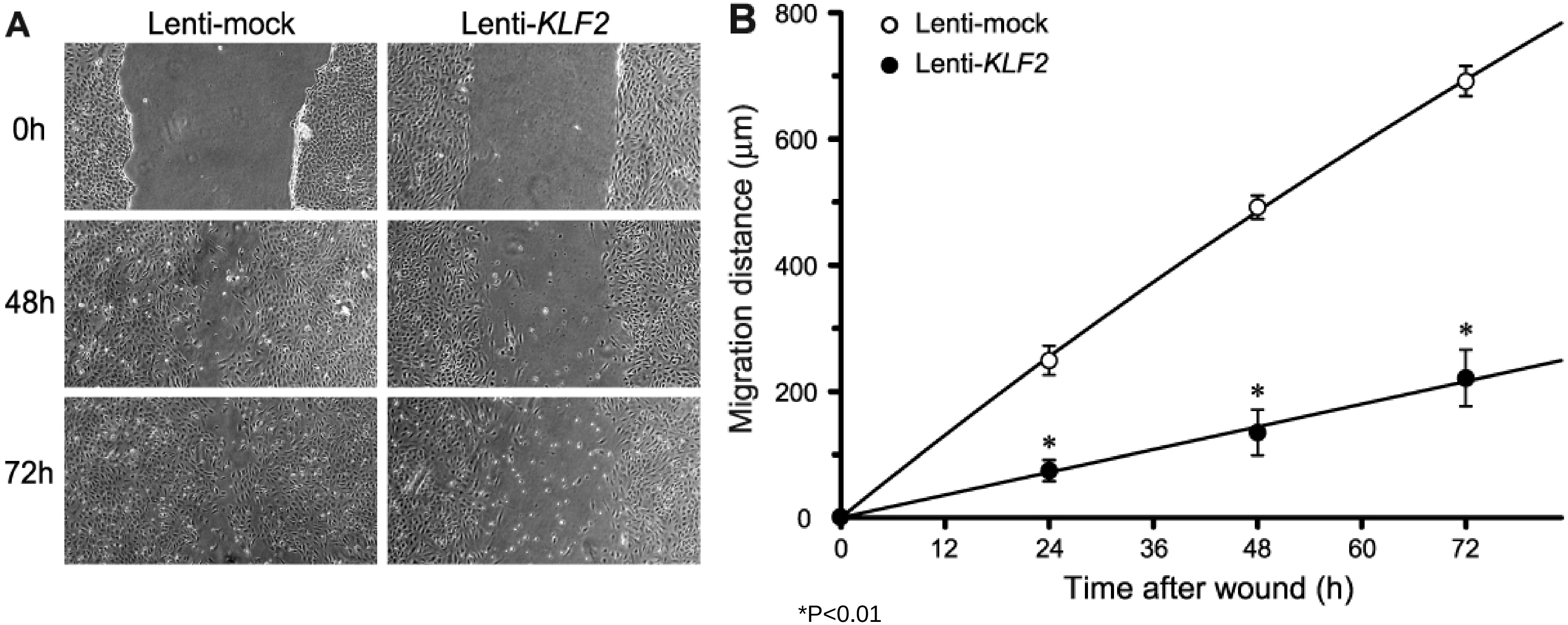
EC mock



EC KLF2

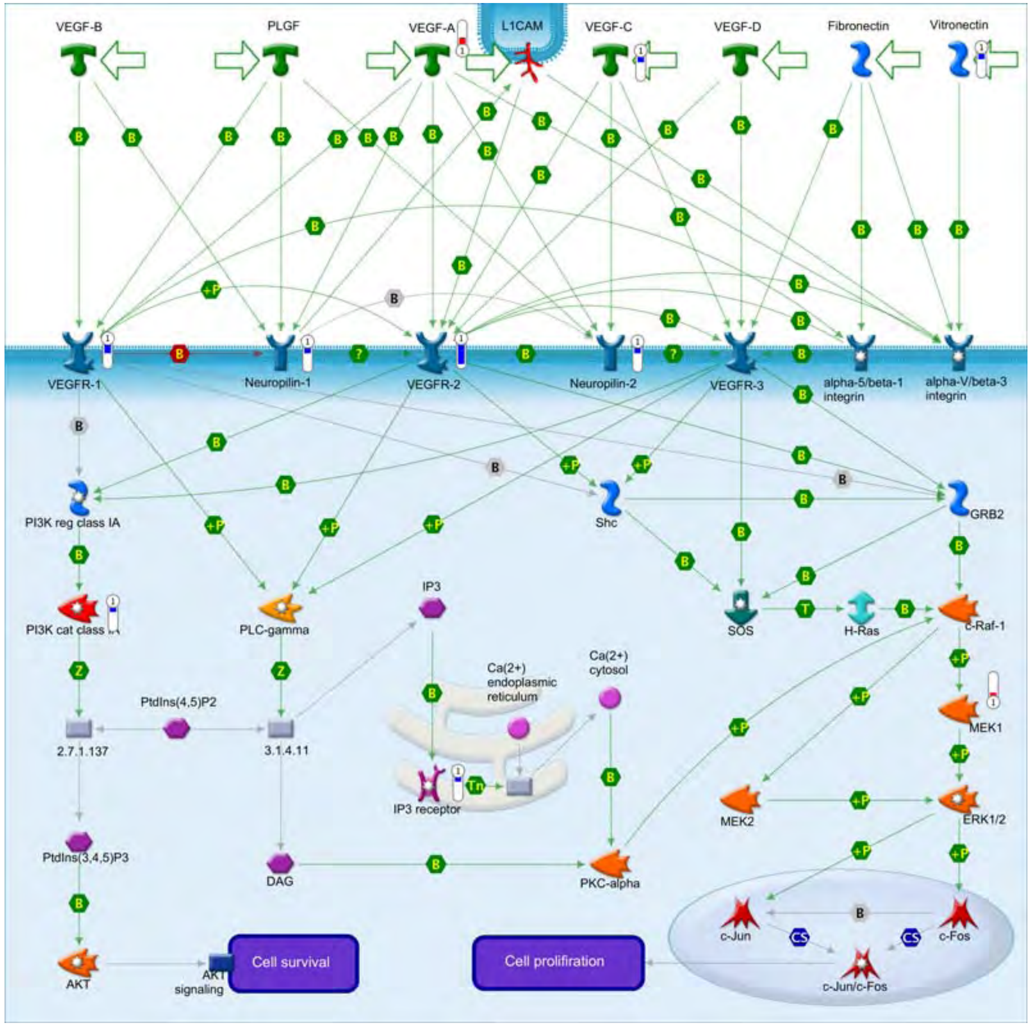


KLF2 attenuates endothelial cell migration



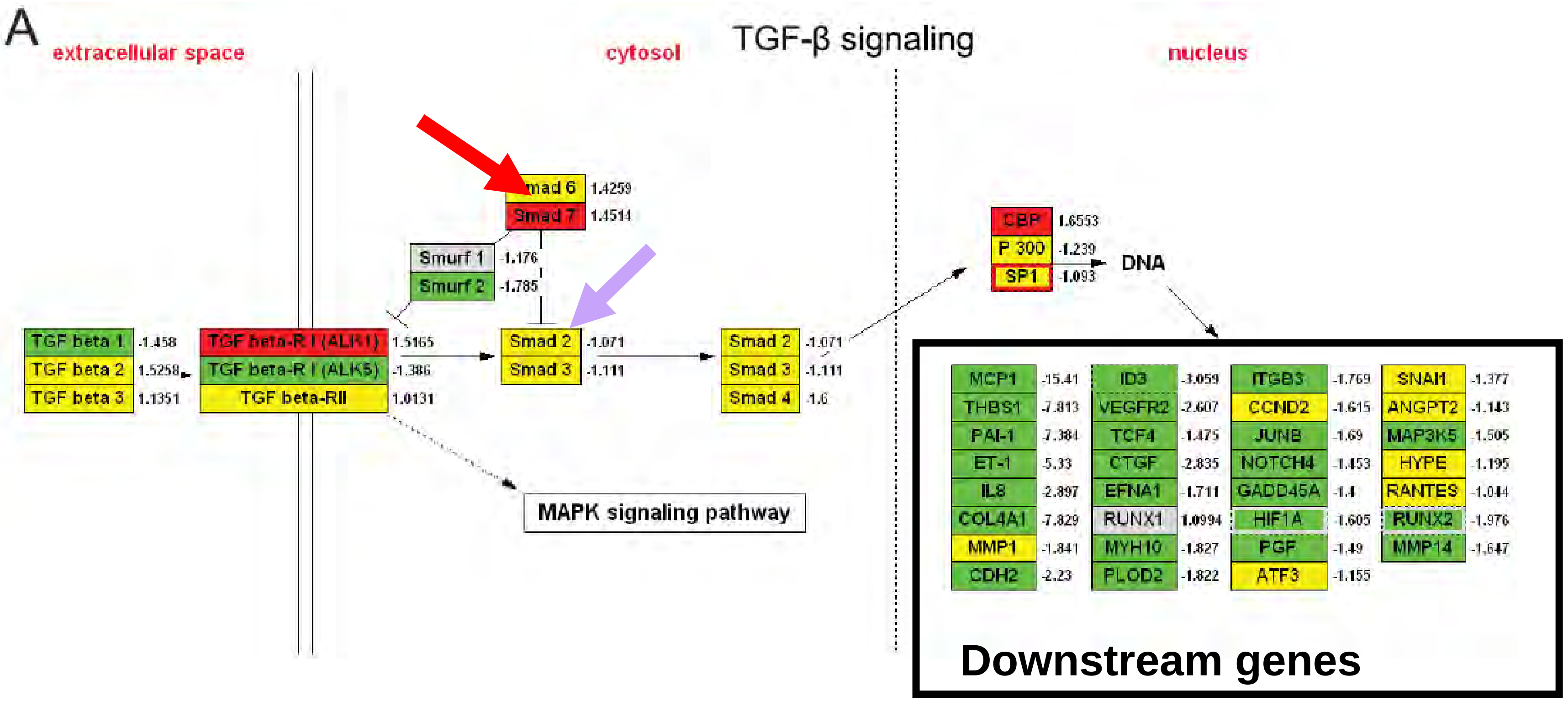
*P<0.01

Many pathway programs only detect pathway members not functional outcome



KLF2 suppresses a large panel of TGFbeta downstream genes

GenMAPP presentation of KLF2 modulation



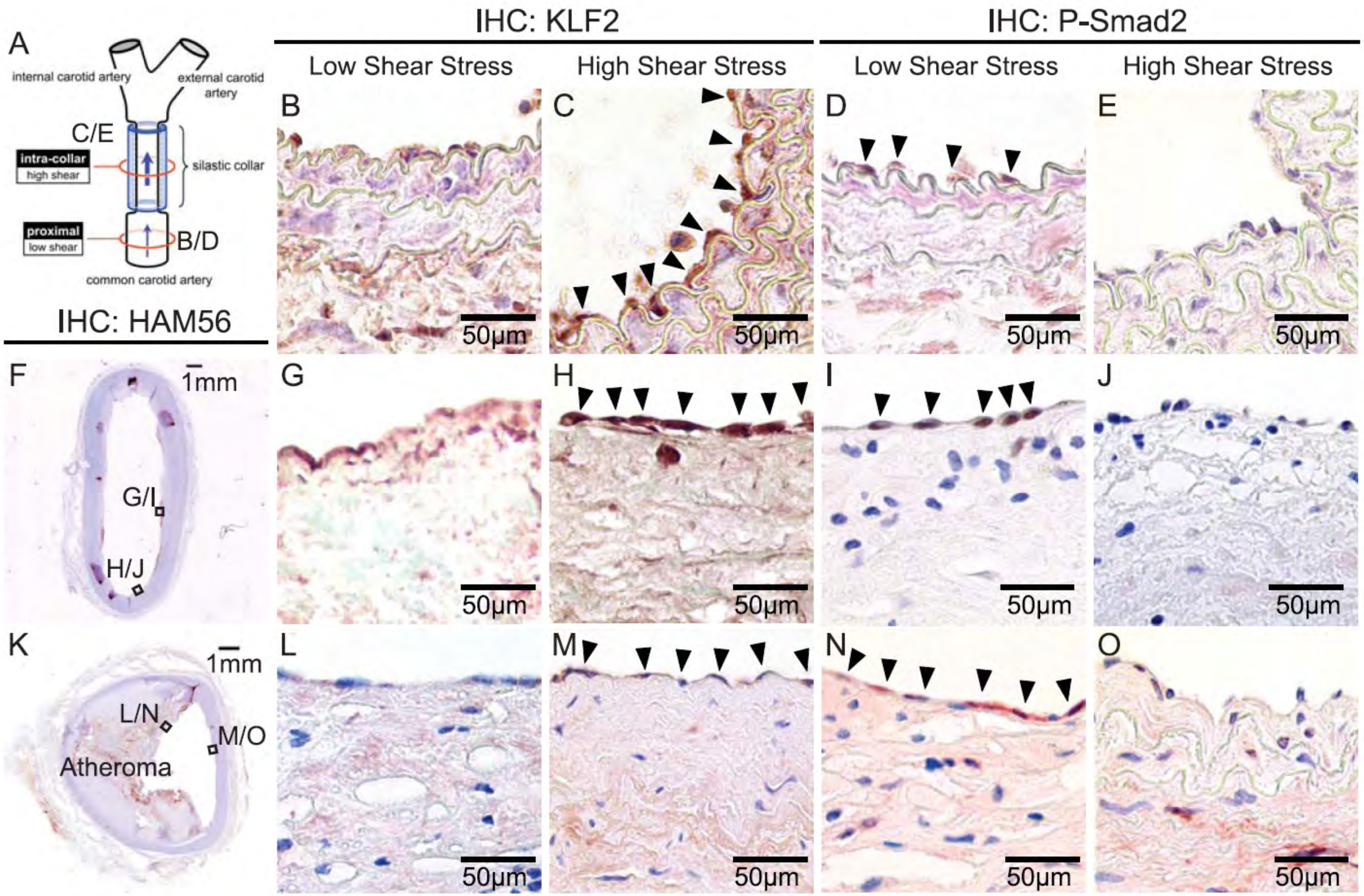
MCP1	-15.41	ID3	-3.059	ITGB3	-1.769	SNAI1	-1.377
THBS1	-7.813	VEGFR2	-2.607	CCND2	-1.615	ANGPT2	-1.143
PAI-1	-7.384	TCF4	-1.475	JUNB	-1.69	MAP3K5	-1.505
ET-1	-5.33	CTGF	-2.835	NOTCH4	-1.453	HYPE	-1.195
IL8	-2.897	EFNA1	-1.711	GADD45A	-1.4	RANTES	-1.044
COL4A1	-7.829	RUNX1	1.0994	HIF1A	-1.605	RUNX2	-1.976
MMP1	-1.841	MYH10	-1.827	PGF	-1.49	MMP14	-1.647
CDH2	-2.23	PLOD2	-1.822	ATF3	-1.155		

🟩 Lower expression (repressed)

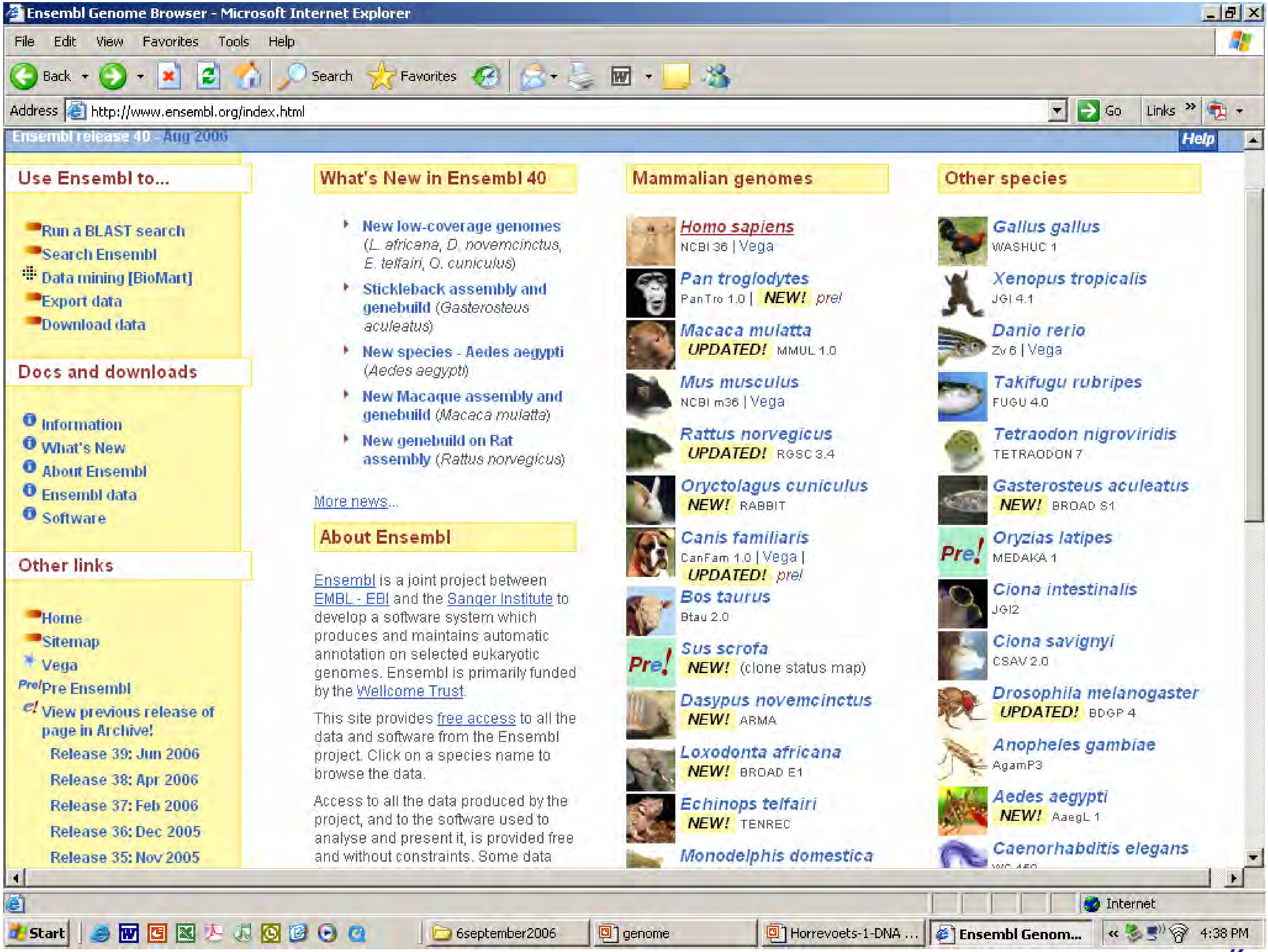
🟥 Higher expression (induced)

Boon et al., ATVB 2007

KLF2 and TGFbeta signaling are mutually exclusive in vivo
detection by phosphospecific antibody: activated proteome



Boon et al., ATVB 2007



Use Ensembl to...

- Run a BLAST search
- Search Ensembl
- Data mining [BioMart]
- Export data
- Download data

Docs and downloads

- Information
- What's New
- About Ensembl
- Ensembl data
- Software

Other links

- Home
- Sitemap
- Vega
- Pre Ensembl
- View previous release of page in Archive!
  - Release 39: Jun 2006
  - Release 38: Apr 2006
  - Release 37: Feb 2006
  - Release 36: Dec 2005
  - Release 35: Nov 2005

What's New in Ensembl 40

- New low-coverage genomes (*L. africana, D. novemcinctus, E. telfairi, O. cuniculus*)
- Stickleback assembly and genebuild (*Gasterosteus aculeatus*)
- New species - Aedes aegypti (*Aedes aegypti*)
- New Macaque assembly and genebuild (*Macaca mulatta*)
- New genebuild on Rat assembly (*Rattus norvegicus*)

More news...

About Ensembl

Ensembl is a joint project between EMBL - EBI and the Sanger Institute to develop a software system which produces and maintains automatic annotation on selected eukaryotic genomes. Ensembl is primarily funded by the Wellcome Trust.

This site provides free access to all the data and software from the Ensembl project. Click on a species name to browse the data.

Access to all the data produced by the project, and to the software used to analyse and present it, is provided free and without constraints. Some data

Mammalian genomes

Homo sapiens
NCBI 36 | Vega

Pan troglodytes
PanTro 1.0 | NEW! pre!

Macaca mulatta
UPDATED! MMUL 1.0

Mus musculus
NCBI m36 | Vega

Rattus norvegicus
UPDATED! RGSC 3.4

Oryctolagus cuniculus
NEW! RABBIT

Canis familiaris
CanFam 1.0 | Vega |
UPDATED! pre!

Bos taurus
Btau 2.0

Sus scrofa
NEW! (clone status map)

Dasypus novemcinctus
NEW! ARMA

Loxodonta africana
NEW! BROAD E1

Echinops telfairi
NEW! TENREC

Monodelphis domestica

Other species

Gallus gallus
WASHUC 1

Xenopus tropicalis
JGI 4.1

Danio rerio
Zv 6 | Vega

Takifugu rubripes
FUGU 4.0

Tetraodon nigroviridis
TETRAODON 7

Gasterosteus aculeatus
NEW! BROAD S1

Oryzias latipes
MEDAKA 1

Ciona intestinalis
JGI2

Ciona savignyi
CSAV 2.0

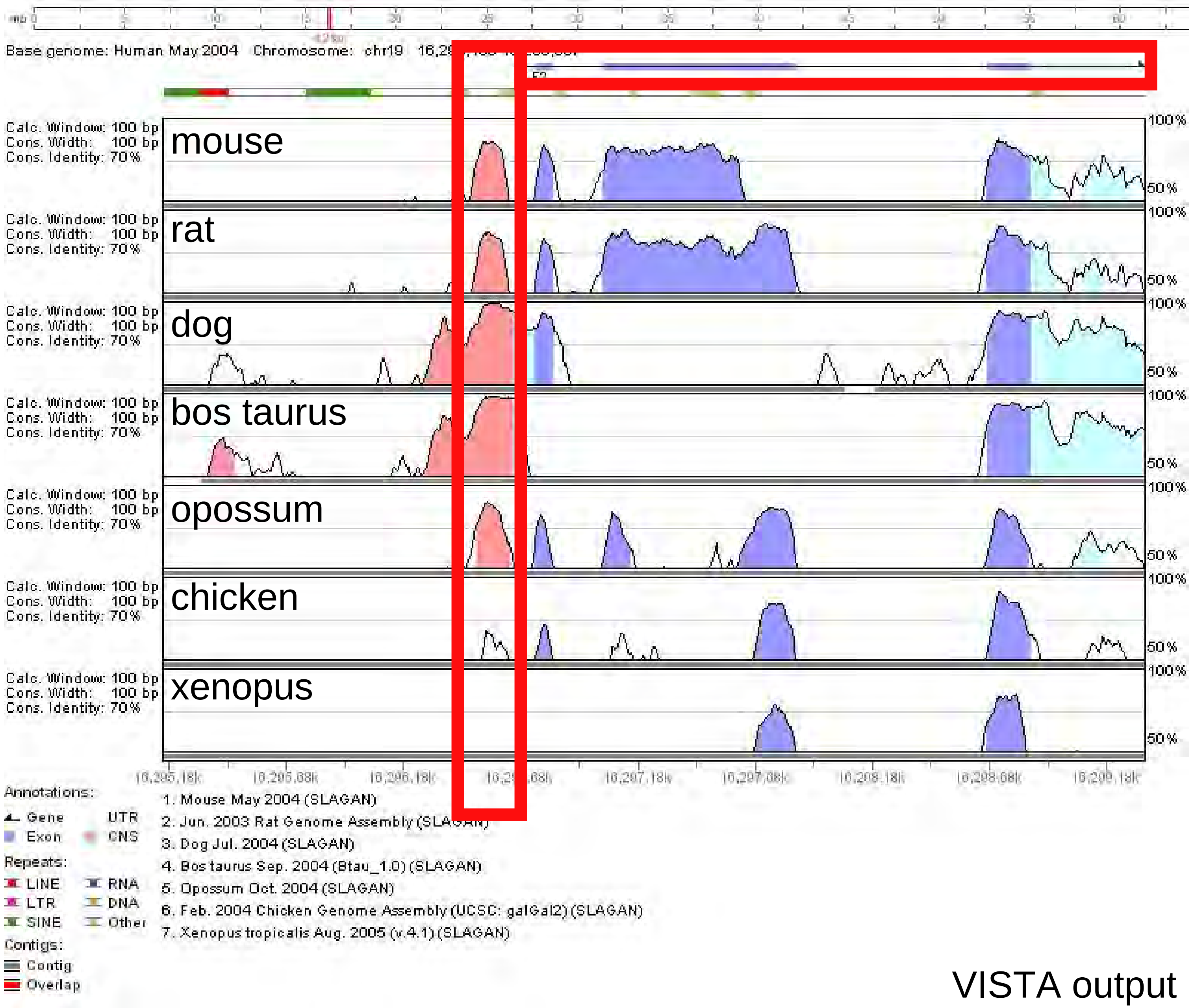
Drosophila melanogaster
UPDATED! BDGP 4

Anopheles gambiae
AgamP3

Aedes aegypti
NEW! AaegL 1

Caenorhabditis elegans

Conservation of cis-regulatory sequences (KLF2)

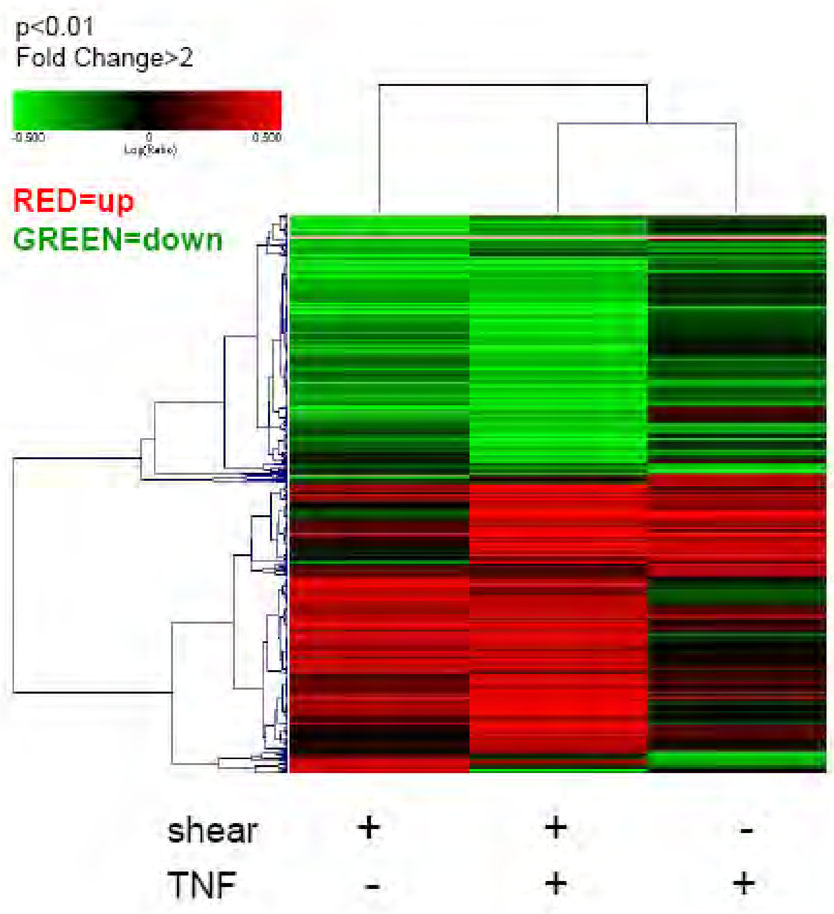


1. Mouse May 2004 (SLAGAN)
2. Jun. 2003 Rat Genome Assembly (SLAGAN)
3. Dog Jul. 2004 (SLAGAN)
4. Bos taurus Sep. 2004 (Btau_1.0) (SLAGAN)
5. Opossum Oct. 2004 (SLAGAN)
6. Feb. 2004 Chicken Genome Assembly (UCSC: galGal2) (SLAGAN)
7. Xenopus tropicalis Aug. 2005 (v.4.1) (SLAGAN)

VISTA output

Functional transcriptomics-promoter analysis

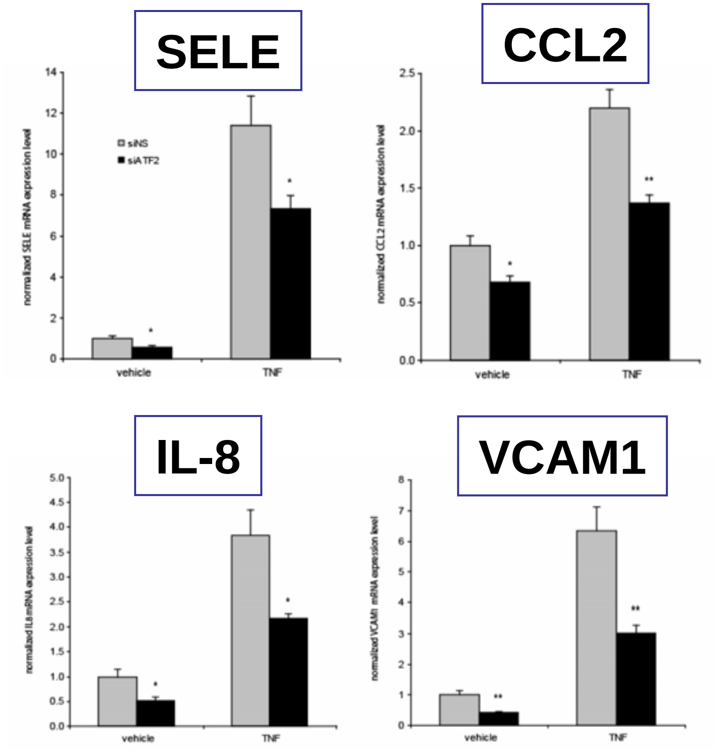
deciphering the KLF2 transcriptional network

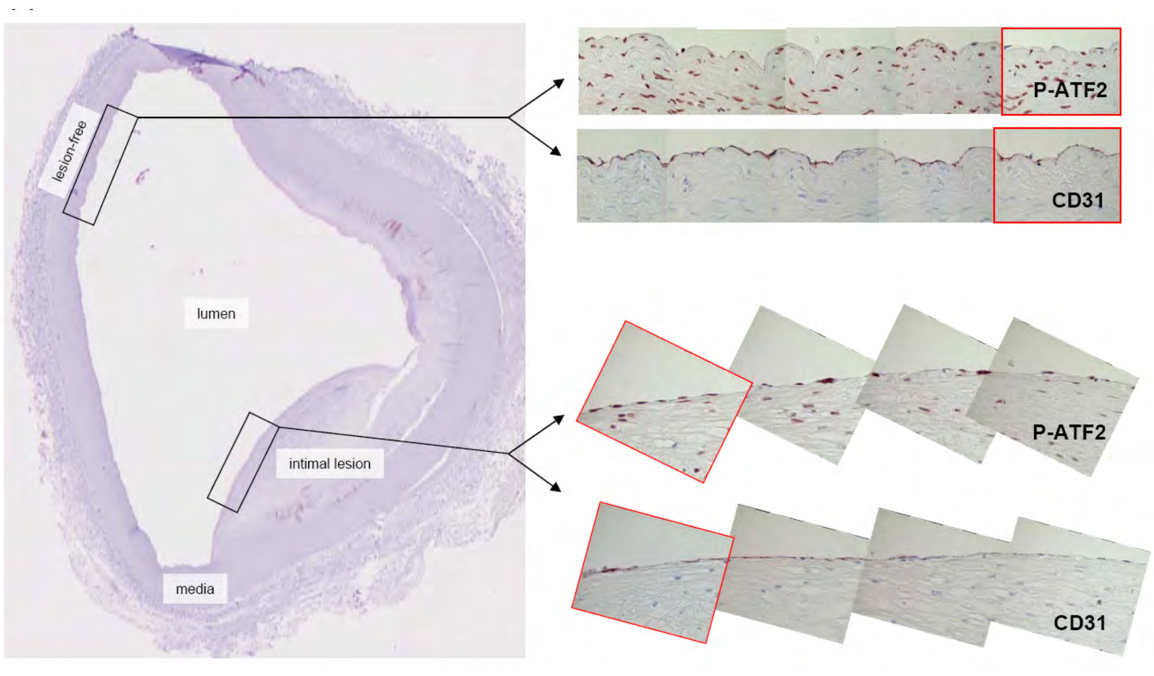


Group	Description	Over-represented TFBS in 500bp upstream region
A	Shear inhibited	ATF SMAD / SOX
B	TNF induced	NF-kB / AP-1 / ATF / NRF2 / ETS / SOX
C	Shear induced	AP-1 NRF2 / XR / PR

Fledderus et al. Blood 2007

si-ATF2 suppresses basal and inducible levels inflammatory genes
Active phospho-ATF2 only in human atherosclerotic lesion EC

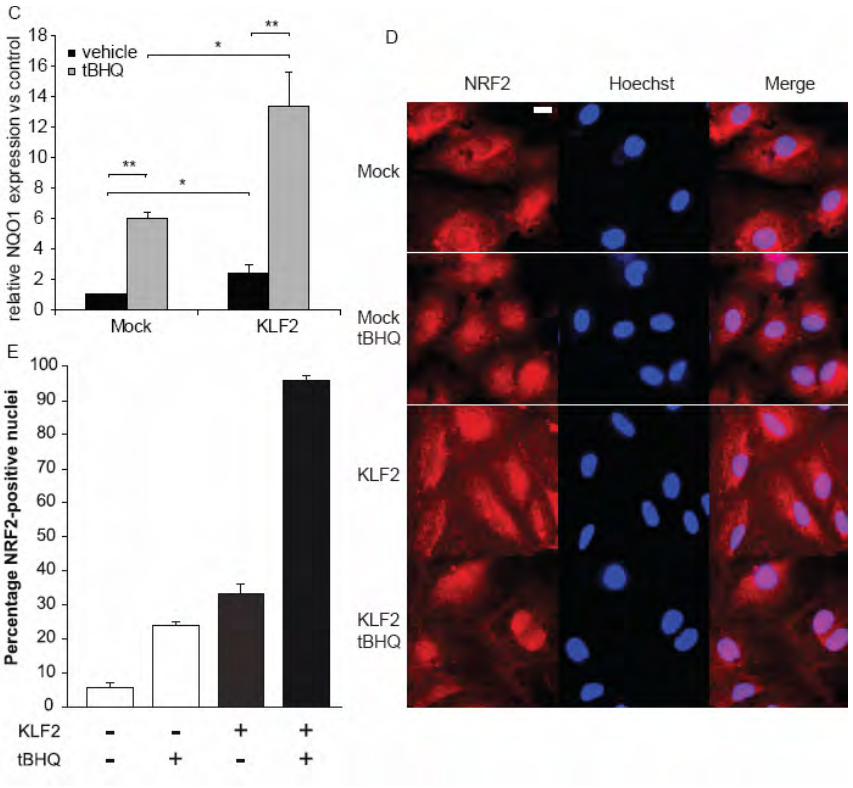




Fledderus et al. Blood 2007

KLF2 augments nuclear localization of anti-oxidant NRF2

This results in enhanced expression of multiple anti-oxidant enzymes



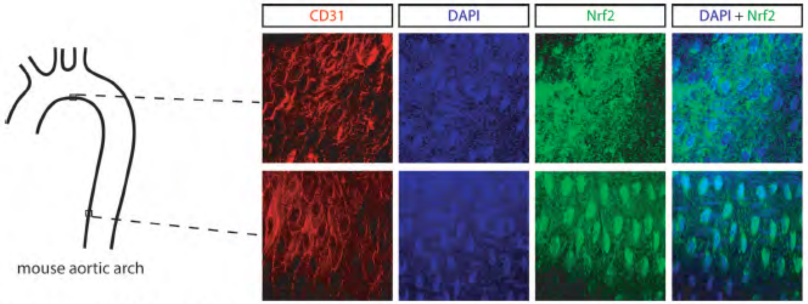


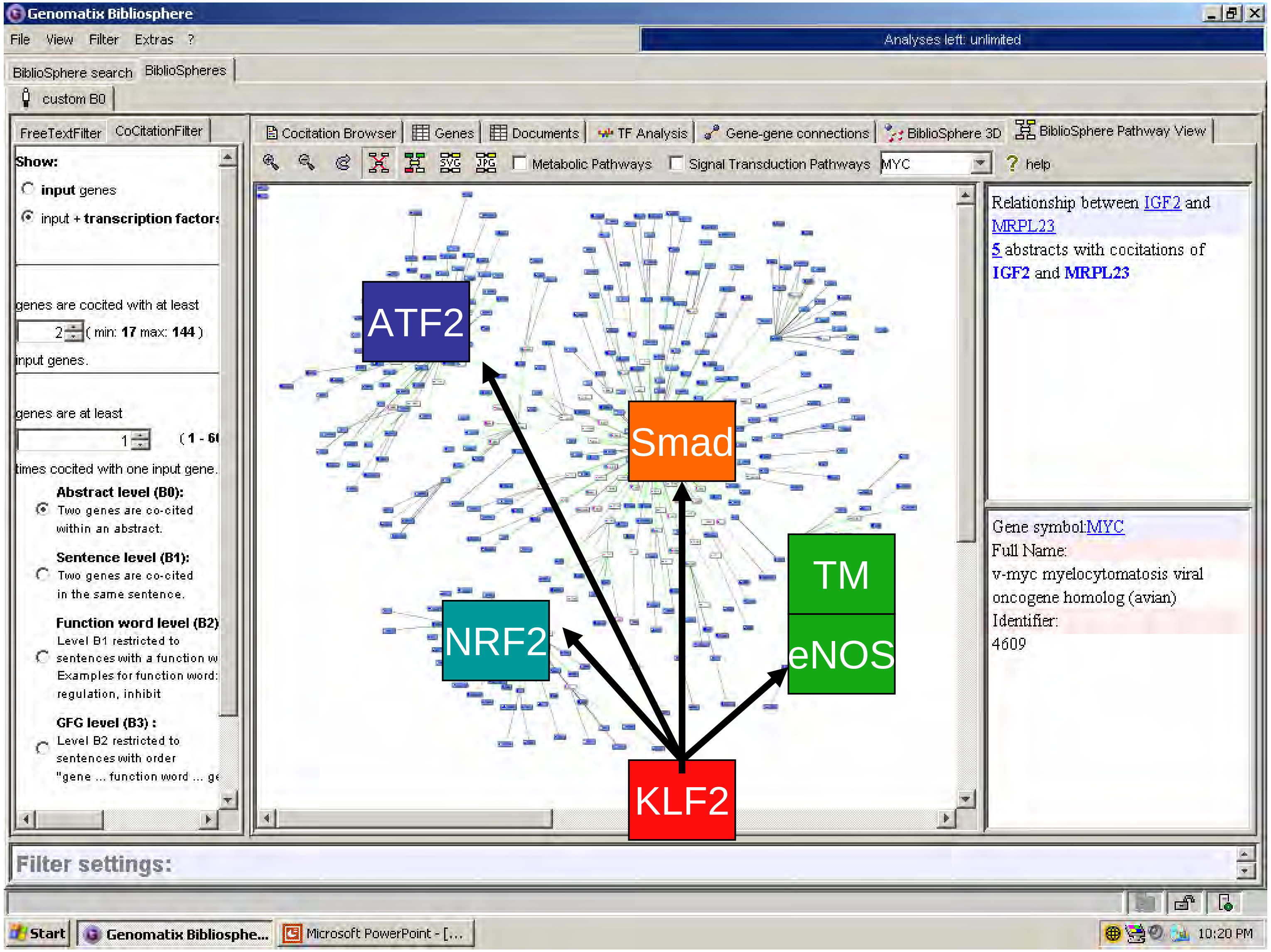
Figure 6. Increased Nrf2 nuclear localization in endothelium in atherosclerosis-resistant regions of the mouse aorta. The aortic

Dai et al. Circ Res. 2007;101:723-733.

Fledderus, Boon et al, ATVB 2008;28:1339-46.

The KLF2-shear stress genetic network

How a single transcription factor controls ~ 1000 genes



Show:

○ **input** genes

● input + **transcription factors**

genes are cocited with at least

2 (min: **17** max: **144**)

input genes.

genes are at least

1 (**1 - 6**

times cocited with one input gene.

● **Abstract level (B0):** Two genes are co-cited within an abstract.

○ **Sentence level (B1):** Two genes are co-cited in the same sentence.

○ **Function word level (B2)** Level B1 restricted to sentences with a function w Examples for function word: regulation, inhibit

○ **GFG level (B3) :** Level B2 restricted to sentences with order "gene ... function word ... ge

Relationship between IGF2 and MRPL23

5 abstracts with cocitations of **IGF2** and **MRPL23**

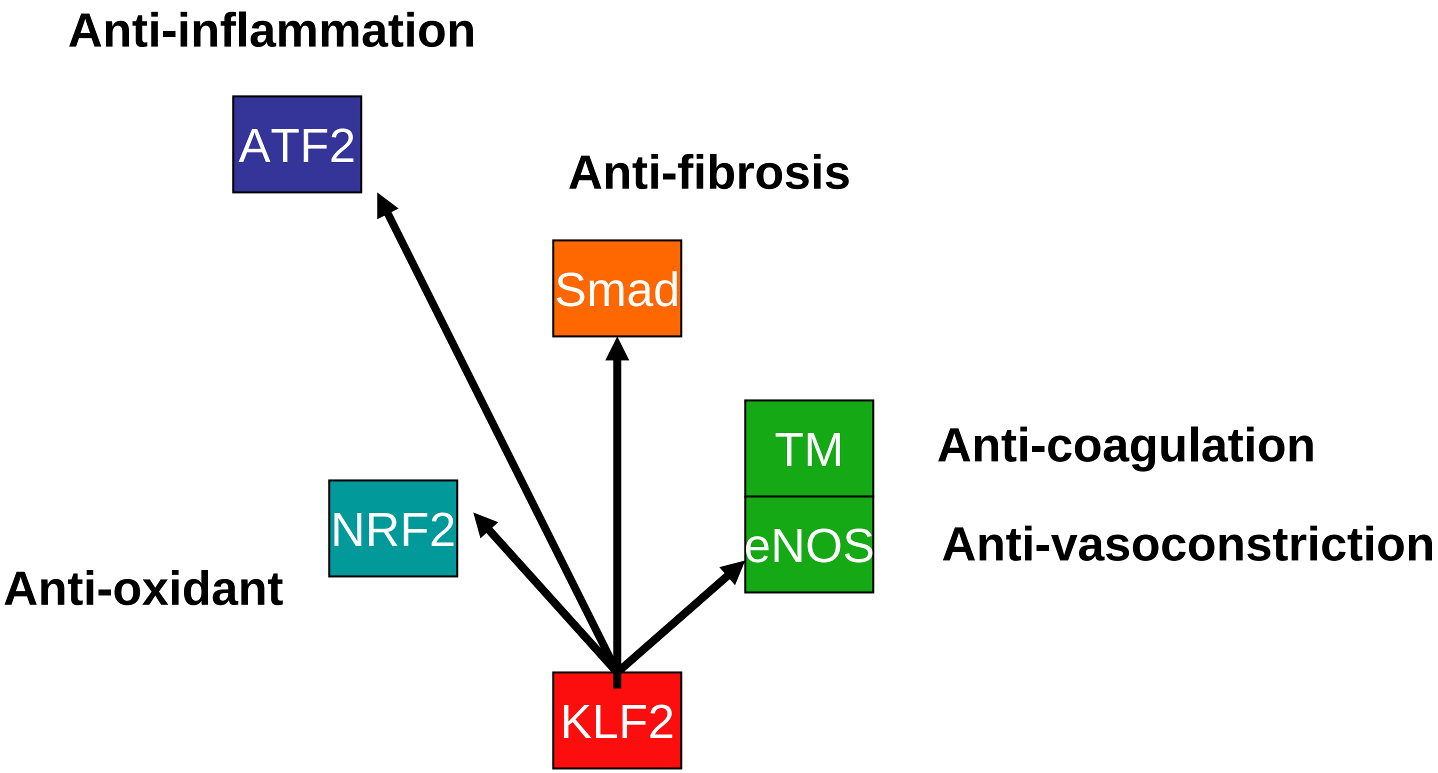
Gene symbol: MYC

Full Name: v-myc myelocytomatosis viral oncogene homolog (avian)

Identifier: 4609

The KLF2-shear stress genetic network

How a single transcription factor controls ~ 1000 genes



Anti-inflammation

ATF2

Anti-fibrosis

Smad

TM

Anti-coagulation

NRF2

eNOS

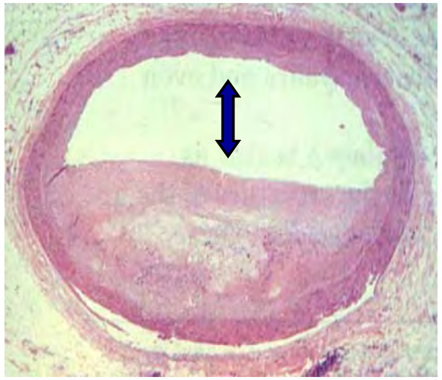
Anti-vasoconstriction

Anti-oxidant

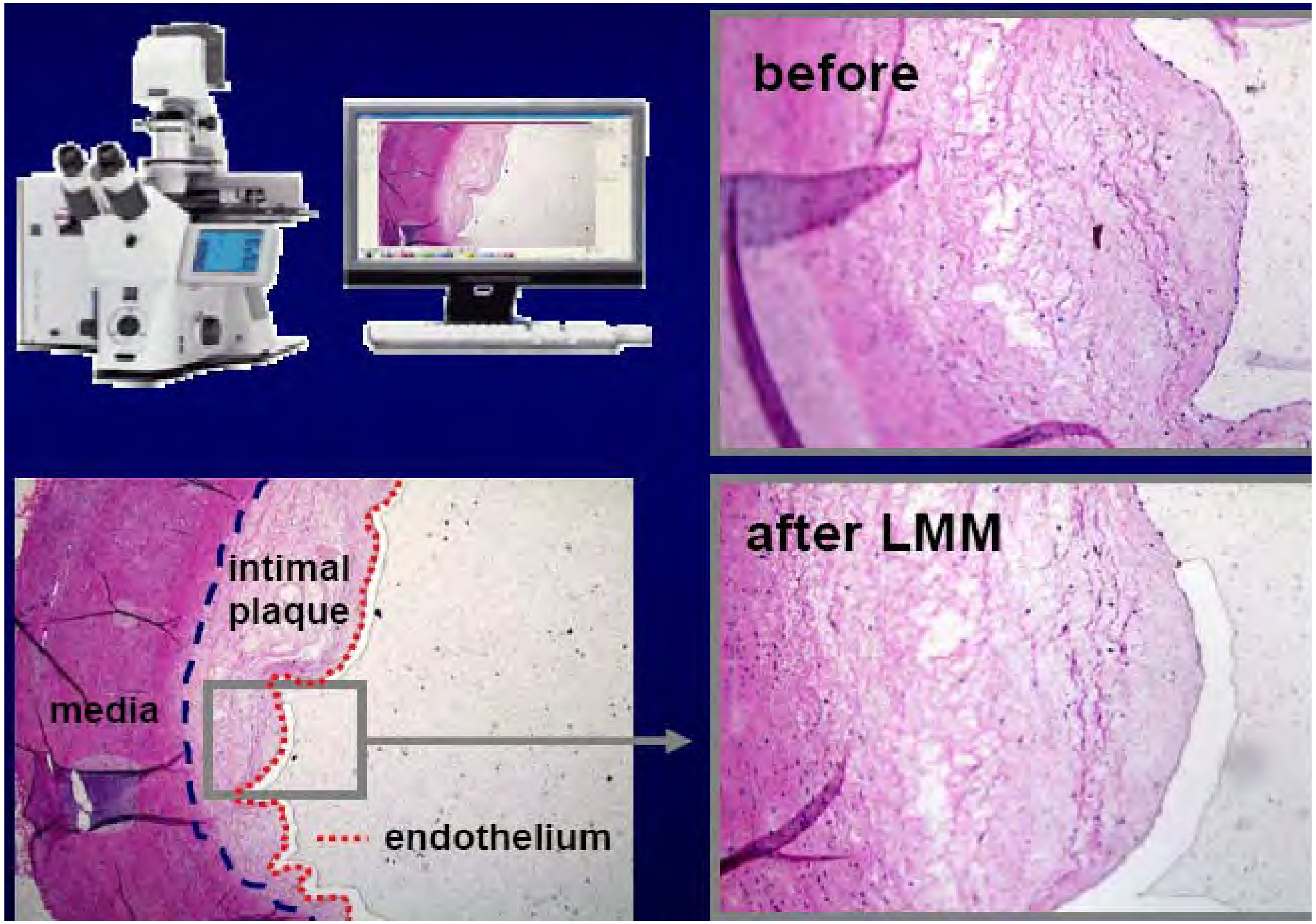
KLF2

Atherosclerosis: a focal arterial inflammatory disease

Laser Microbeam Microdissection (LMM) arterial endothelium



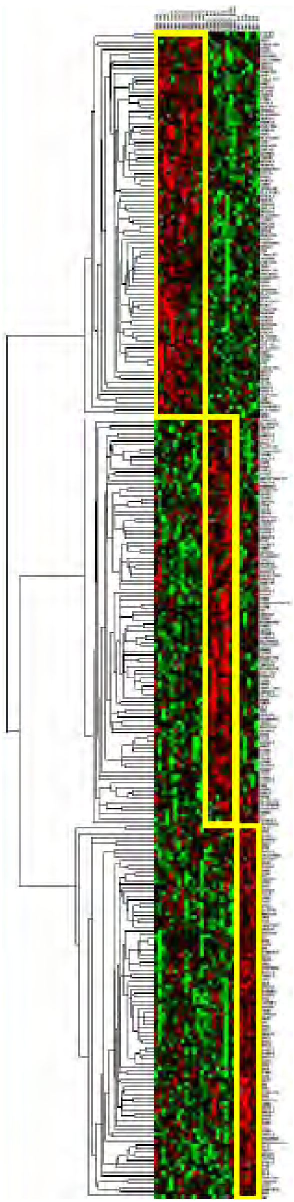
Focality of lesions



25 x

100 x

Stage-specific EC surface markers

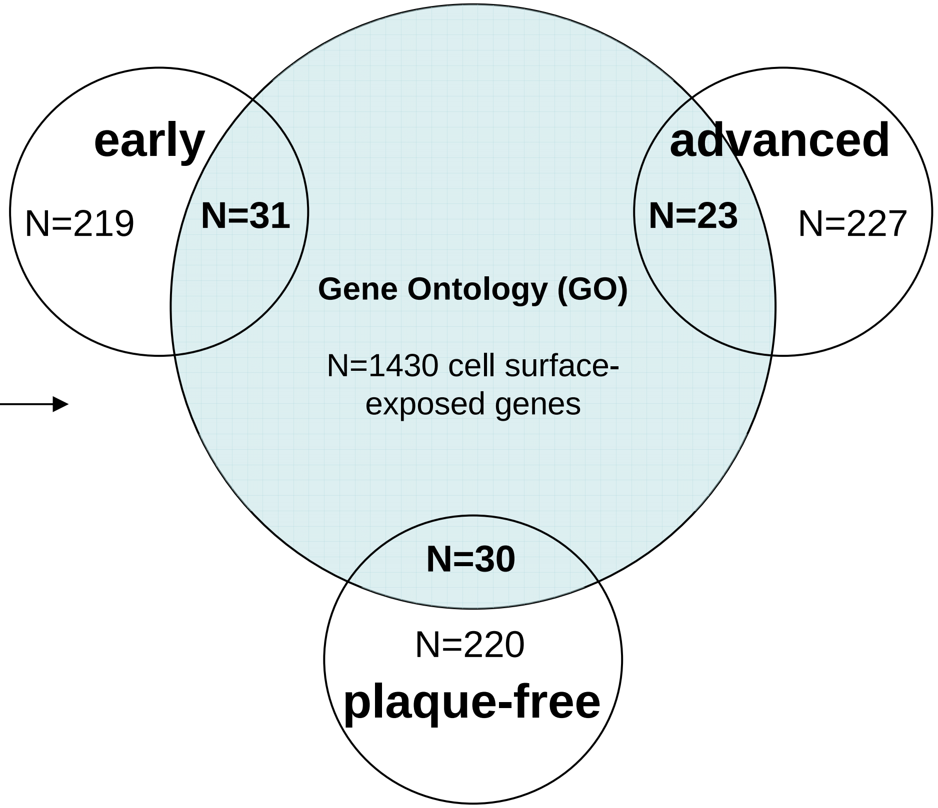


1) plaque-free

2) early lesions

3) advanced lesions

A) Gene Set Enrichment Analyses (GSEA)



early

N=219

N=31

advanced

N=23

N=227

Gene Ontology (GO)

N=1430 cell surface-exposed genes

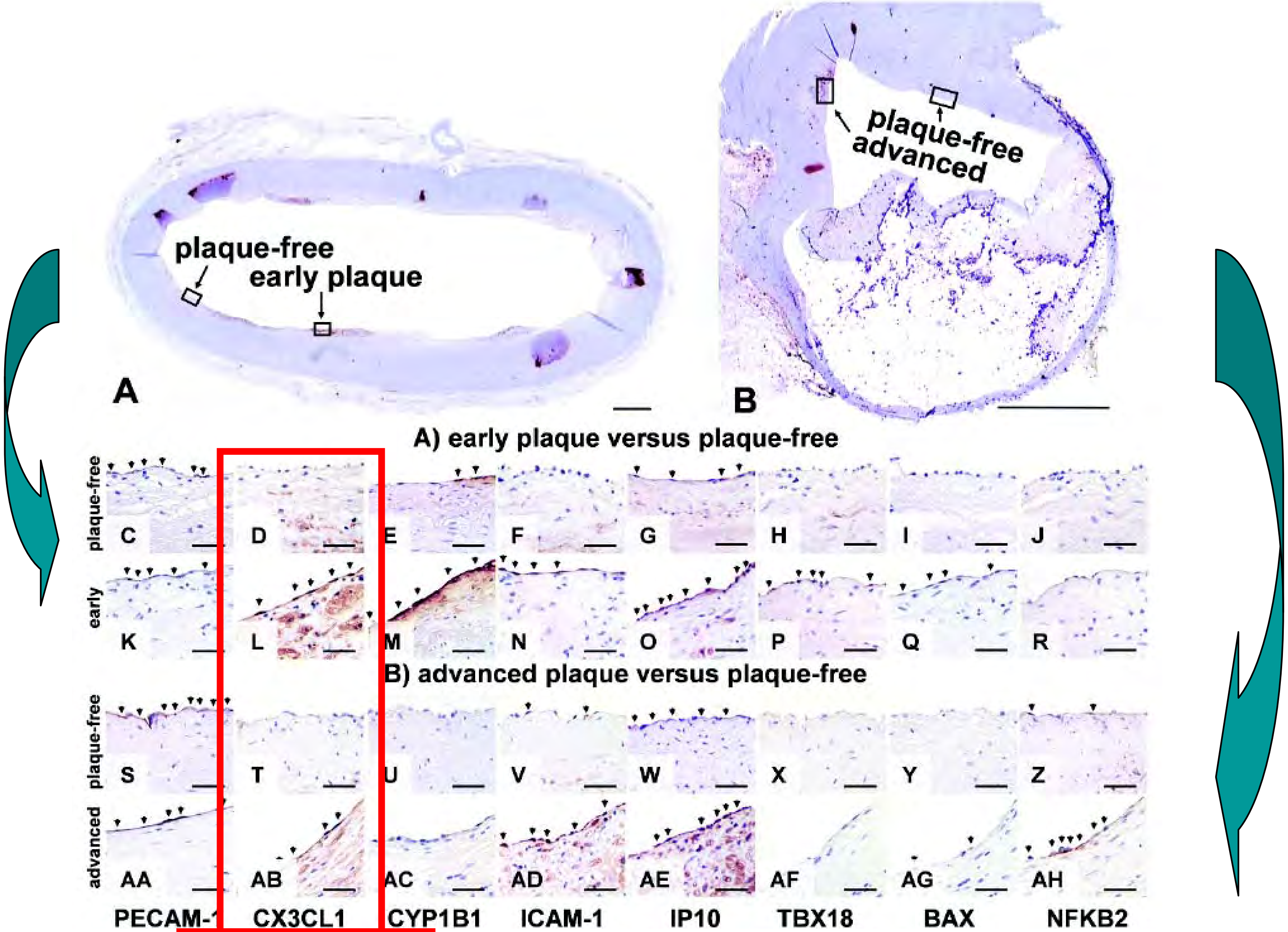
N=30

N=220

plaque-free

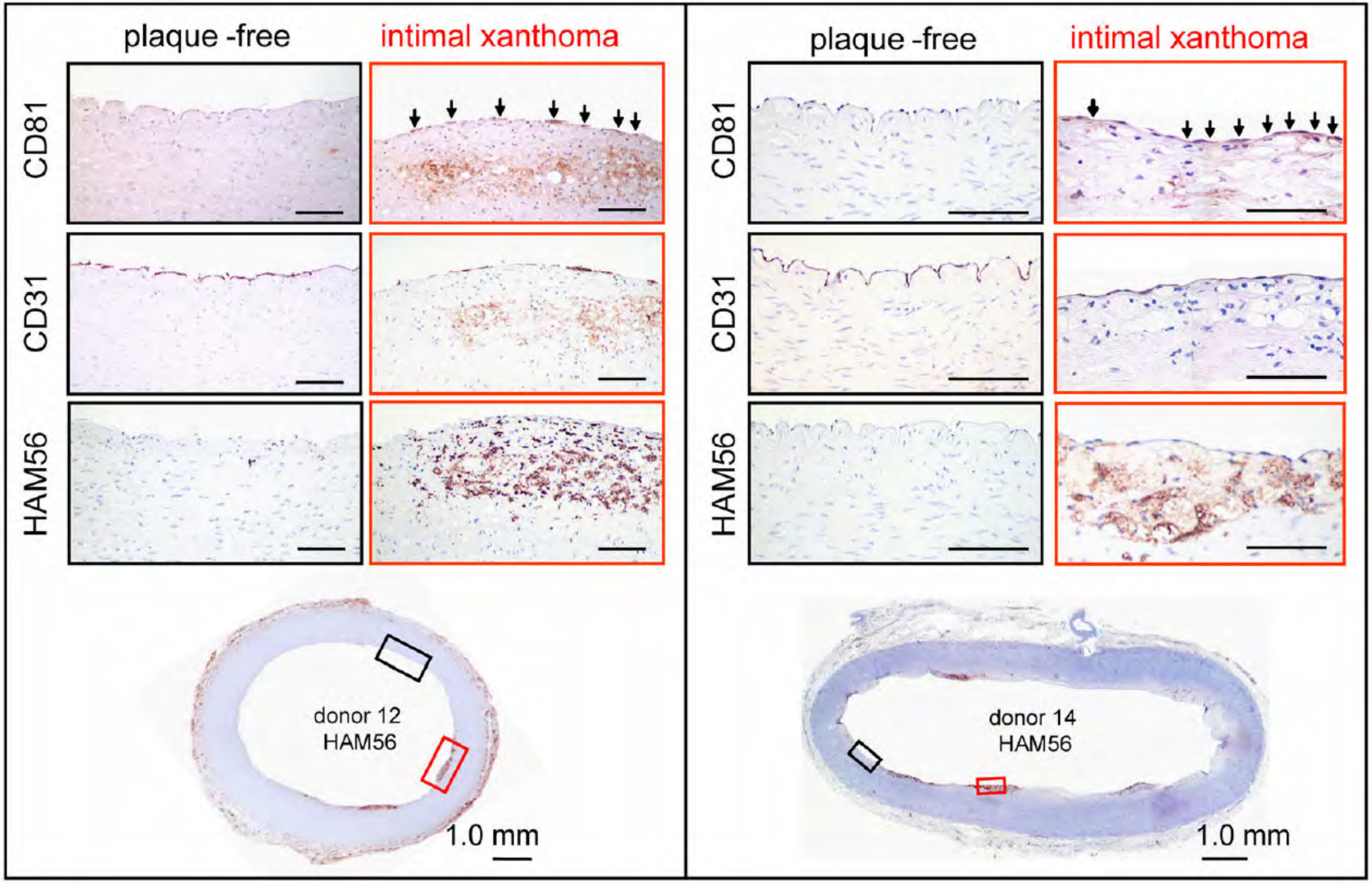
B) Venn-analysis

Fractalkine (CX3CL1) as specific marker for inflamed lesion

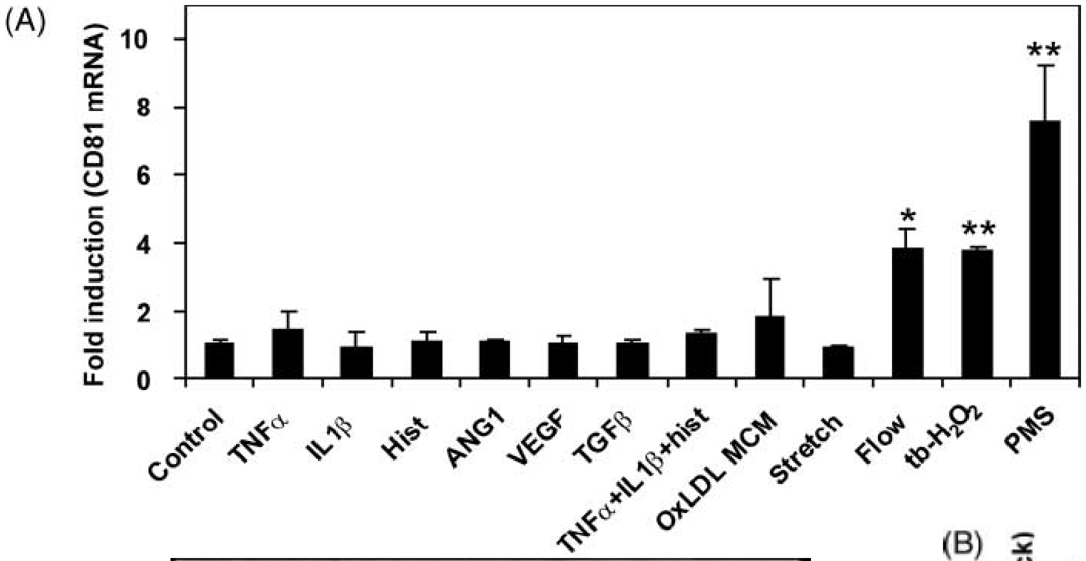


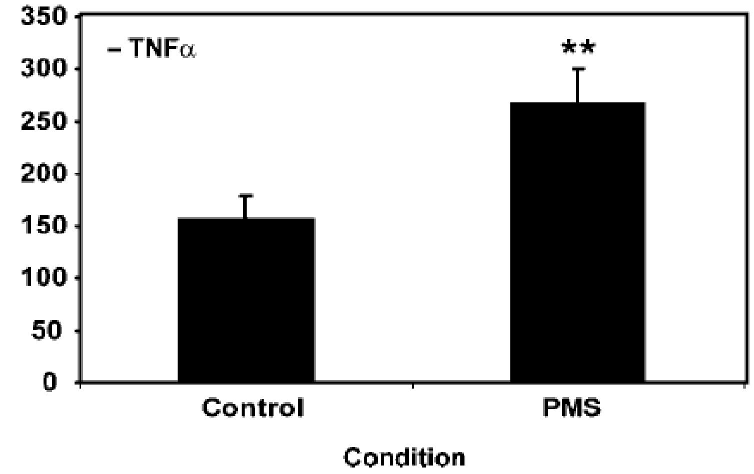
Fractalkine

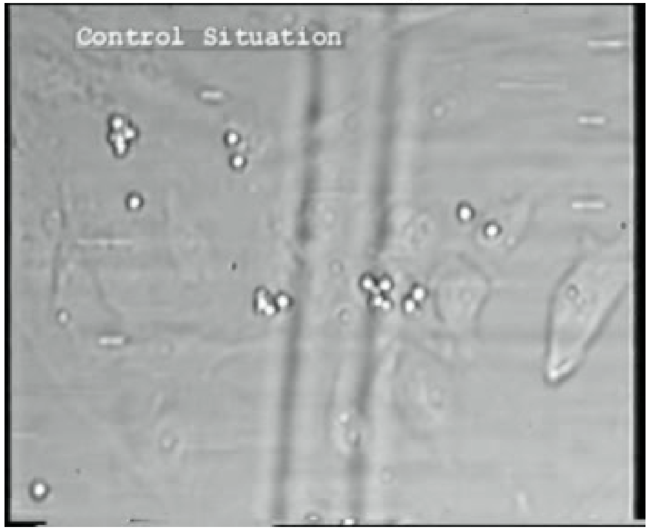
CD81 is specifically expressed in EC overlying inflamed early lesions

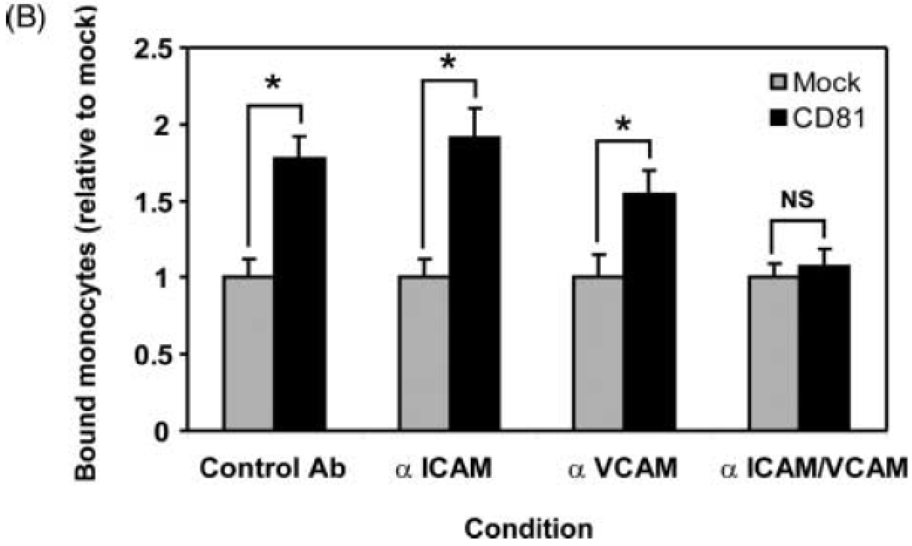


CD81: ROS-induced monocyte adhesion by ICAM and VCAM clustering

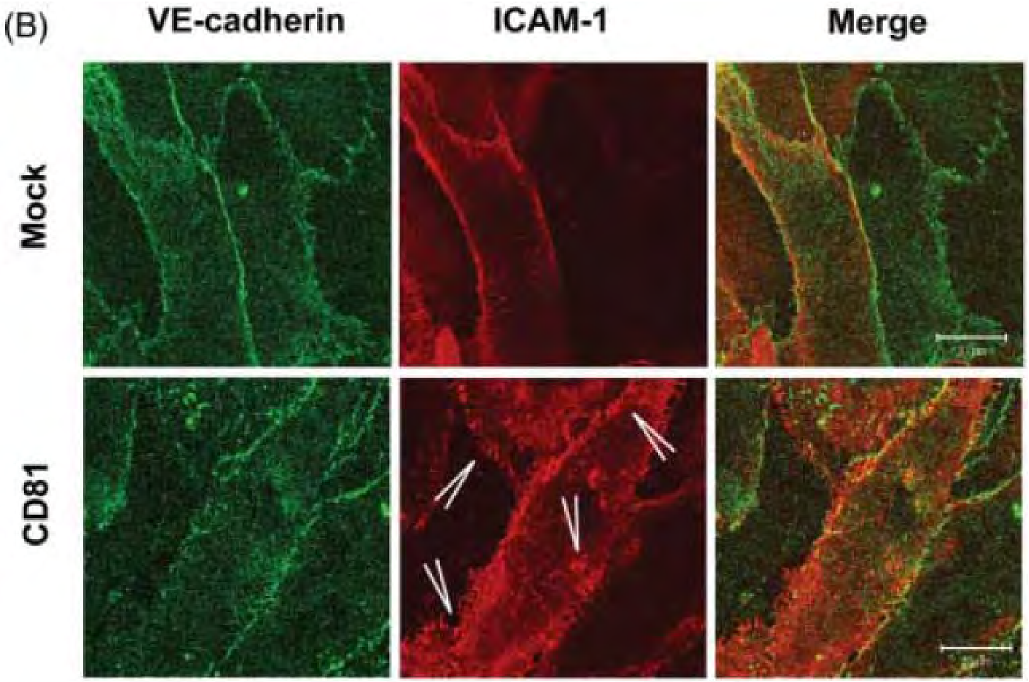


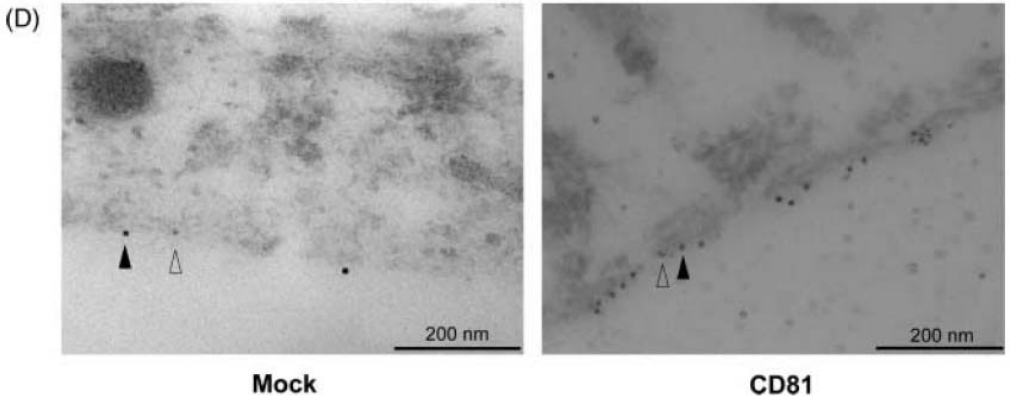


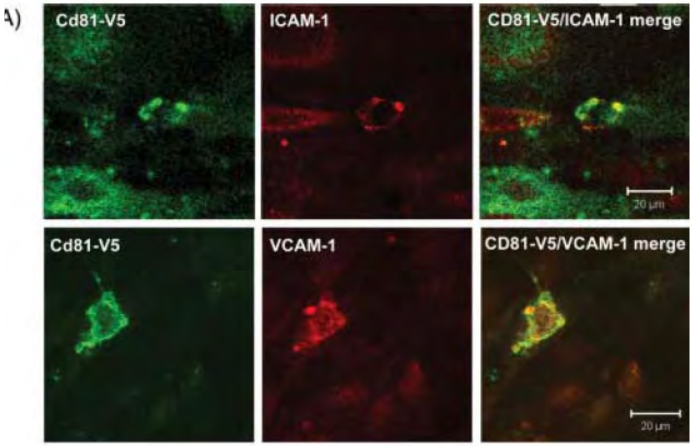


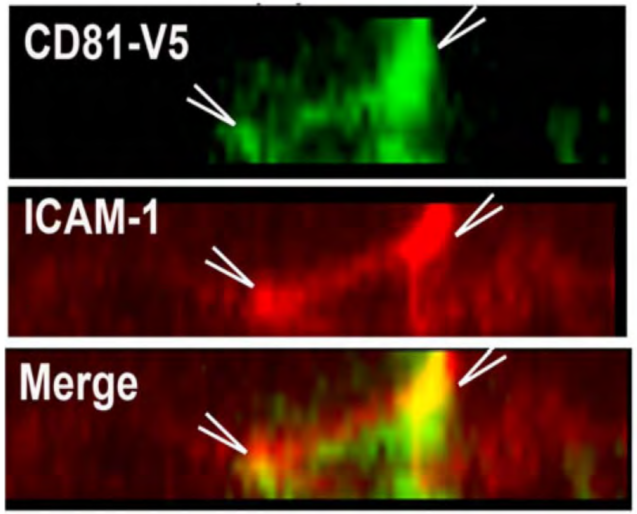


CD81 clusters ICAM1+VCAM1 in membrane rafts to become adhesion cups upon monocyte adhesion









- **Medical genomics:**

  translating expression data to diagnosis and therapy

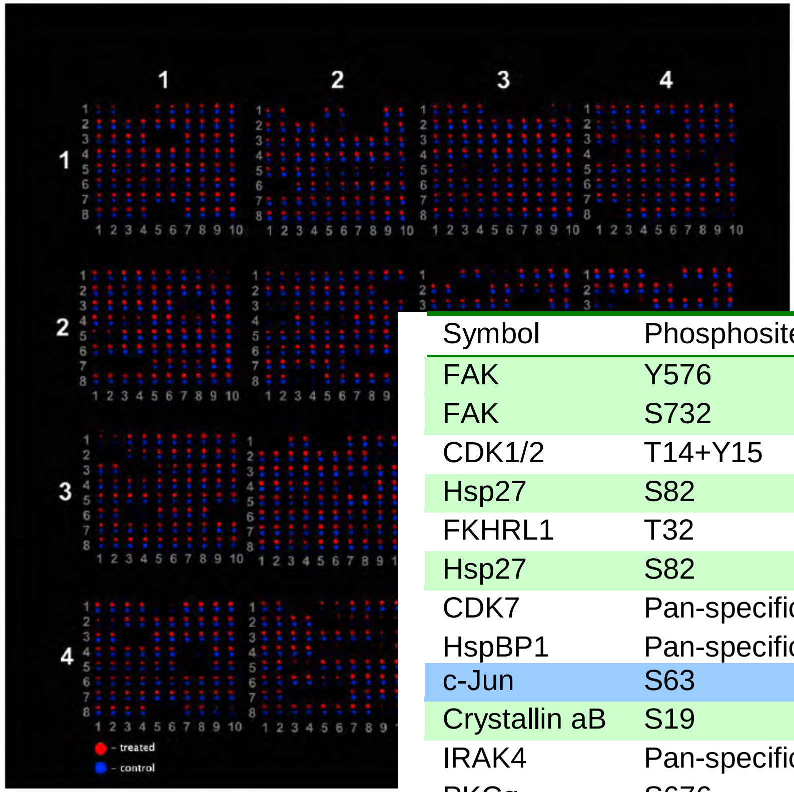
- **Functional genomics:**

  translating gene expression data to signaling pathways and transcription factor networks

- **Systems Biology and network theory:**

  integrating and modeling multiscale data

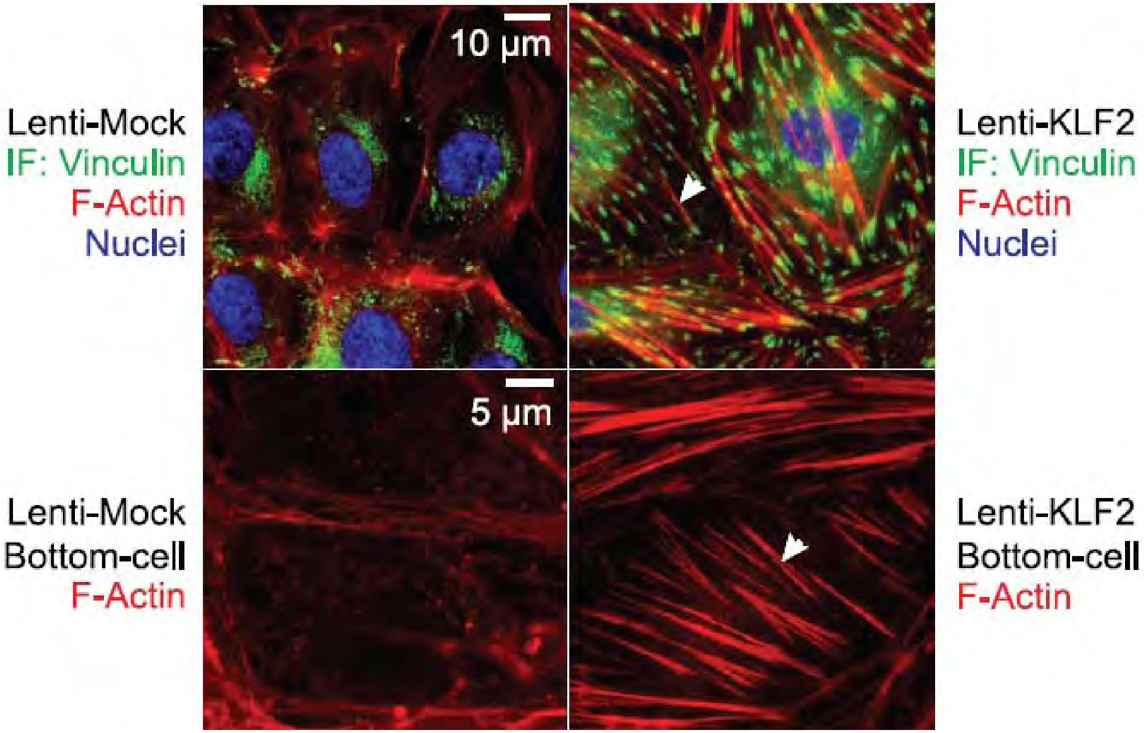
Kinome analysis: Actin rather than MAPK



Symbol	Phosphosite	Bayes.p	Fold	Symbol	Phosphosite	Bayes.p	Fold
FAK	Y576	0.0005	-3.02	PKCg	T514	0.0036	2.24
FAK	S732	0.0008	-2.81	Abl	Y412	0.0048	1.62
CDK1/2	T14+Y15	0.0091	-1.67	RSK1/2	S363/S369	0.0117	3.16
Hsp27	S82	0.0150	-1.93	Src	Pan-specific	0.0179	1.61
FKHRL1	T32	0.0155	-3.65	HO2	Pan-specific	0.0267	2.04
Hsp27	S82	0.0169	-2.41	ATF2	T51+T53	0.0273	1.44
CDK7	Pan-specific	0.0203	-1.45	p38a	Pan-specific	0.0336	1.48
HspBP1	Pan-specific	0.0217	-1.49	PKCb2	T641	0.0380	2.42
c-Jun	S63	0.0324	-3.54	STAT5A	Y694	0.0418	3.41
Crystallin aB	S19	0.0351	-1.57	S6Ka	T389	0.0462	2.53
IRAK4	Pan-specific	0.0426	-4.10	Bad	S75	0.0506	1.42
PKCq	S676	0.0472	-1.39	EGFR	Pan-specific	0.0570	1.54
Ksr1	Pan-specific	0.0489	-1.68	PKCg	Pan-specific	0.0575	2.04
Rb	S780	0.0498	-1.62	FAK	Y397	0.0667	1.81
PP6C	Pan-specific	0.0586	-1.34	Erk4	Pan-specific	0.0668	1.33
Tau	S518	0.0595	-1.28	Kit	Y730	0.0690	1.20
EGFR	Y1148	0.0602	-1.94				
ERK5	T218+Y220	0.0618	-1.44				

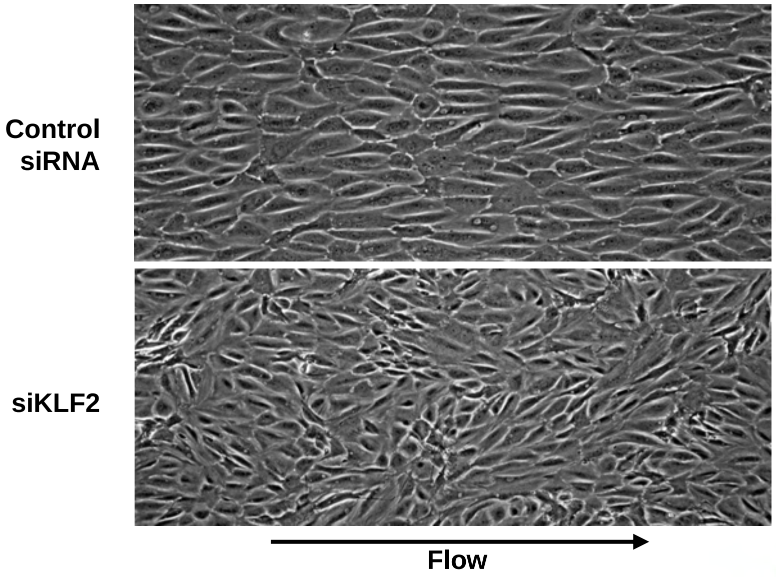
Boon et al, Blood 2010

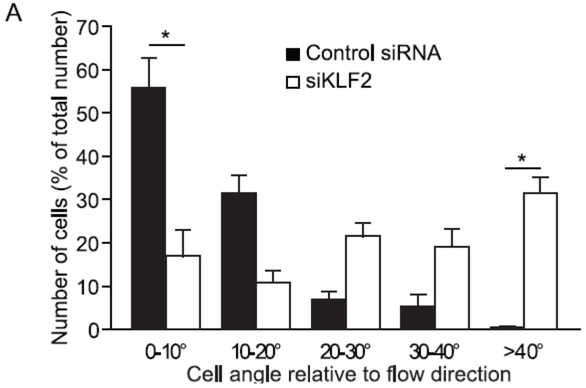
KLF2 fibers are attached to focal adhesions and localize on the basal side of endothelium

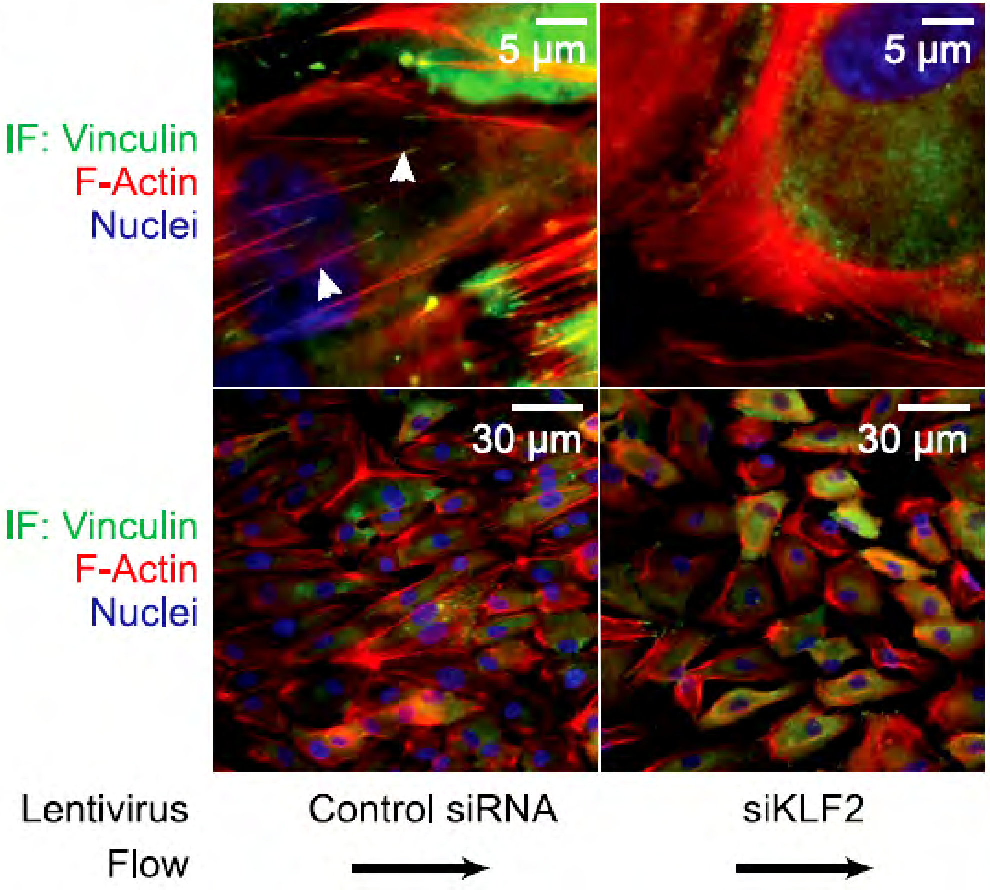


Boon *et al.* (2010) *Blood*. **115(12)**, p2533

KLF2 is important for cell alignment and flow-induced shear fibers







Boon *et al.* (2010) *Blood*. **115(12)**, p2533

blood

JOURNAL OF
THE AMERICAN
SOCIETY OF
HEMATOLOGY

VOLUME 115
NUMBER 12
25 MARCH 2010

A systems biology approach to hematopoiesis and its disorders (p 2339)

Prolonged administration of hydroxyurea in sickle cell anemia (p 2354)

Alternative CD20 transcripts and response to rituximab (p 2420)

Plasmodium PI3 kinase and hemoglobin trafficking (p 2500)

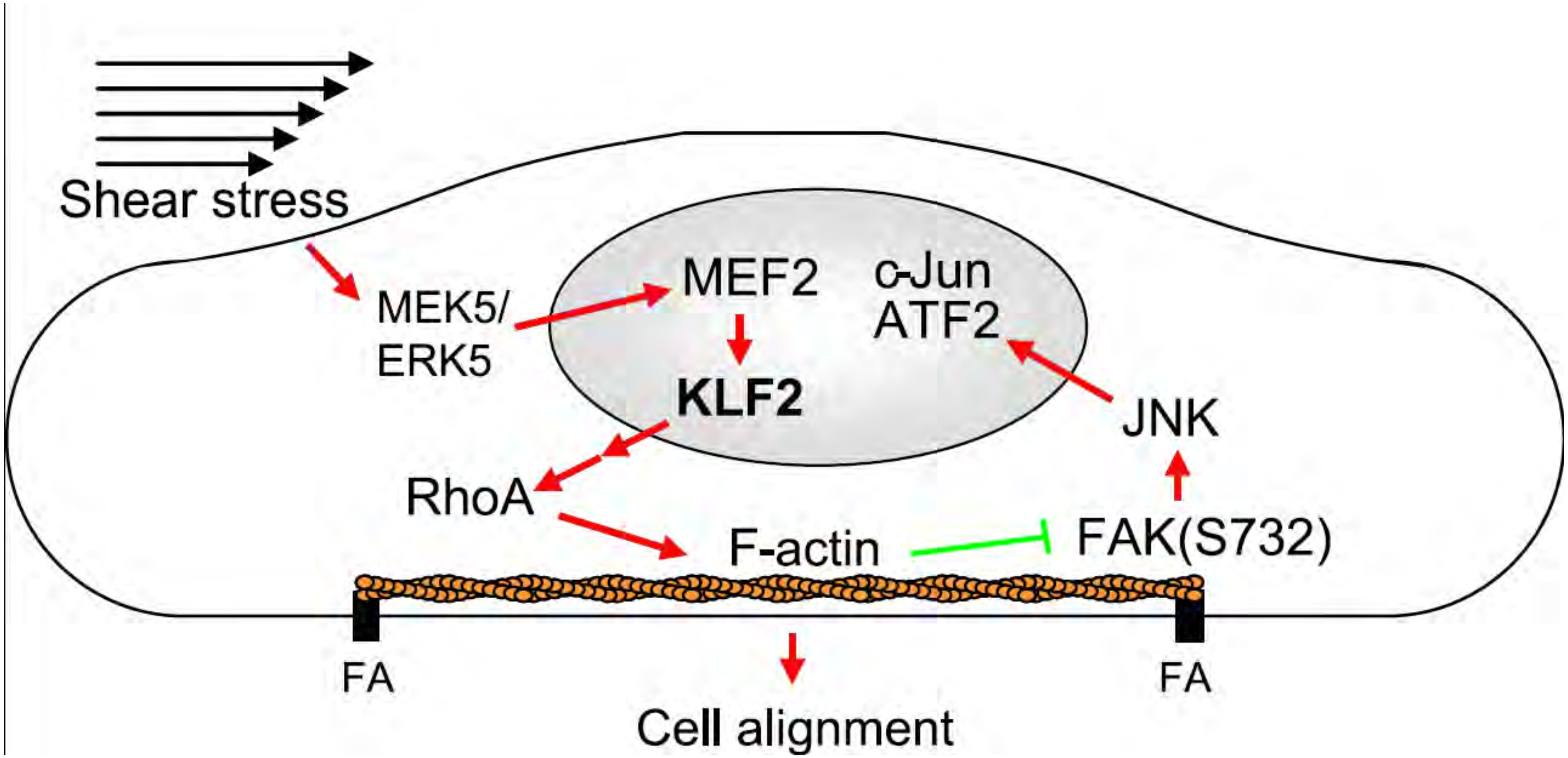
Long-term quality of life after hematopoietic stem cell transplantation (p 2508)

Cover:
KLF2-induced actin shear fibers in vascular endothelium (p 2533)

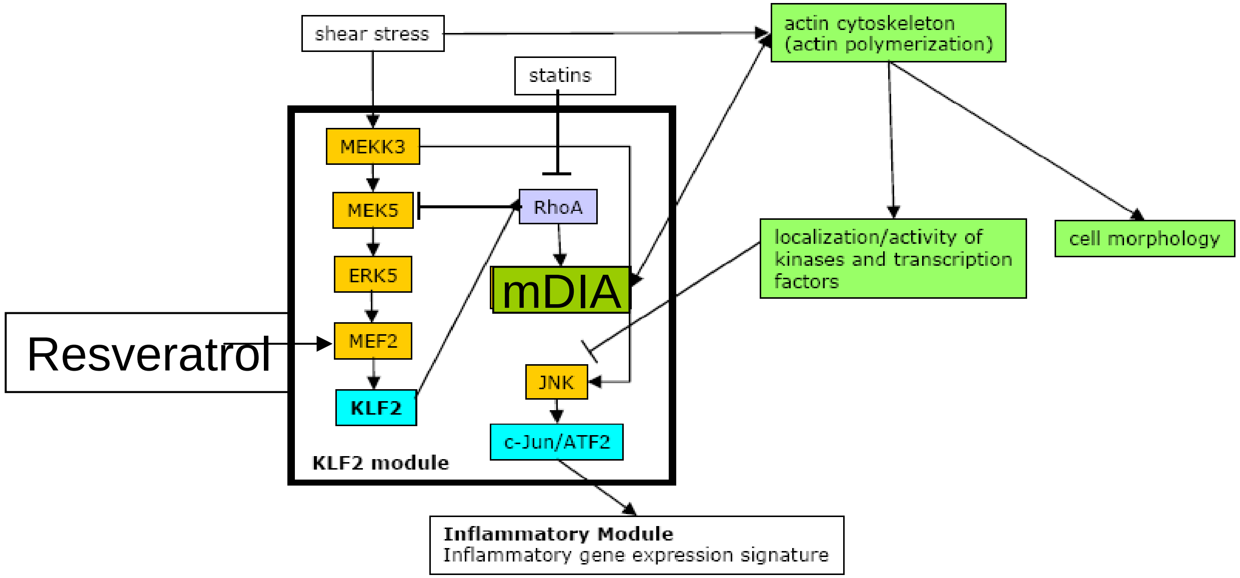
www.bloodjournal.org

Boon et al, Blood 2010

Cell alignment to flow is directly coupled to anti-inflammatory effect through actin cytoskeleton



Kinome allow reverse engineering signalling cascade



shear stress

statins

actin cytoskeleton (actin polymerization)

MEKK3

MEK5

RhoA

ERK5

mDIA

Resveratrol

MEF2

KLF2

JNK

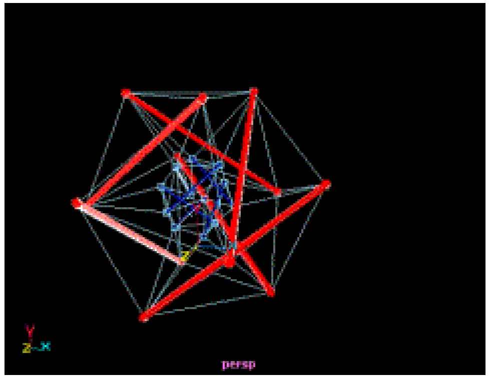
c-Jun/ATF2

KLF2 module

localization/activity of kinases and transcription factors

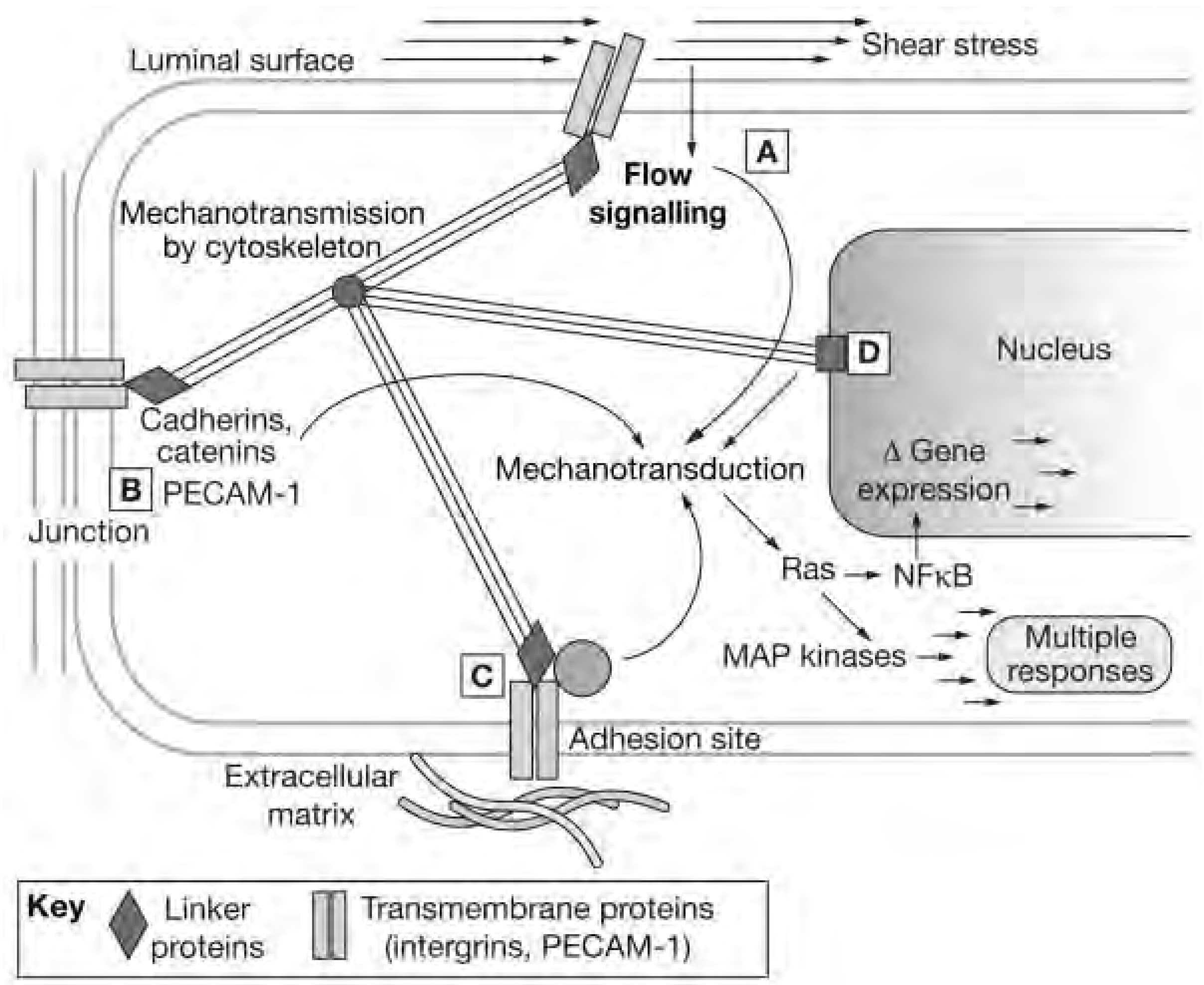
cell morphology

Inflammatory Module
Inflammatory gene expression signature

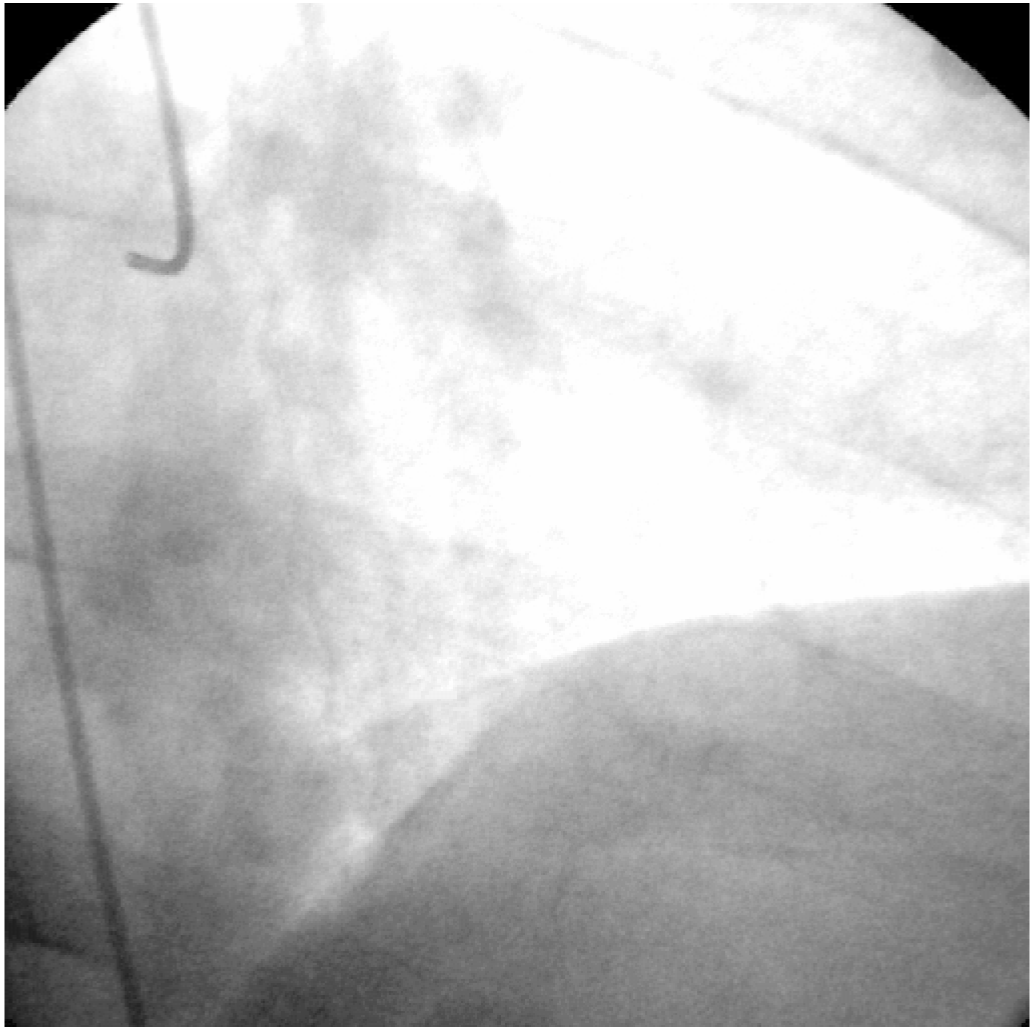


Ingber Tensegrity website

Boon et al, Blood 2010

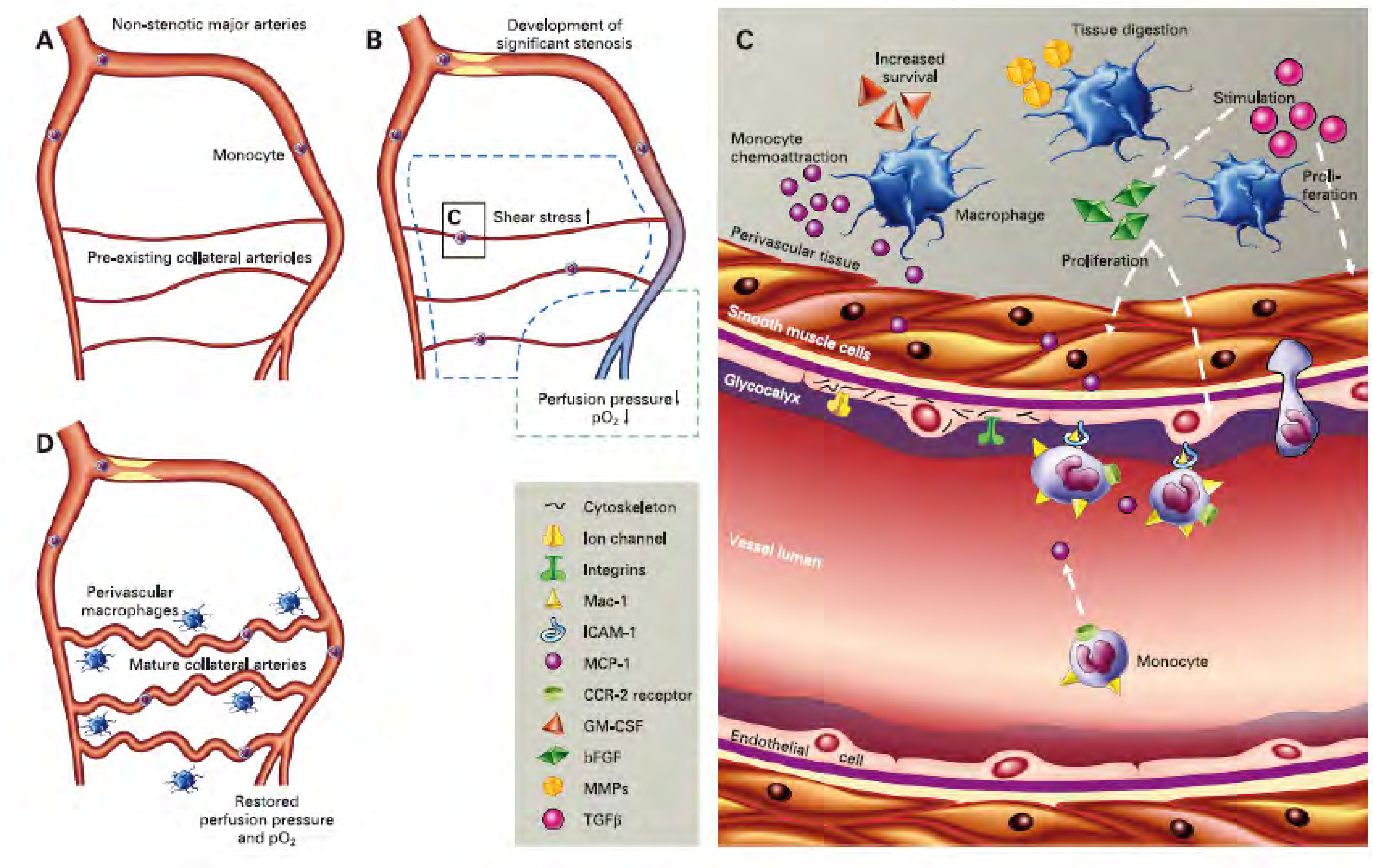

Luminal surface
Shear stress
A
Flow signalling
Mechanotransmission by cytoskeleton
D
Nucleus
Cadherins, catenins
B
PECAM-1
Junction
Mechanotransduction
Δ Gene expression
Ras
NFκB
MAP kinases
Multiple responses
C
Adhesion site
Extracellular matrix
Key
Linker proteins
Transmembrane proteins (intergrins, PECAM-1)

Large interindividual differences in coronary collateral formation in response to arterial occlusion



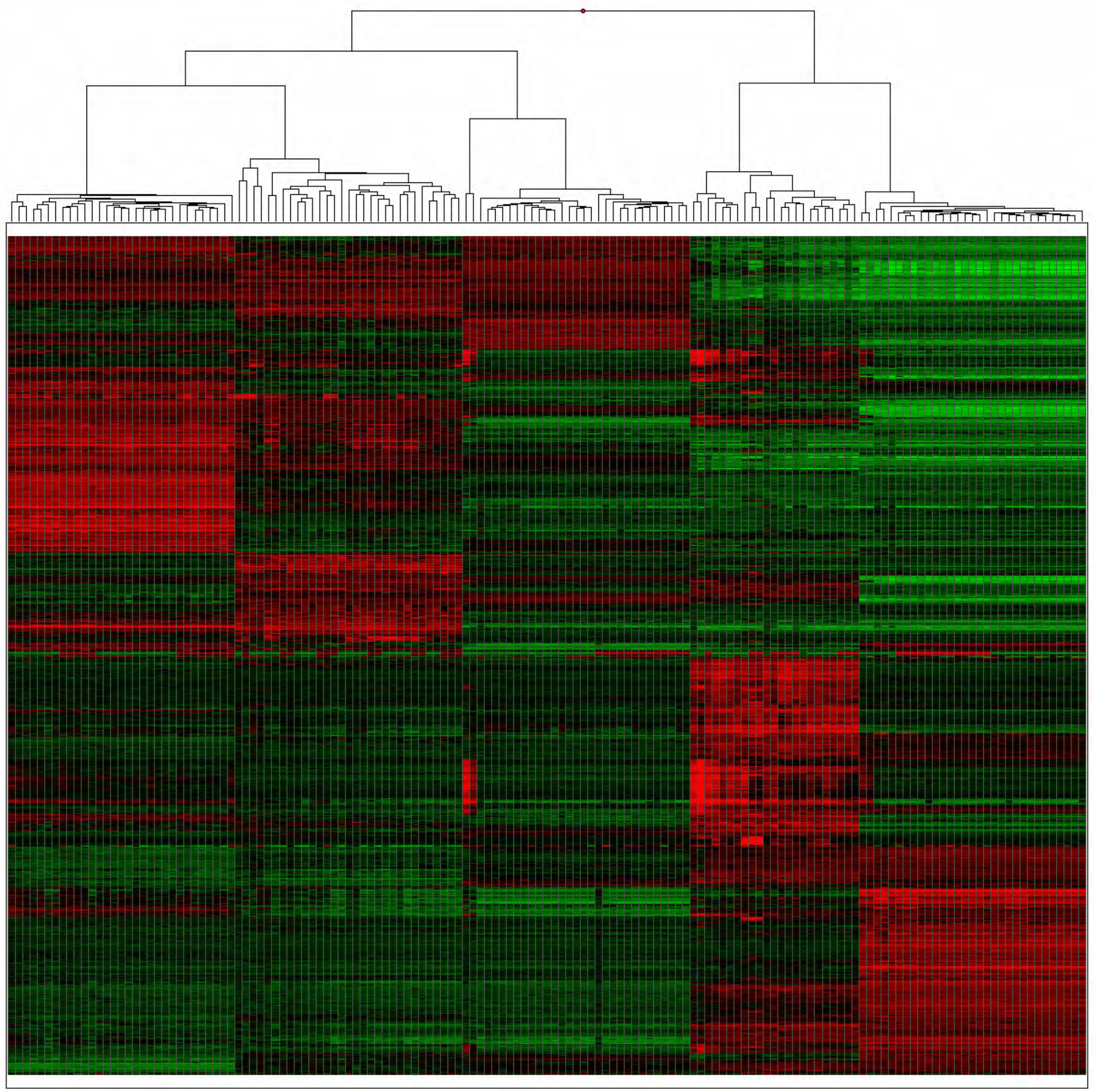
Knaapen P et al, Circulation 2006

Collateral artery remodeling / arteriogenesis: driven by shear stress, executed by inflammatory cells



Schirmer SH et al, Heart 2009;95:191–197.

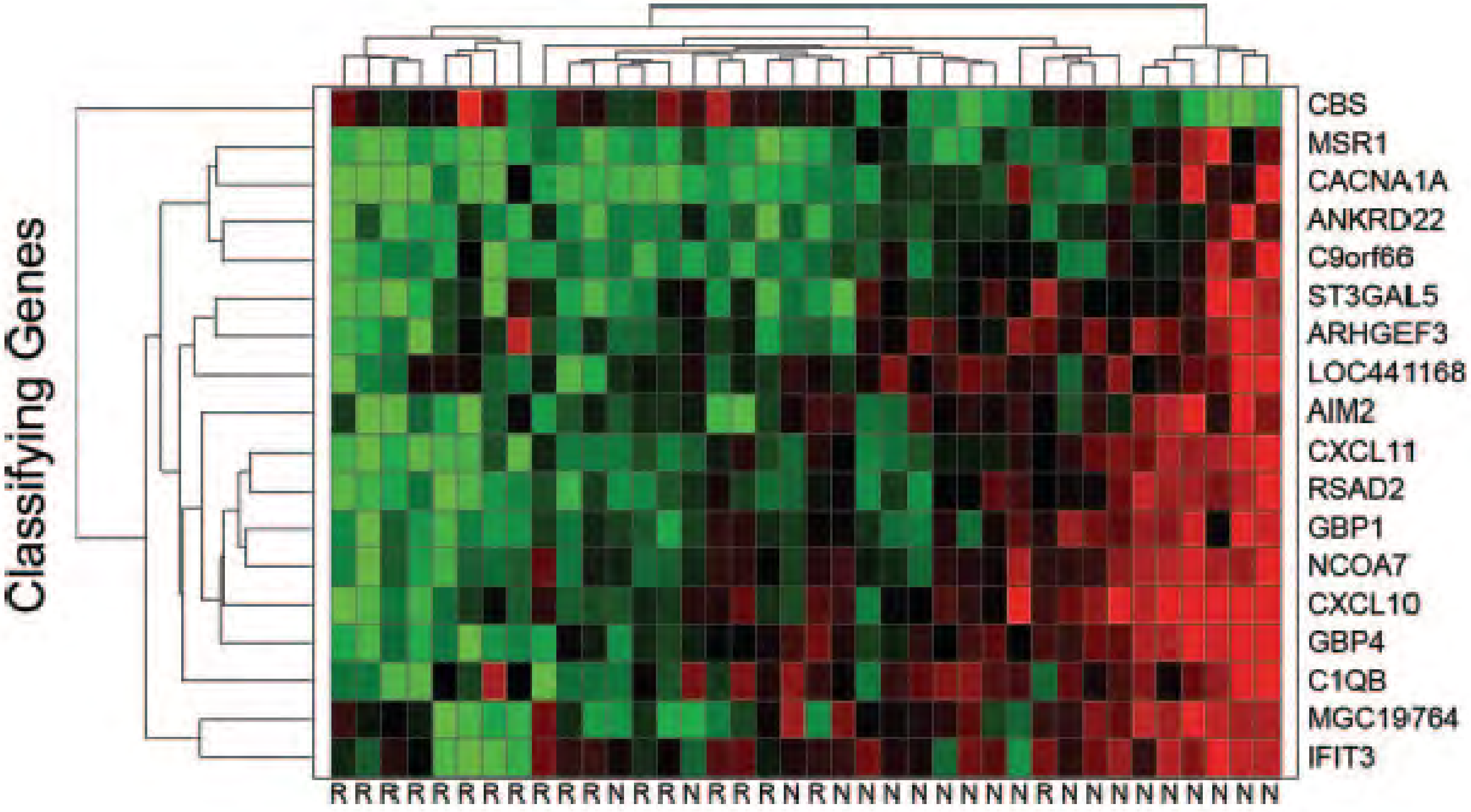
Hierarchical clustering analysis of the five circulating cell populations.



stimulated monocytes macrophages resting monocytes CD34+ cells   T-cells

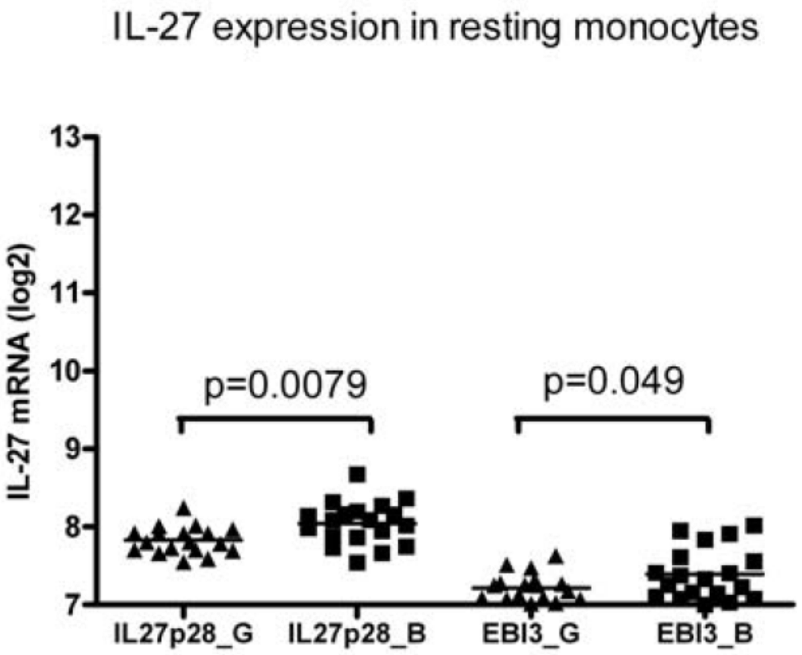
Schirmer, Circ Res 2008

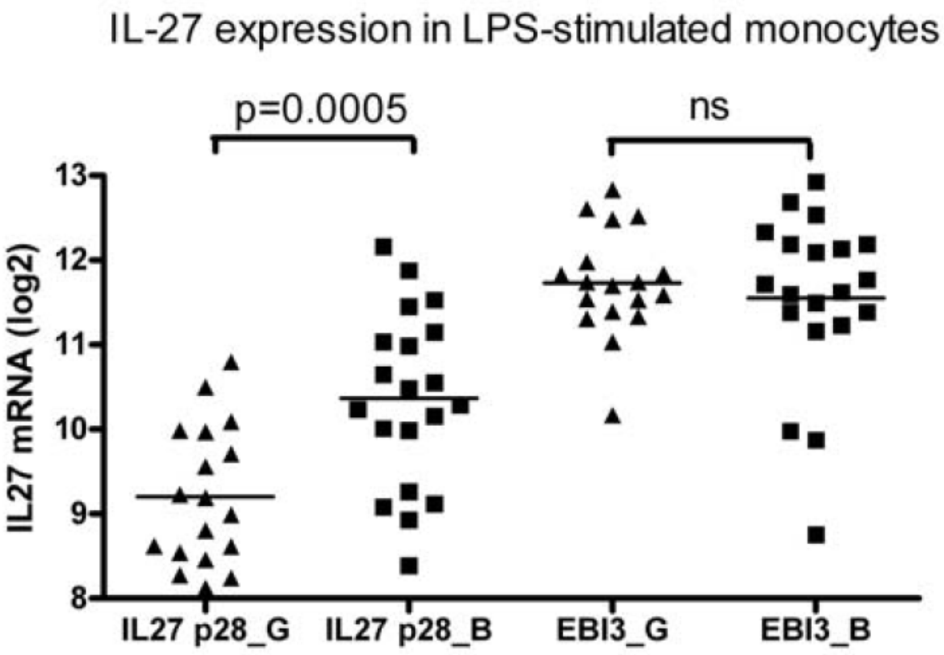
Classifier discriminates Good versus Poor collateral responders
only in LPS-stimulated cells



Schirmer, Circ Res 2008

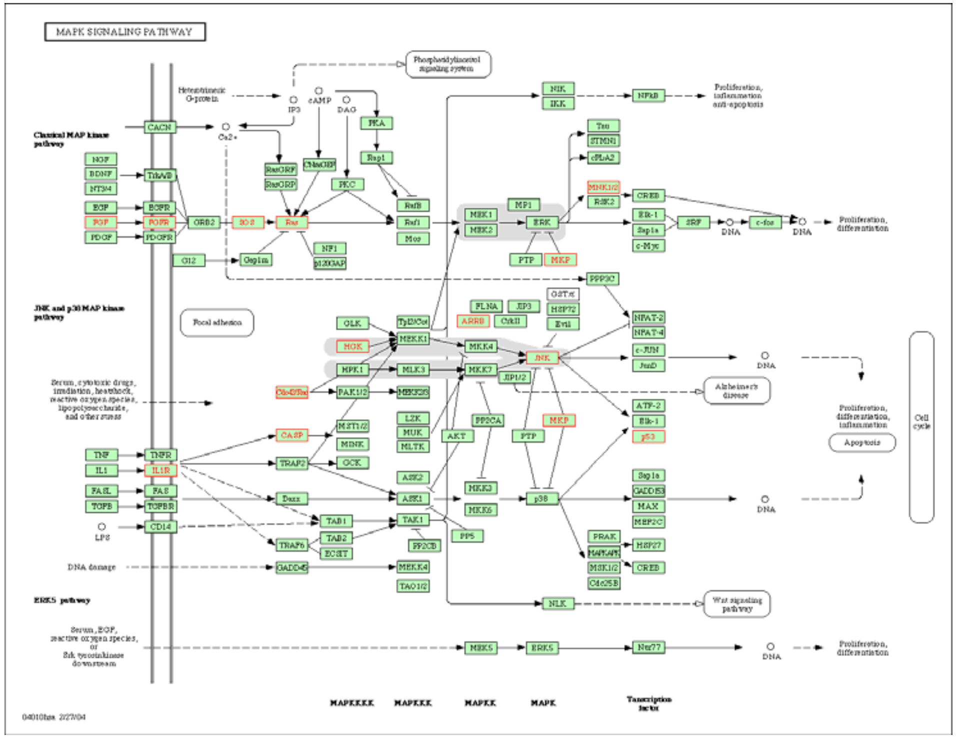
Biomarkers versus functional modules single genes do not classify patients

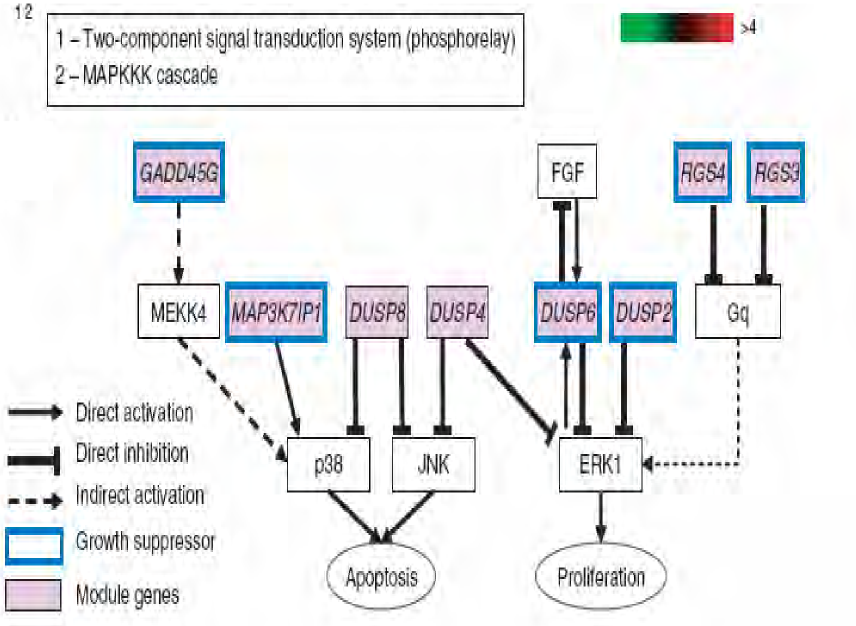


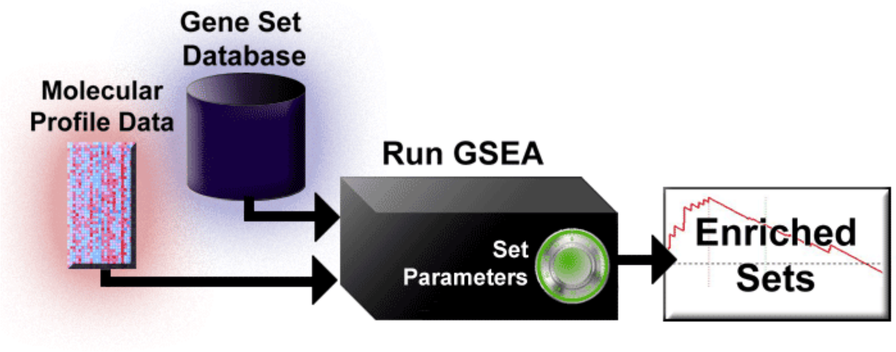


Vascular cell gene sets and modules:

Complete pathways are broken up into functional modules and processes







Subramanian et al. PNAS, 2005

GSEA analysis: pathways

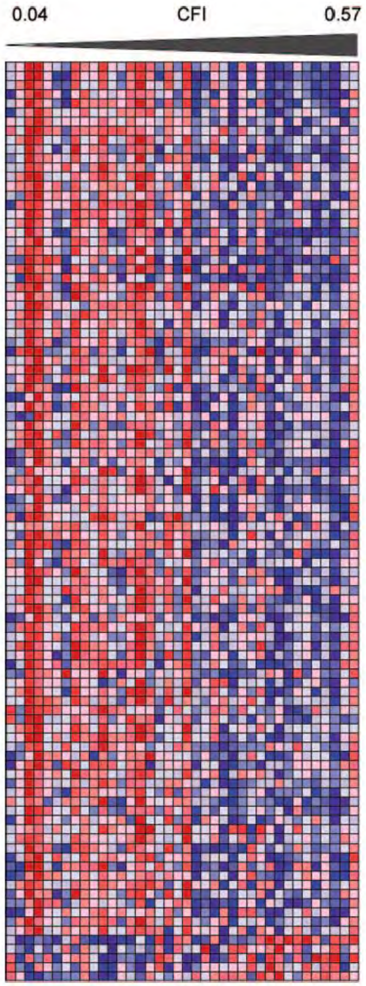


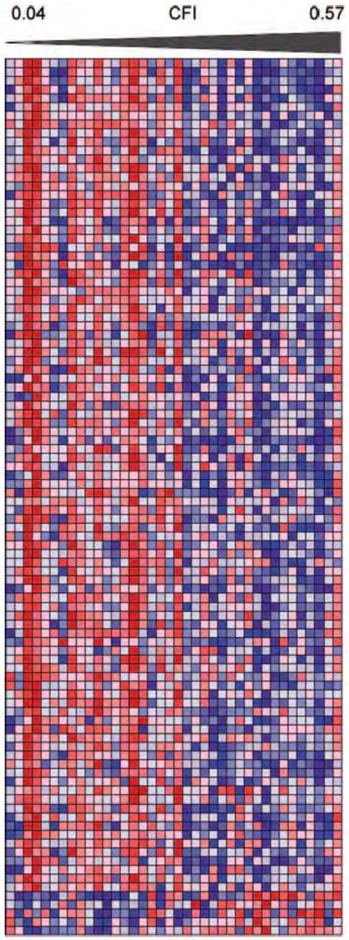
Figure 1. Heat map showing most differentially expressed genes. Significantly differentially regulated genes (adjusted *P*, <0.05) of LPS-stimulated monocyte samples from responders (n=18) and nonresponders (n=20) were sorted according to their fold change. The 100 genes with the largest fold change are visualized in a heat map, in which patients were sorted by CFI (columns). Columns range from patients with the lowest (left) to highest (right) CFI. Red denotes genes that are relatively higher expressed; blue, those that are relatively lower expressed. Of note, of these 100 most differentially expressed genes, 95% show stronger induction in nonresponders.

Table 3. Differentially Expressed Pathways Between Responders and Nonresponders

No.	Metacore Pathway Name	*P*
1	IFN-α/β signaling pathway	4.07×10^{-5}
2	Role of TLRs 3 and 4 in cell response: TICAM1-specific signaling pathways	1.70×10^{-4}
3	Role of IAP-proteins in apoptosis	3.14×10^{-4}
4	Cytoplasm/mitochondrial transport of proapoptotic proteins Bid, Bmf and Bim	9.72×10^{-4}
5	TNFR1 signaling pathway	1.33×10^{-3}
6	EPO-induced MAPK pathway	1.50×10^{-3}
7	Methionine-cysteine-glutamate metabolism	2.09×10^{-3}
8	Apoptotic TNF family pathways	3.21×10^{-3}
9	Methionine metabolism	5.41×10^{-3}
10	Crosstalk VEGF and angiopoietin-1 signaling	5.58×10^{-3}

Genes found differentially expressed in stimulated monocytes between responders and nonresponders were subjected to pathway analysis. The most significant pathways (sorted by *P*) are shown here. Genes related to immunity or apoptosis were found overexpressed almost exclusively in nonresponders (for all significant differential pathways, please see supplemental Table VIII). EPO indicates erythropoietin; IAP, inhibitor of apoptosis; MAPK, mitogen-activated protein kinase; TNFR, TNF receptor; VEGF, vascular endothelial growth factor.

GSEA analysis: transcription



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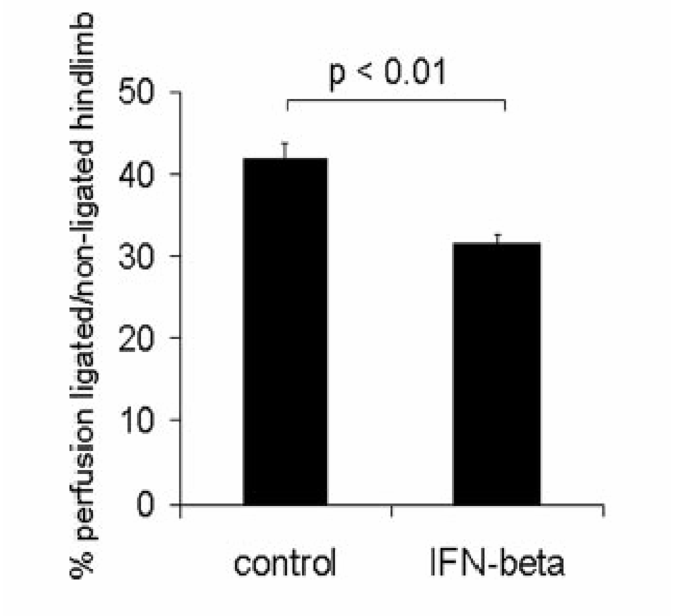
Transcription factor binding sites enriched in non-responders

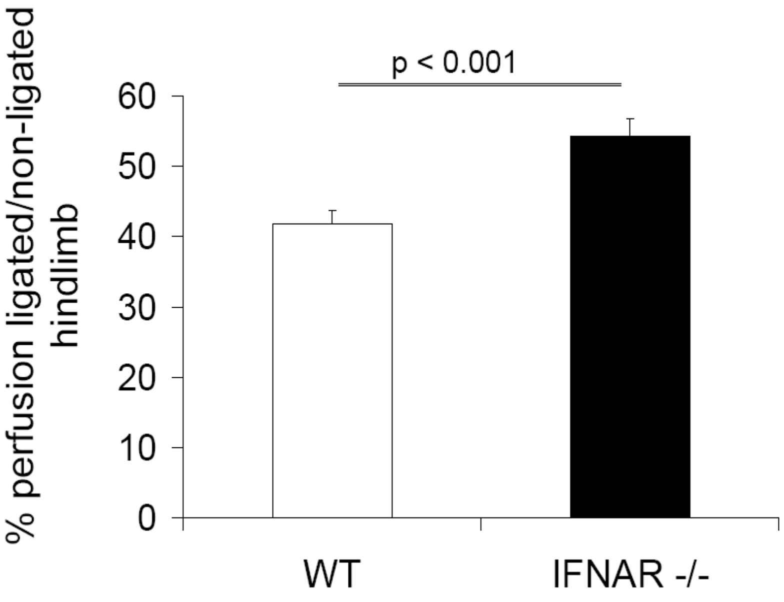
Gene set enrichment analysis (GSEA) was performed, using one hundred permutations on transcription factor binding sites to find motifs enriched in responders and non-responders. This analysis yielded 52 motifs significantly (FDR<25%) enriched in non-responders. Transcription factor binding sites with an FDR<5% are shown in this table. Of these 14 significant motifs, 10 are IFN-related.

Name	FDR q-value
IRF	0.0068
ICSBP	0.0090
ISRE	0.0099
IRF	0.0106
Unknown	0.0109
IRF1	0.0110
IRF7	0.0127
Unknown	0.0136
STAT3	0.0251
TCF4	0.0380
ETS2	0.0380
IRF2	0.0393
STAT5B	0.0429
IRF1	0.0489

IFN-beta inhibits arteriogenesis in mice



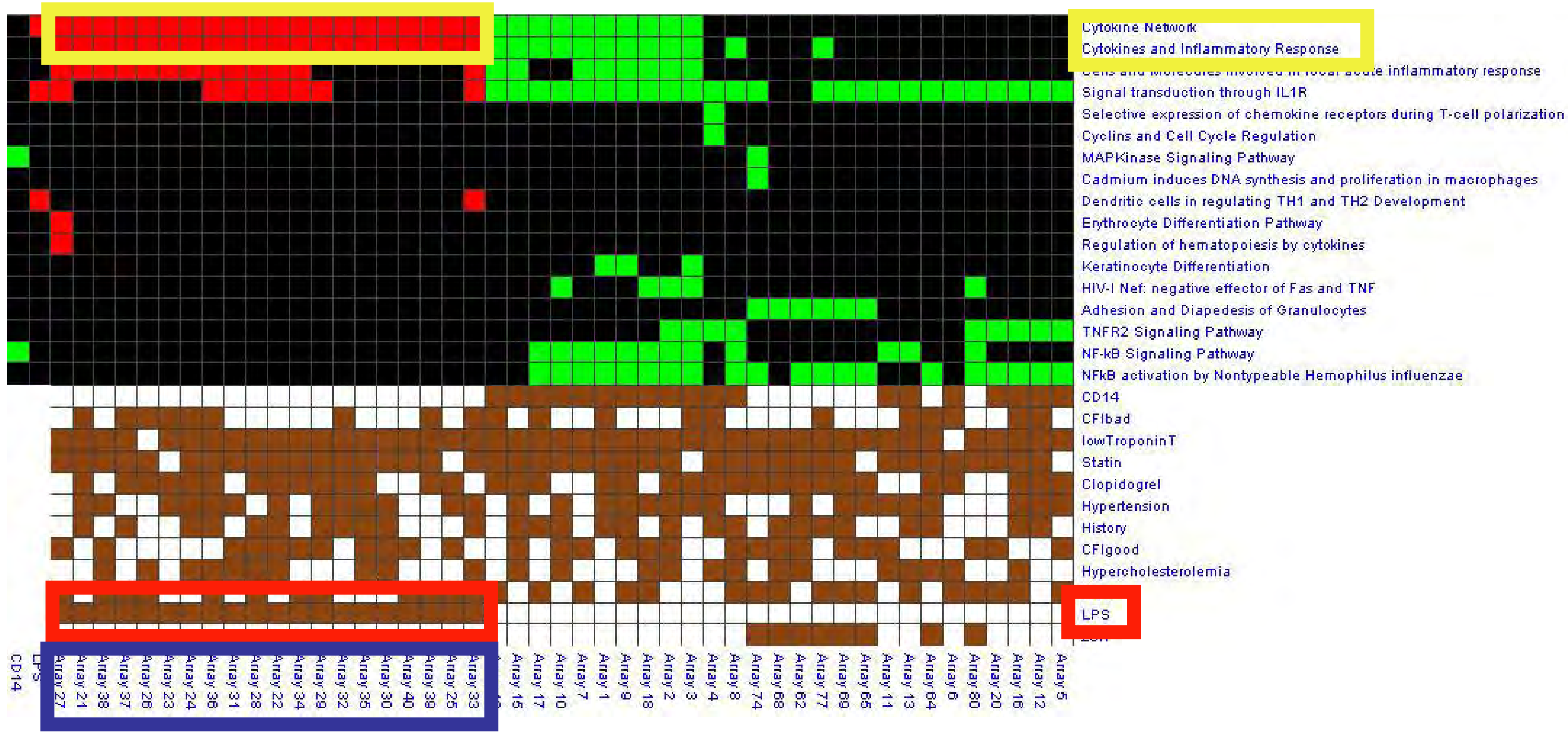
Schirmer, Circ Res 2008



Schirmer, 2008, submitted

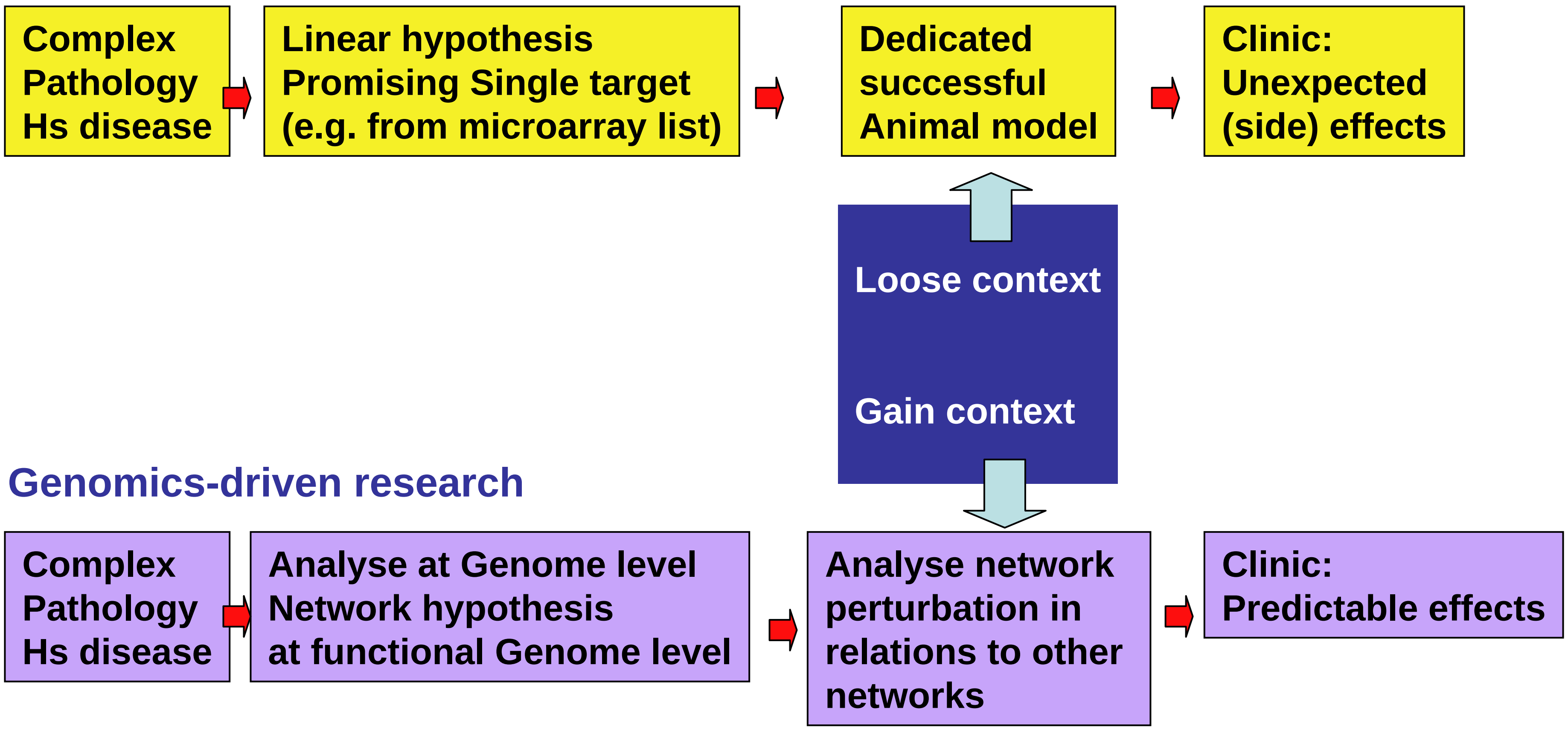
GENOMICA

MODULE map: Links patient arrays to pathways to clinical metadata



Segal, Science 2004

The promise of genomics research



Hypothesis-driven research

Complex Pathology Hs disease → Linear hypothesis Promising Single target (e.g. from microarray list) → Dedicated successful Animal model → Clinic: Unexpected (side) effects

Loose context

Gain context

Genomics-driven research

Complex Pathology Hs disease → Analyse at Genome level Network hypothesis at functional Genome level → Analyse network perturbation in relations to other networks → Clinic: Predictable effects

Translate transcriptomics and kinomics data to functional and regulatory pathways and networks yields:

*An integrated insight in cellular responses

*Identifies key regulatory proteins

*Can classify patients for targeted therapies

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GENOMICS
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GENETICS
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Acknowledgements

VUmc/AMC
Reinier Boon
Rob Dekker
Joost Fledderus
Ruud Fontijn
Jakub Rohlena
Oscar Volger
Thomas Leyen
Cansu Yildirim
Tineke van der Pouw Kraan

AMC Amsterdam
Perry Moerland
Ed van Bavel
Allard van der Wal
Stephan Schirmer
Niels van Royen

VUmc Amsterdam
Victor van Hinsbergh
Geerten van Nieuw Amerongen

Univ Maastricht-Pathology
Mat Daemen
Erik Biessen

Univ Leiden-LACDR
Johan Kuiper
Theo van Berkel

Univ Leiden-MCB-II
Lia Pardali
Peter ten Dijke

Sanquin Research Amsterdam
Jaap van Buul
Peter Hordijk

Goethe University Frankfurt
Reinier Boon
Stefanie Dimmeler

EV-GN EUROPEAN VASCULAR GENOMICS NETWORK

Nederlandse Hartstichting
Molecular Cardiology Program

NWO
Genomics

IOP
Genomics

Institute for Cardiovascular Research

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vrije Universiteit amsterdam