



Icahn School
of Medicine at
**Mount
Sinai**

Department of Pharmacology and
System Therapeutics

GTEX

Gene expression changes with aging

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Ma'ayan Lab

GOAL

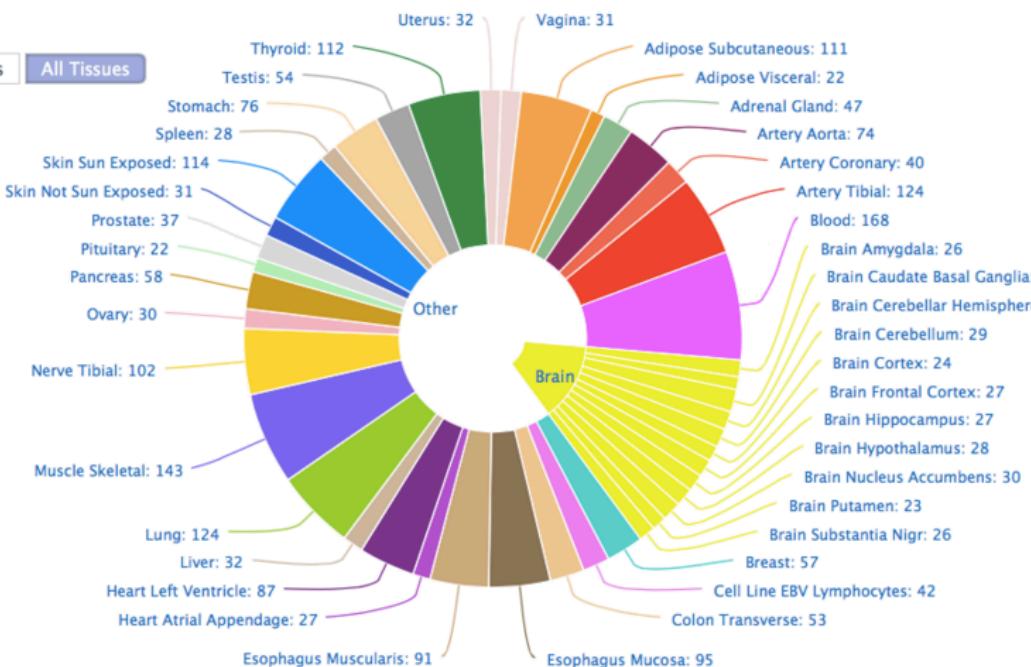
- Compare gene expression data from different age groups.
- Find genes differentially expressed between young and old groups.
- Find possible drug candidates to reverse gene expression

GTEX

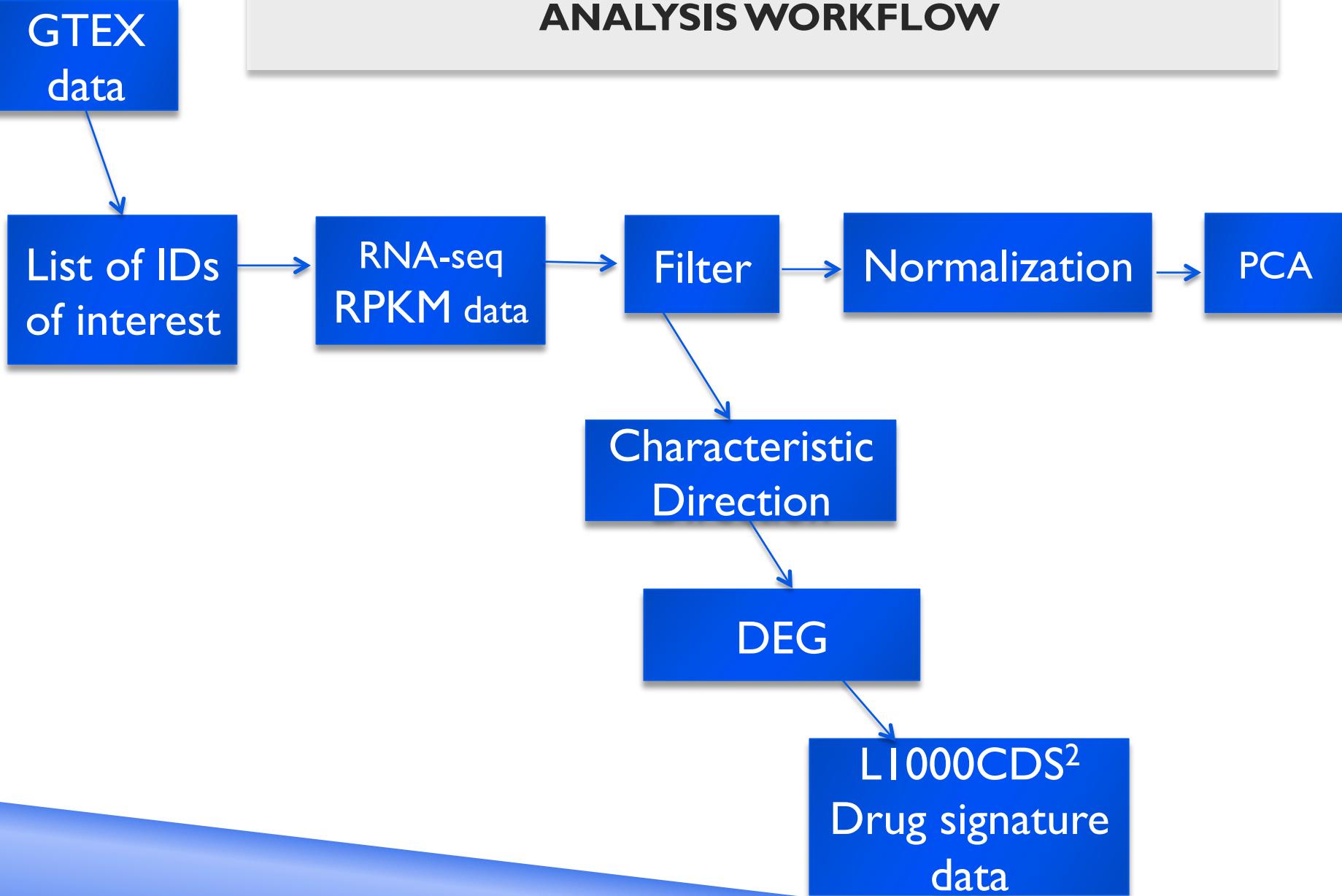
Explore All Tissues

- Genotype-Tissue Expression project.
- Collect and analyze multiple human tissues from donors who are also densely genotyped, to assess genetic variation within their genomes.
- RPKM RNA-seq non-normalized data.
- Has available metadata.

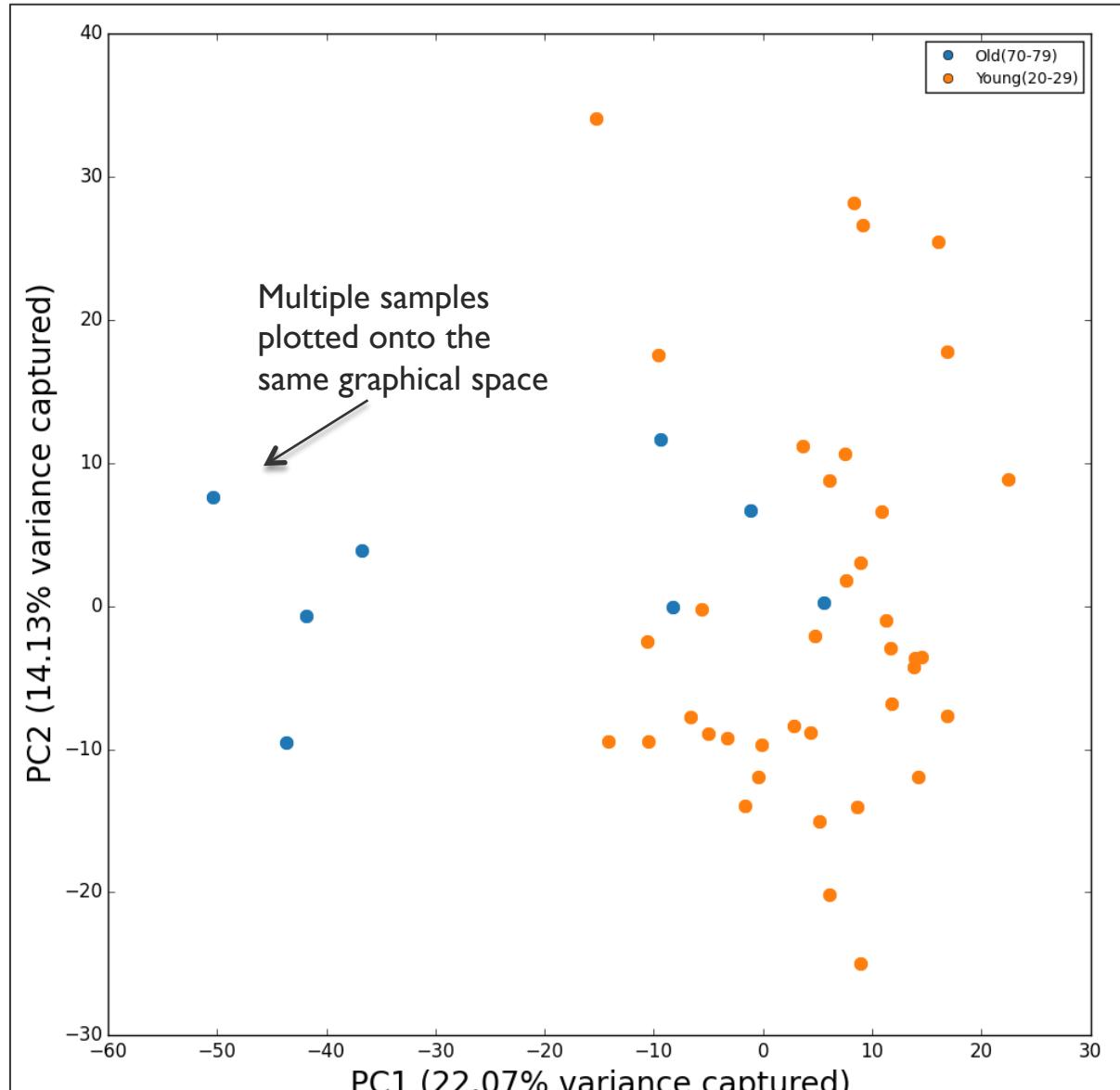
eQTL Tissues All Tissues



ANALYSIS WORKFLOW

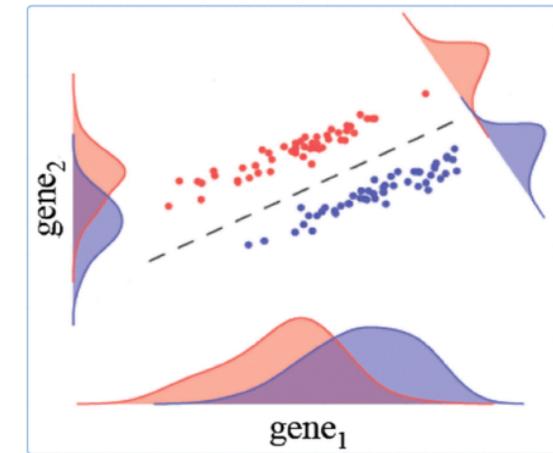
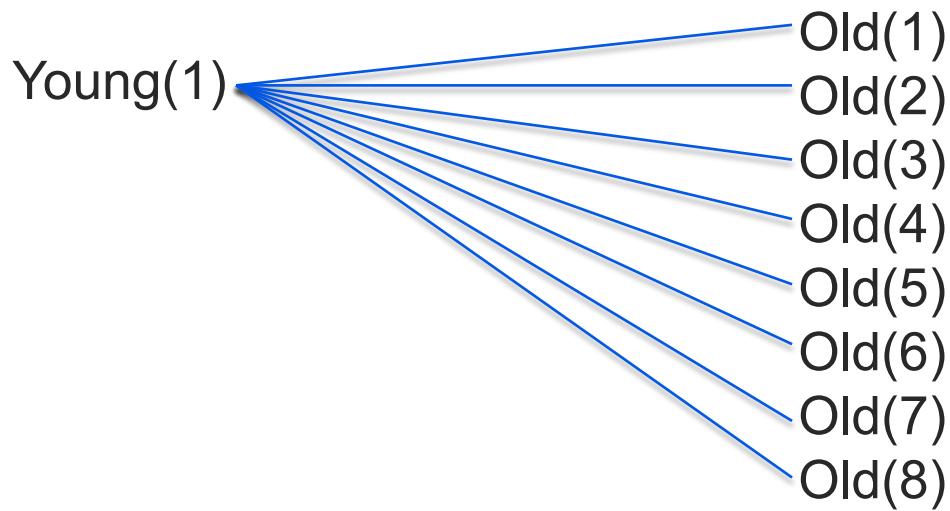


PCA plot of the muscle data, filtered and normalized for the 8 youngest and 8 oldest GTEx donors.

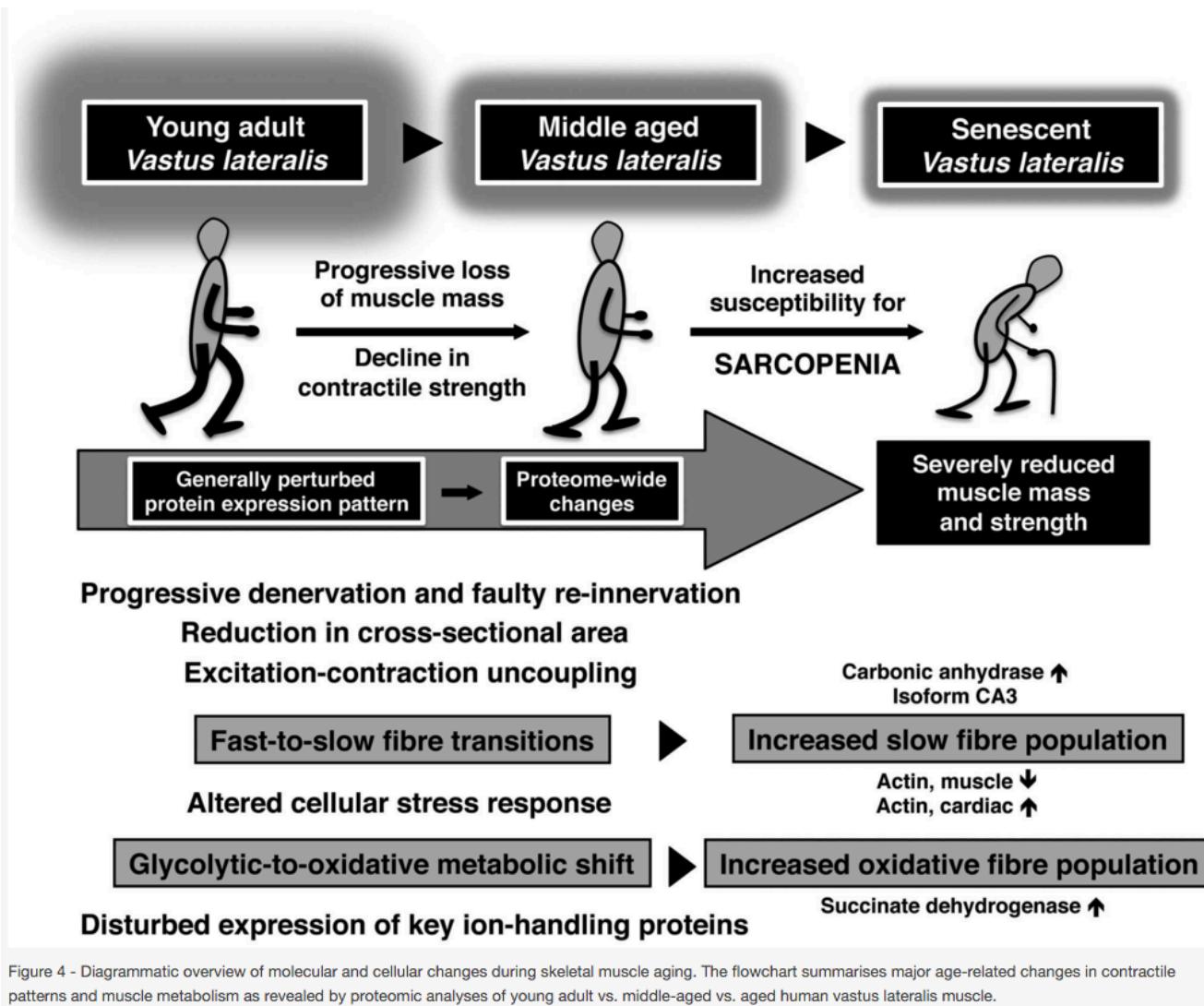


Skeletal muscle

CHARACTERISTIC DIRECTION

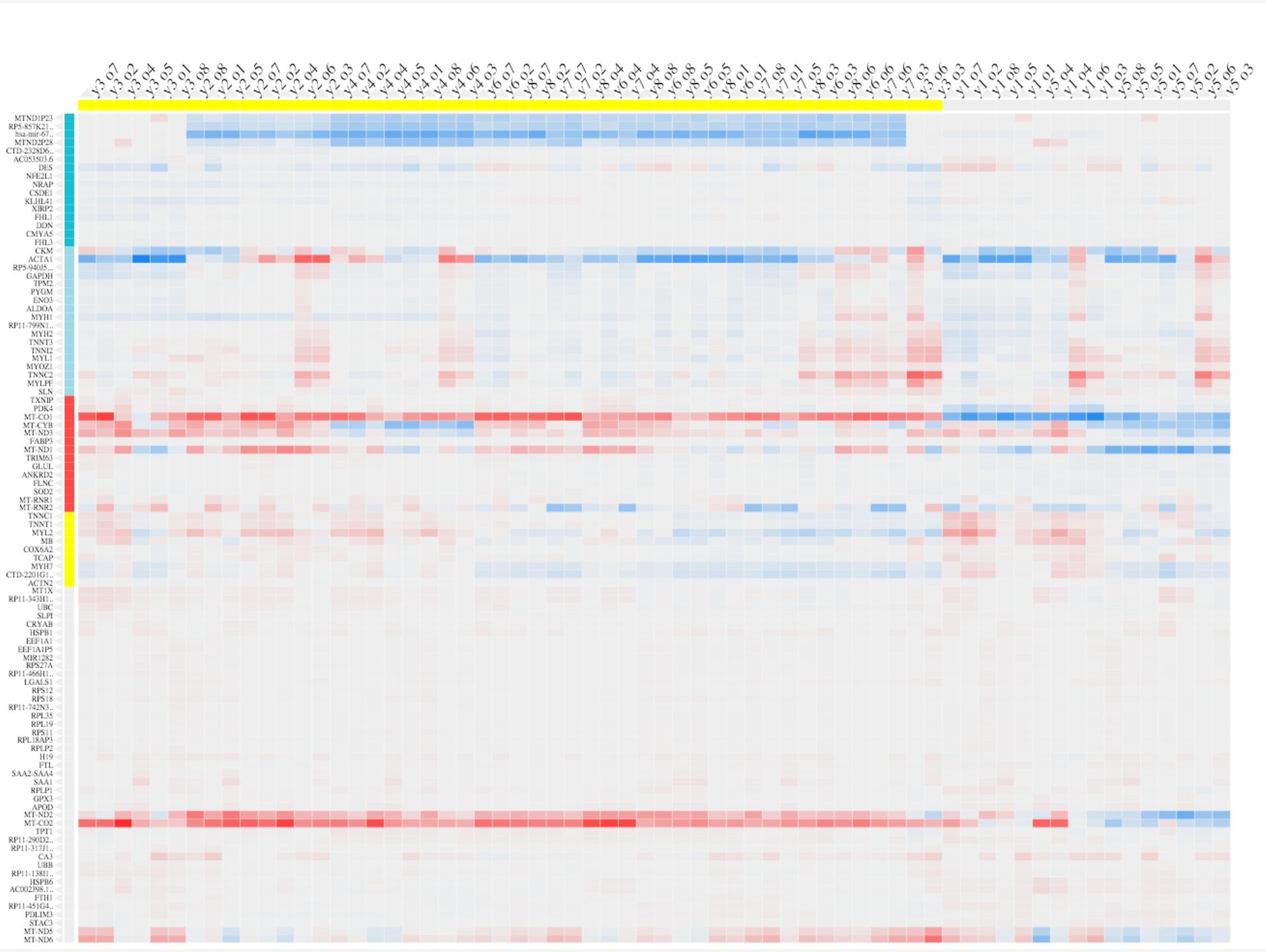


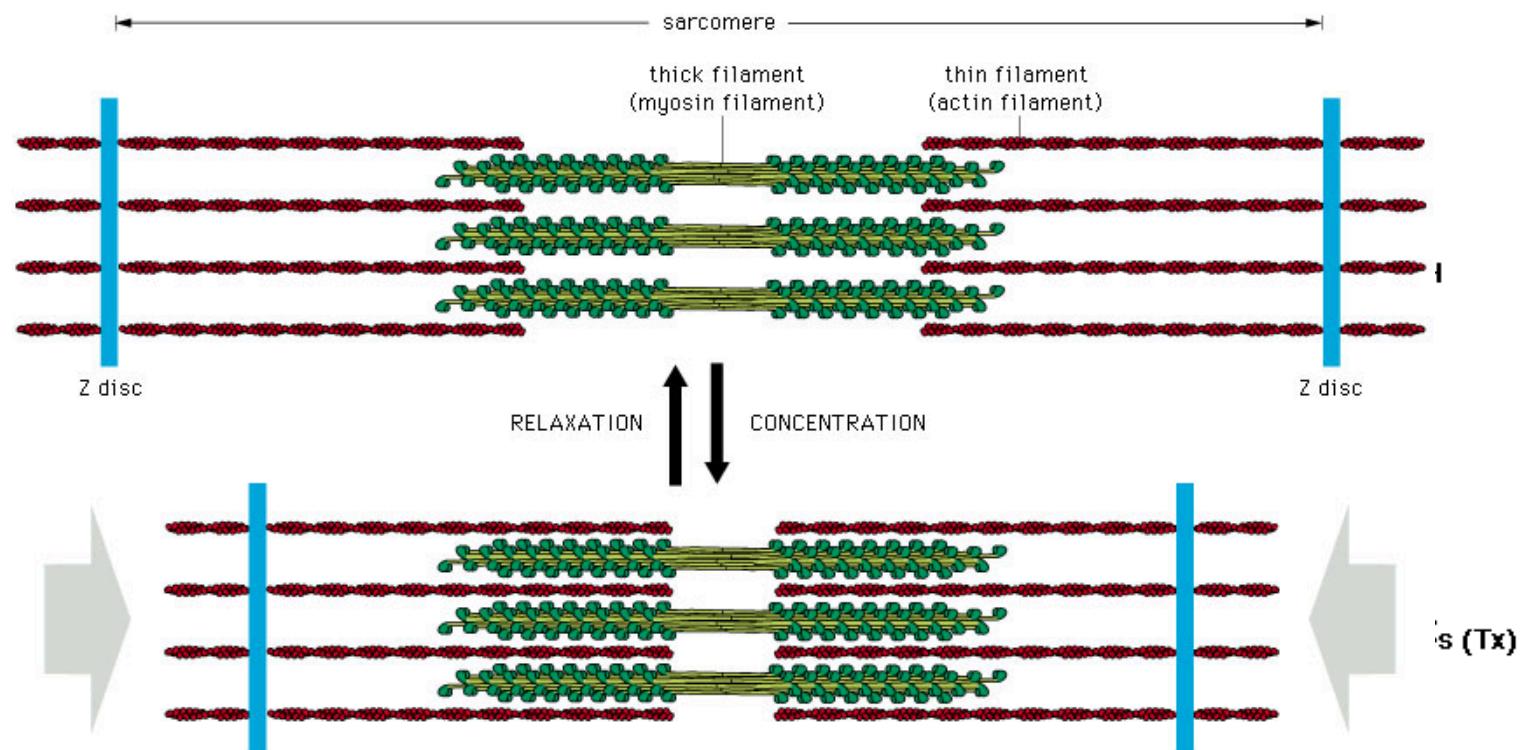
SKELETAL MUSCLE

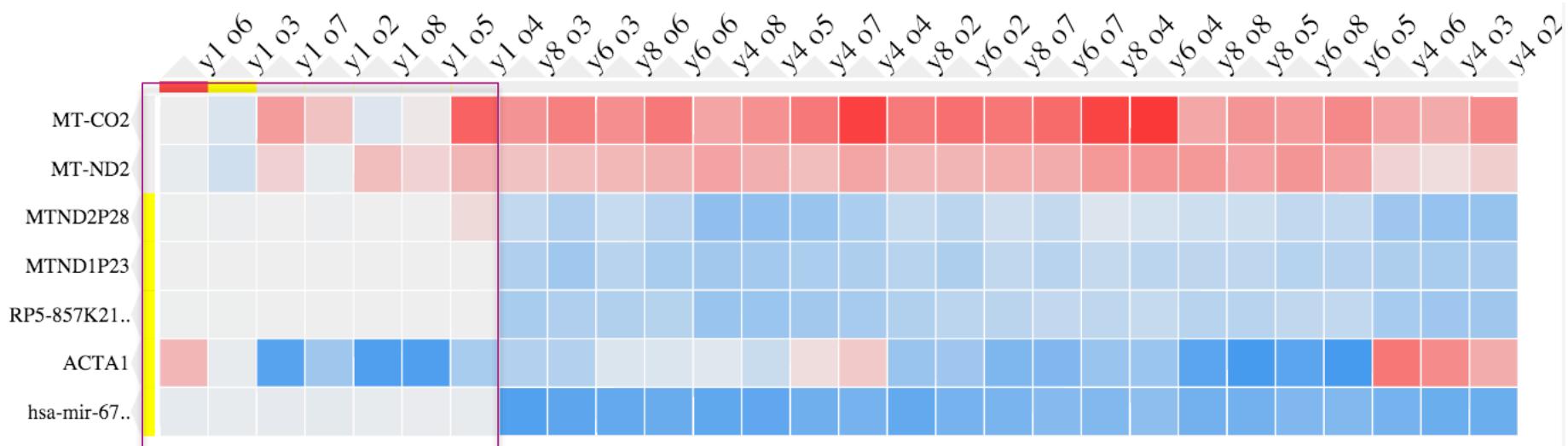


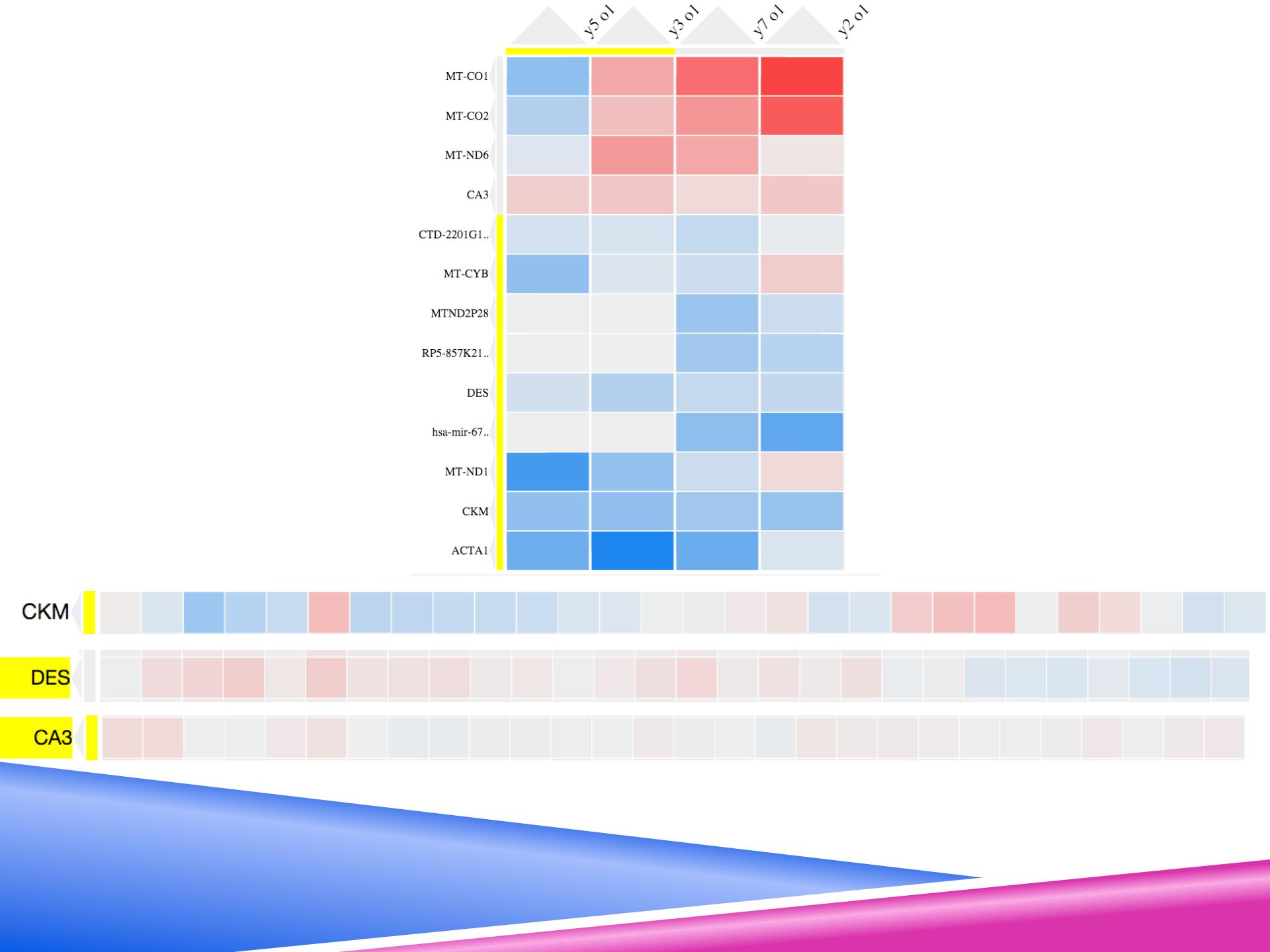
16 donors

Skeletal Muscle		
Donors	ID	SEX
GTEX-O5YT-1626-SM-32PK6	Y1	M
GTEX-PX3G-1626-SM-2S1PT	Y2	F
GTEX-POMQ-1926-SM-3NB1Y	Y3	F
GTEX-PW2O-1726-SM-2S1OO	Y4	M
GTEX-PWCY-2026-SM-5SI8R	Y5	F
GTEX-QESD-1626-SM-2S1RB	Y6	M
GTEX-RU1J-1726-SM-2TF5S	Y7	F
GTEX-QEG5-0426-SM-2I5GJ	Y8	M
GTEX-X638-0326-SM-47JY1	O1	F
GTEX-SUCS-1626-SM-32PLS	O2	M
GTEX-ZAKK-0326-SM-5EGHA	O3	M
GTEX-148VJ-0326-SM-5QGQE	O4	M
GTEX-13IVO-0626-SM-5LZYJ	O5	M
GTEX-13N1W-0526-SM-5MR4I	O6	M
GTEX-13OVH-0626-SM-5L3EI	O7	M
GTEX-13SLW-0326-SM-5RQK5	O8	M









Rank	1-cos(α) ⓘ	α	Perturbation	Cell-line	Dose	Time	Overlap	Target	Signature
1	1.1350	↖	K784-3131	L P	SKB	10.0um	24.0h	II	○ ↴
2	1.1185	↖	NP-004102	L P	SKB	10.0um	24.0h	II	○ ↴
3	1.1128	↖	K784-3188	L P	SKB	10.0um	24.0h	II	○ ↴
4	1.1019	↖	BRD-K51290057	L P	SKB	10.0um	24.0h	II	○ ↴
5	1.0953	↖	geldanamycin	L P	MCF10A	0.04um	3h	II	○ ↴
6	1.0948	↖	CYT387	L P	HS578T	0.04um	3h	II	○ ↴
7	1.0932	↖	BRD-K10207760	L P	SKB	10.0um	24.0h	II	○ ↴
8	1.0896	↖	BRD-A46747628	L P	SKB	10.0um	24.0h	II	○ ↴
9	1.0870	↖	TWS119	L P	VCAP	10.0um	24.0h	II	○ ↴
10	1.0867	↖	BRD-A68930007	L P	SKB	10.0um	24.0h	II	○ ↴
11	1.0855	↖	BRD-K73109821	L P D	SKB	10.0um	24.0h	II	○ ↴
12	1.0847	↖	AICAR	L P	A673	10.0um	6.0h	II	○ ↴
13	1.0846	↖	BRD-K73395020	L P	SKB	10.0um	24.0h	II	○ ↴
14	1.0830	↖	BRD-K88329126	L P	SKB	10.0um	24.0h	II	○ ↴

All donors

93 **K784-3131**
 72 vorinostat
 64 K784-3188
 63 NP-004102
 62 BRD-A68930007
 62 BRD-K10207760
 61 BRD-K73395020
 60 BRD-K51290057
 55 BRD-A46747628
 53 OSSK_645668
 48 MLS-0435555.0001
 46 BRD-K72895815
 45 BRD-K88329126
 45 K784-3187
 44 BRD-A28970875
 42 L-6307
 41 AICAR
 40 BRD-K80786583
 36 E3380
 36 saracatinib

Male donors

43 **K784-3131** (28 out of 28)
 33 Vorinostat (22 out of 28 donors)
 28 K784-3188
 27 BRD-A68930007
 27 BRD-K10207760
 27 BRD-K51290057
 27 NP-004102
 27 OSSK_645668
 26 BRD-K73395020
 22 BRD-A46747628
 22 MLS-0435555.0001
 20 BRD-K88329126
 19 K784-3187
 18 AICAR
 18 BRD-K72895815
 17 BRD-K63606607
 16 BRD-A28970875
 16 BRD-K36055864
 16 BRD-K80786583

Female donors

5 **K784-3131** (4 out of 4)
 4 BRD-K10207760
 4 BRD-K51290057
 4 BRD-K63606607
 4 BRD-K72895815
 4 BRD-K73395020
 4 BRD-K80786583
 4 BRD-K88329126
 4 HY-11068
 4 K784-3187
 4 K784-3188
 4 NP-004102
 4 STOCK1S-53863
 4 saracatinib
 3 BRD-K03816923
 3 BRD-K08316444
 3 BRD-K54704028
 3 BRD-K60230970
 3 BRD-K73109821
 3 BRD-K87158025

K784-3131

LINCS ID : LSM-1796

PubChem CID : [4381125](#)

Bio Availability 

Lipinsky 3 

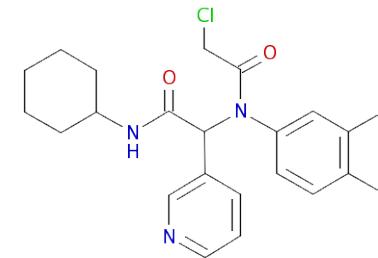
Facility ID : BRD-A76490030

Lipinsky 5 

Lead Likeness 

Lipinski rule of 5

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

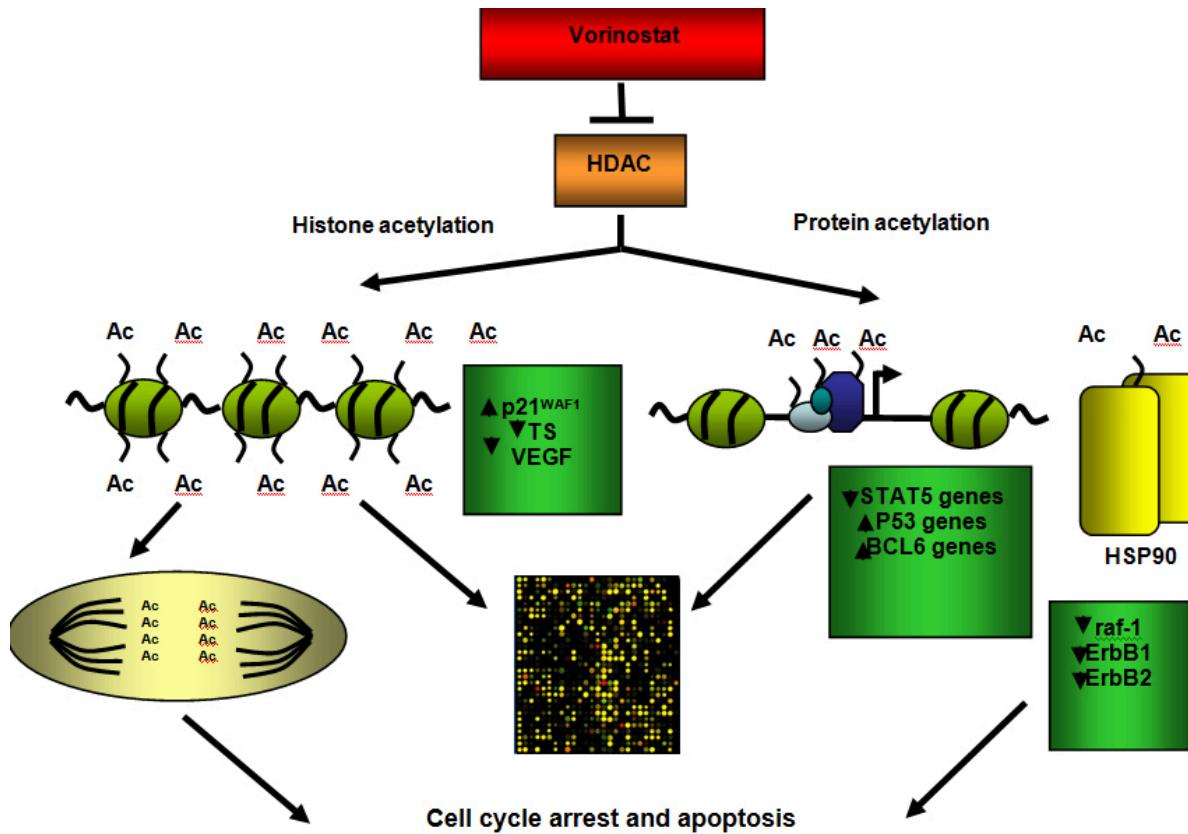


LSM-1796

SmallMolecule	Cell	Time Point (hrs)	Concentration (μM)	Endpoint	Value	Gene Name
K784-3131	VCaP	24	10	up regulation	23.504	HMOX1
K784-3131	A-375	6	10	up regulation	21.727	CXCL2
K784-3131	A-375	6	10	up regulation	21.293	EGR1
K784-3131	PC-3	6	10	up regulation	20.758	HMOX1
K784-3131	VCaP	6	10	up regulation	20.723	HMOX1
K784-3131	PC-3	6	10	up regulation	17.601	HMOX1
K784-3131	A-375	6	10	up regulation	16.966	SFN
K784-3131	A549	6	10	up regulation	16.553	EGR1
K784-3131	A-375	6	10	up regulation	16.127	EGR1

SmallMolecule	Cell	Time Point (hrs)	Concentration (μM)	Endpoint	Value	Gene Name
K784-3131	VCaP	6	10	down regulation	-0.517	HSPA8
K784-3131	VCaP	6	10	down regulation	-1.009	ABCF3
K784-3131	VCaP	6	10	down regulation	-1.029	CDK7
K784-3131	VCaP	6	10	down regulation	-1.073	PSMD9
K784-3131	VCaP	6	10	down regulation	-1.129	DNAJA3
K784-3131	VCaP	6	10	down regulation	-1.281	RFC2
K784-3131	VCaP	6	10	down regulation	-1.292	CCNA2

VORINOSTAT



HDAC inhibitor.

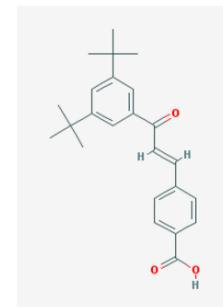
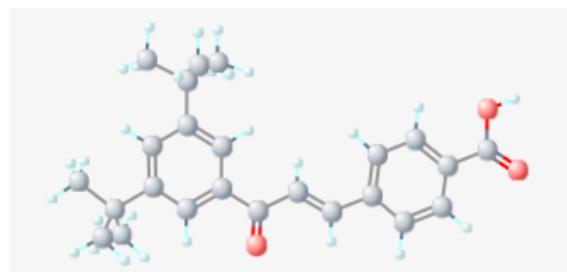
Used to treat cutaneous T-cell lymphoma

* Did not show as a potential drug for females.

BRD-K51290057

3,5-DI-TERT-BUTYLCHALCONE 4'-CARBOXYLIC ACID

First common to all 3 was
BRD-K51290057

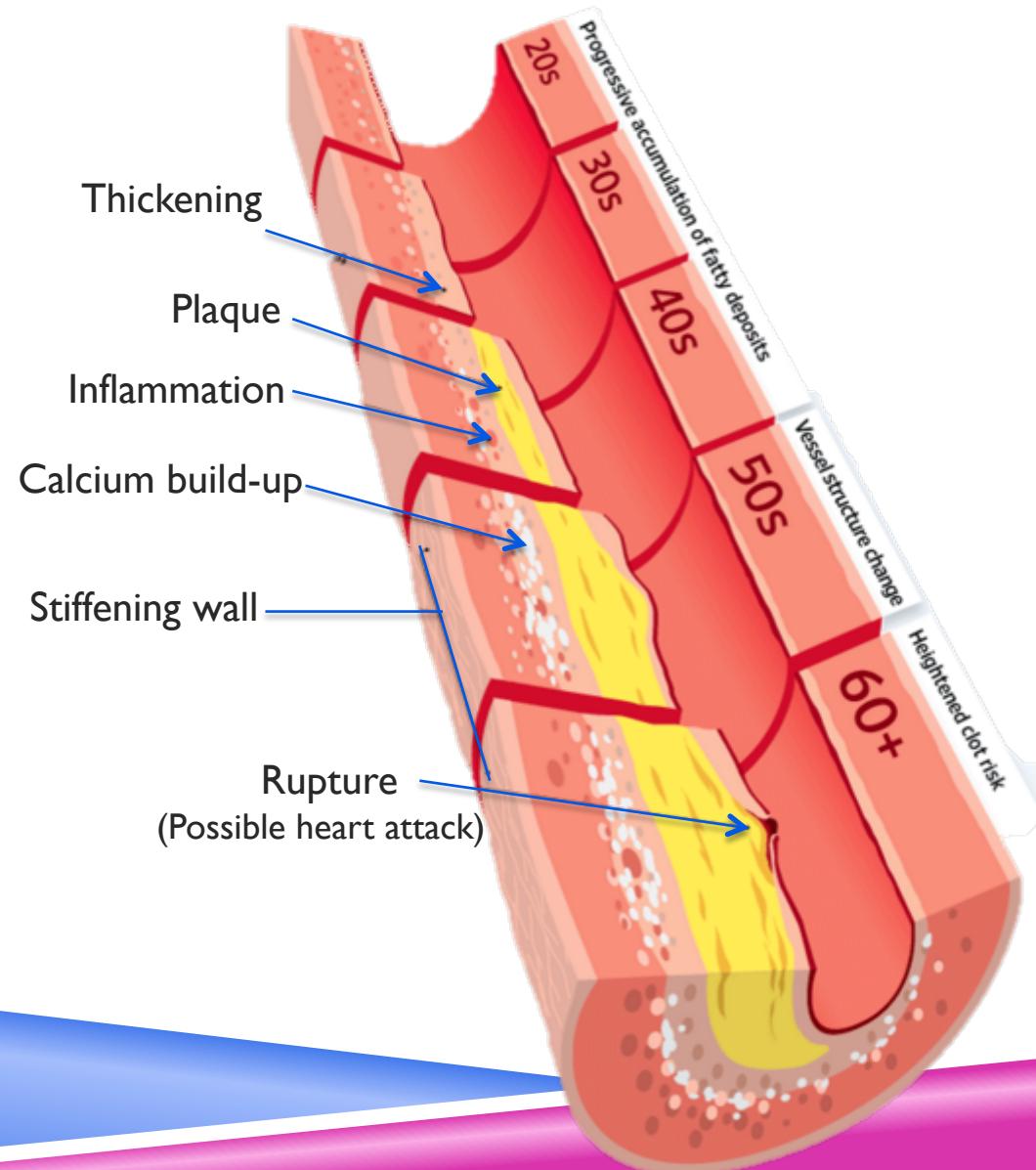


Activity	Substance	BioAssay
active Potency: 19.9526μM	26753189	qHTS Assay for Inhibitors and Substrates of Cytochrome P450 3A4 [AID: 884]
active Potency: 12.5893μM	26753189	qHTS Assay for Anthrax Lethal Toxin Internalization [AID: 912]
active Potency: 7.0795μM	26753189	qHTS for inhibitors of ROR gamma transcriptional activity [AID: 2551]
active ED50: 0.0029μM	103205963	Ability to induce differentiation of human promyelocytic leukemia cell line HL-60 to mature granulocytes. [AID: 82163]
active ED50: 0.00021μM	103205963	Differentiation inducing activity towards human promyelocytic leukemia cell line HL-60 assayed by nitroblue tetrazolium reduction [AID: 82170]
active active active	26753189 485052 485052	qHTS Multiplex Assay to Identify Dual Action Probes in a Cell Model of Huntington: Cytoprotection (ATP) [AID: 1471] NCI AIDS Antiviral Assay [AID: 179] NCI human tumor cell line growth inhibition assay. Data for the SNB-75 Central Nervous System cell line [AID: 55]

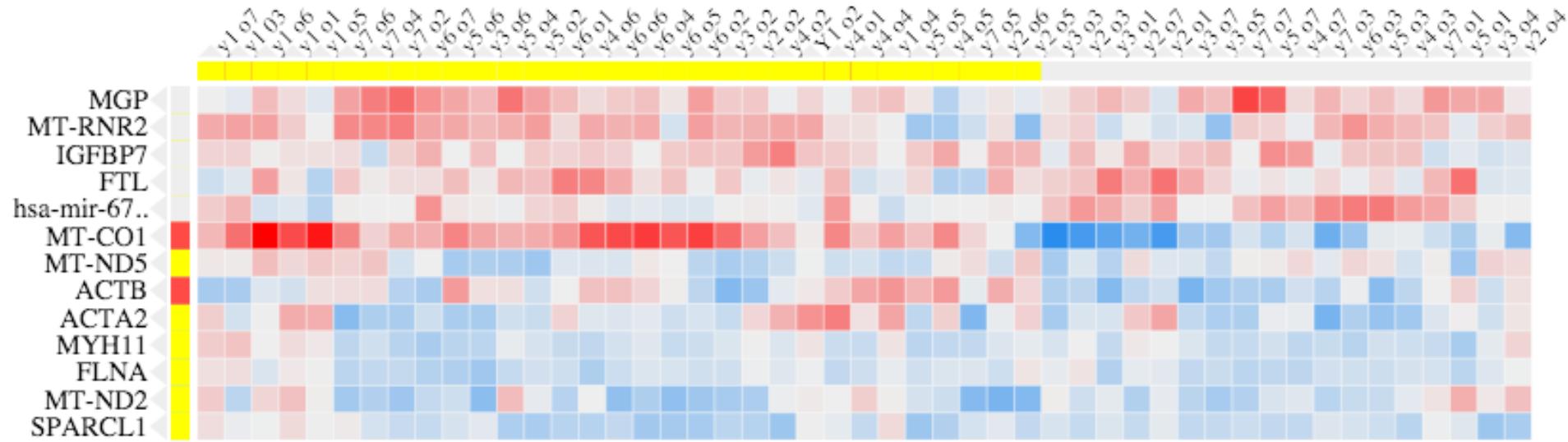
BLOOD VESSEL

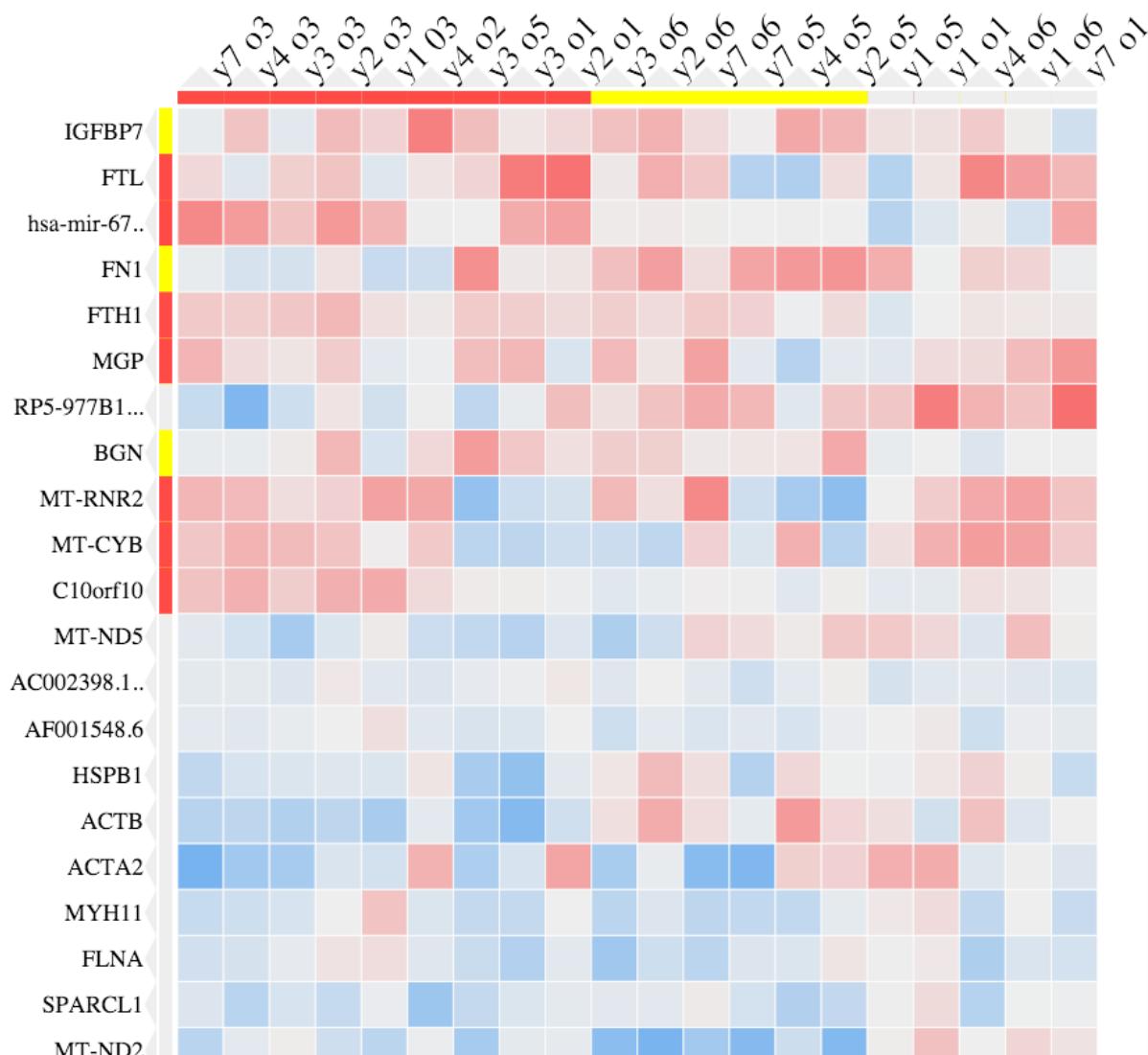
14 donors

BLOOD VESSEL		
Donors	ID	SEX
GTEX-QEG5-0626-SM-2S1PP	Y1	M
GTEX-WFG7-0626-SM-4LMK6	Y2	M
GTEX-XPT6-0326-SM-4B66V	Y3	M
GTEX-ZAB4-0526-SM-5HL7Z	Y4	M
GTEX-PWCY-0326-SM-43IRU	Y5	F
GTEX-P4PP-0426-SM-3NM9H	Y6	F
GTEX-U3ZH-0426-SM-4DXSE	Y7	M
GTEX-131XF-2526-SM-5EQ68	O1	M
GTEX-131YS-1226-SM-5K7VE	O2	F
GTEX-REY6-1126-SM-48FDU	O3	M
GTEX-RWS6-2326-SM-2XCB4	O4	F
GTEX-S4Z8-2026-SM-3K2A9	O5	M
GTEX-Y5V6-2826-SM-4VDSF	O6	M
GTEX-QLQ7-1926-SM-2S1R6	O7	F



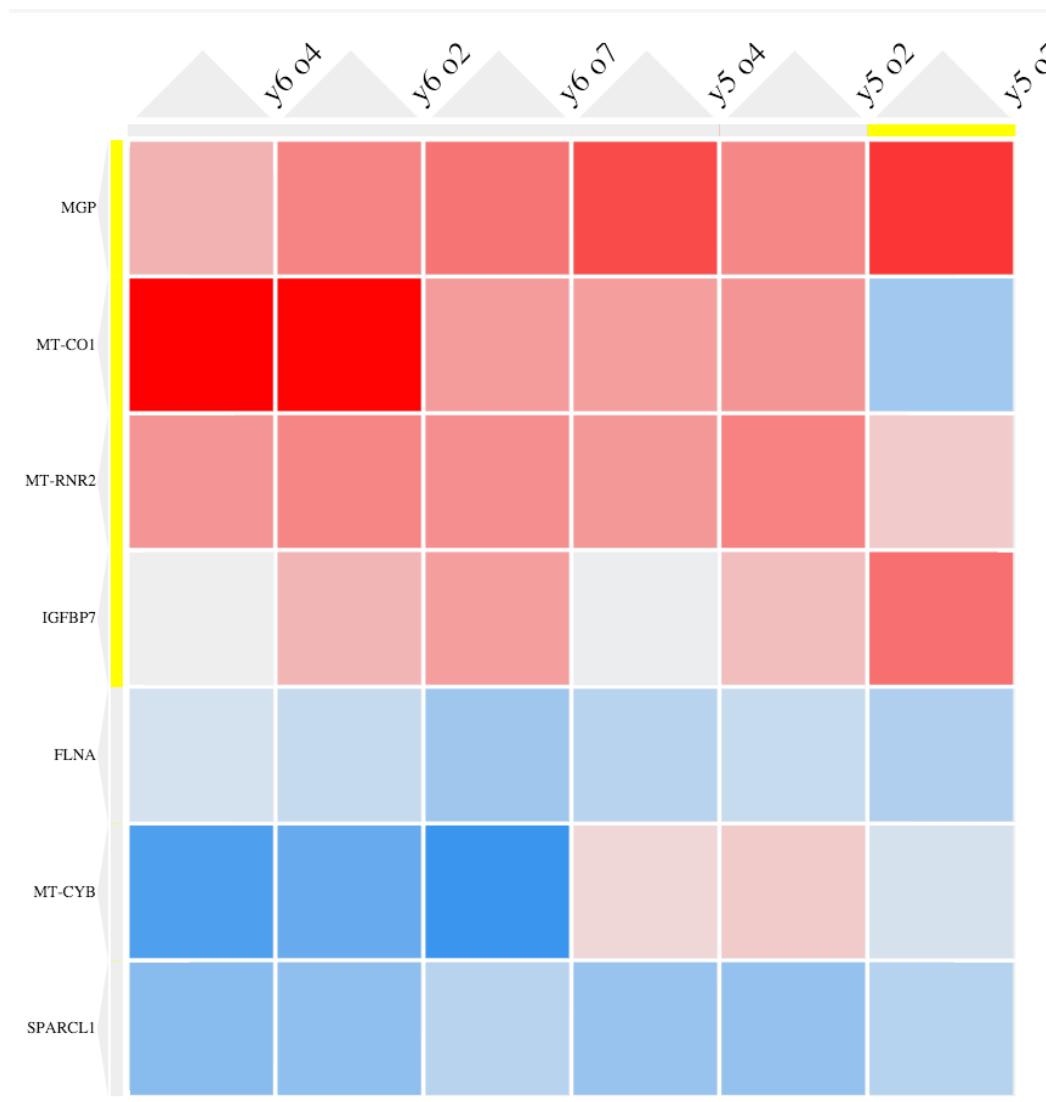
ALL 40%





Female 40%

MT-CYB



ALL DONORS

63	K784-3131
60	SB-525334
57	BRD-A28970875
54	dasatinib
52	BRD-K60230970
49	BRD-K94325918
45	OSI-930
45	T5212475
44	BRD-A17065207
42	BRD-K51290057
36	KIN001-043
35	BRD-K74305673
35	NP-004102
34	K784-3188
33	BRD-A40431293
32	BRD-A50737080
32	XMD11-85H
31	KIN001-055
29	BRD-K88329126
28	STK397047
28	withaferin-a

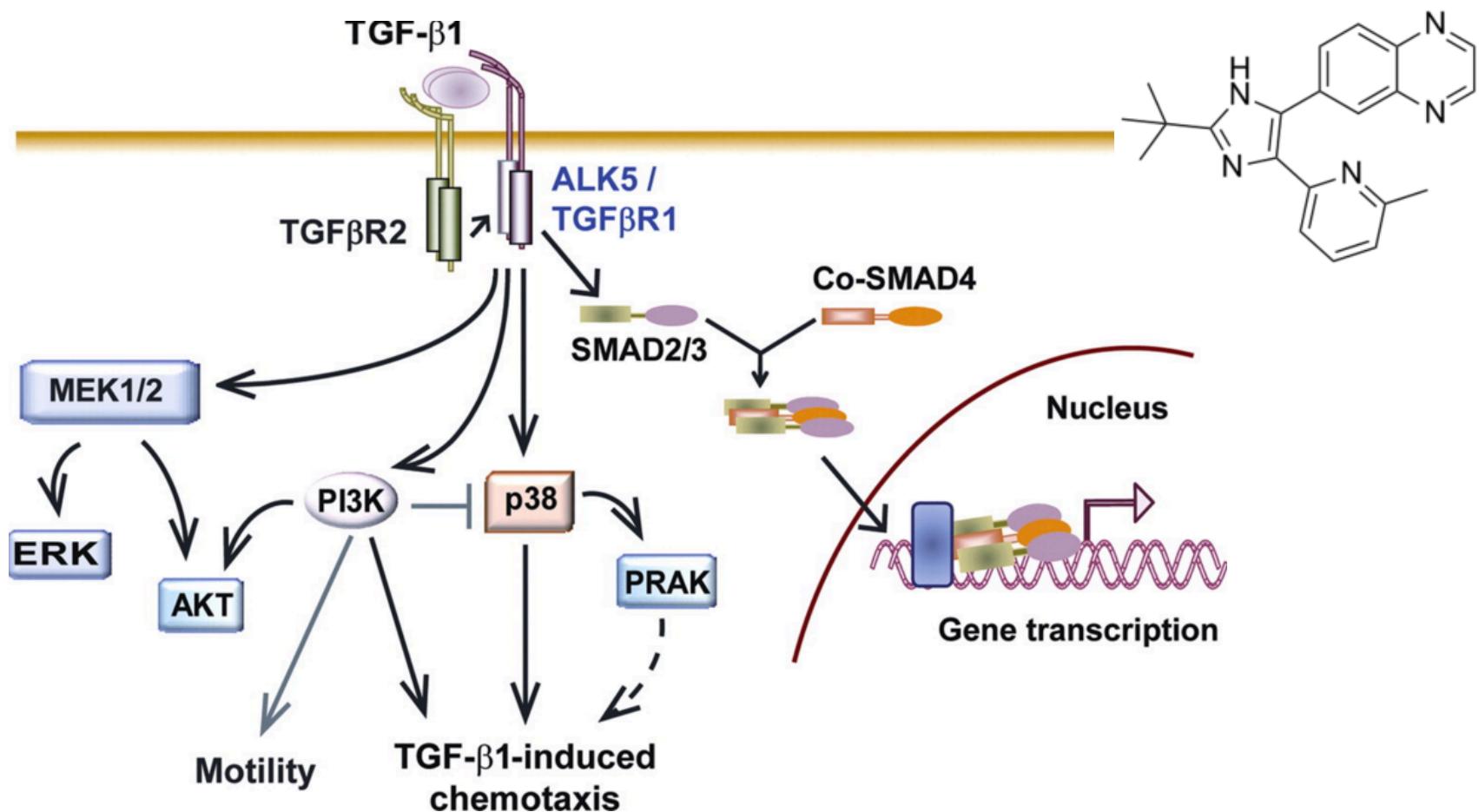
MALE

26	K784-3131
25	SB-525334
24	BRD-A28970875
23	BRD-K60230970
20	BRD-A17065207
20	BRD-K94325918
19	BRD-A40431293
19	BRD-K74305673
19	T5212475
19	dasatinib
18	NP-004102
17	OSI-930
16	BRD-K51290057
16	XMD11-85H
13	BI-2536
13	BRD-A10715913
12	BRD-A50737080
12	CHIR-99021
12	K784-3188
12	SB590885

FEMALE

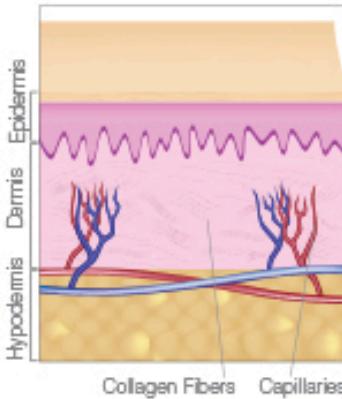
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8	dasatinib
7	BRD-K60230970
7	SB-525334
7	withaferin-a
6	BRD-A28970875
6	BRD-K51290057
6	BRD-K88329126
6	BRD-K94325918
6	K784-3188
6	OSI-930
5	BRD-A50737080
4	364947
4	BRD-K54256913
4	BRD-K88198340
4	BRD-K92301463
4	NCGC00183401-01
4	QL-XI-92
4	T5212475
4	pelitinib

SB-525334



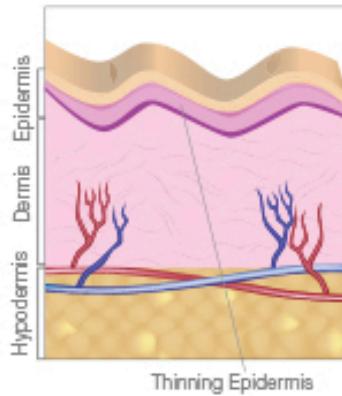
DOI: <http://dx.doi.org/10.1093/cvr/cvr100> First published online: 8 April 2011

SKIN



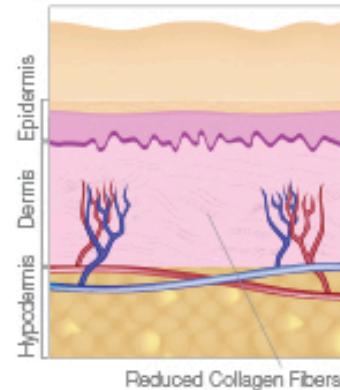
20s

Environmental damage and constant exposure to damaging UV rays begin to take their toll on skin. Free radicals attack the skin's structural integrity. Cell renewal and turnover rates begin to decline.



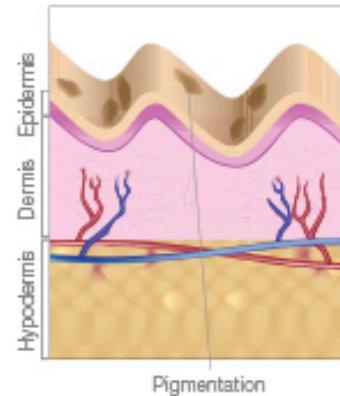
40s

By our 40s, the skin is thinner, barrier lipids are not as pronounced and dehydration can be an issue. More prominent signs of skin aging may also appear, such as dark spots and significant dullness.



30s

In our 30s, collagen and elastin degrade, resulting in our first wrinkles. Cell renewal and turnover continue to decline, leading to a duller complexion and uneven skin tone.

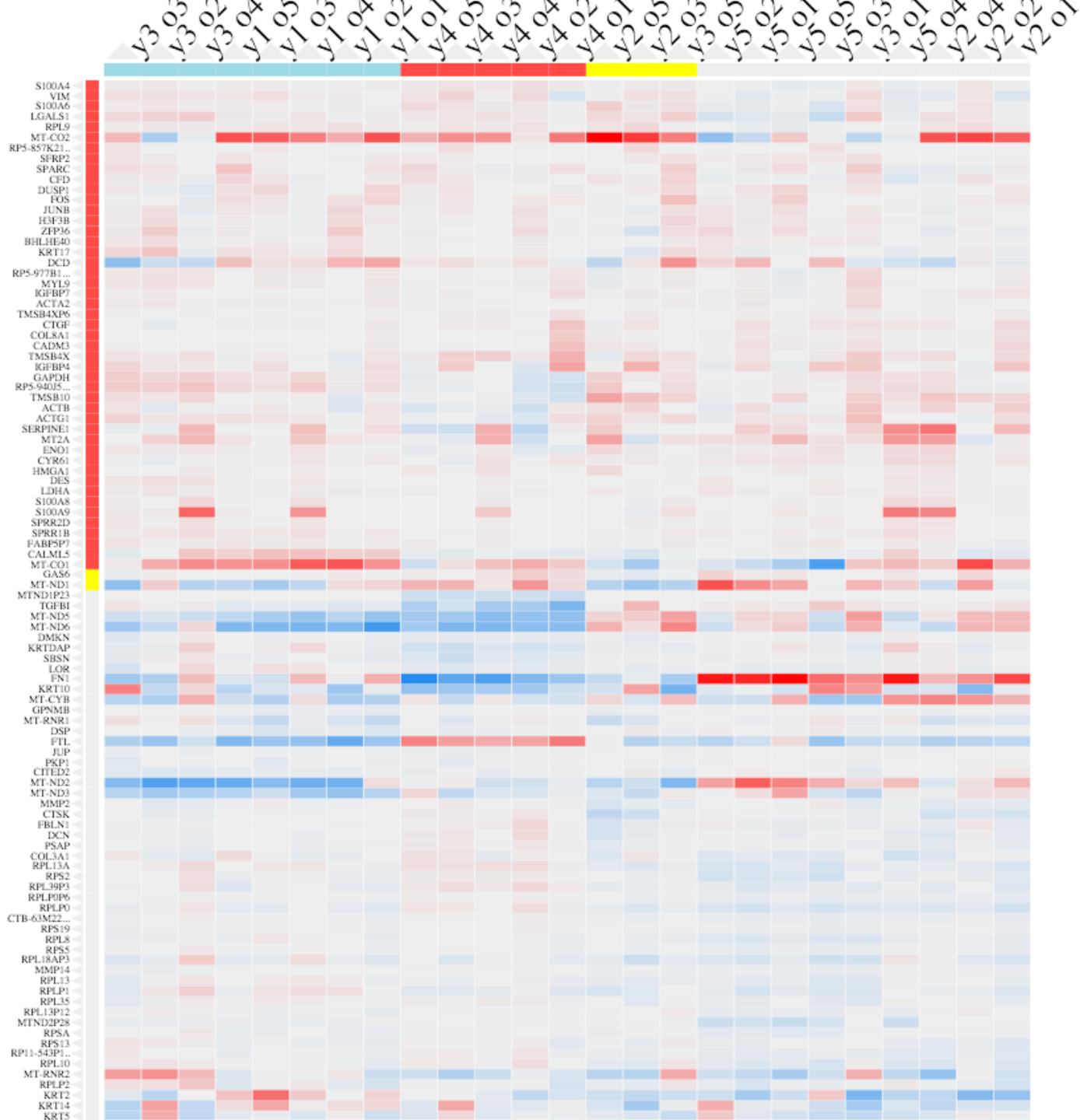


50s+

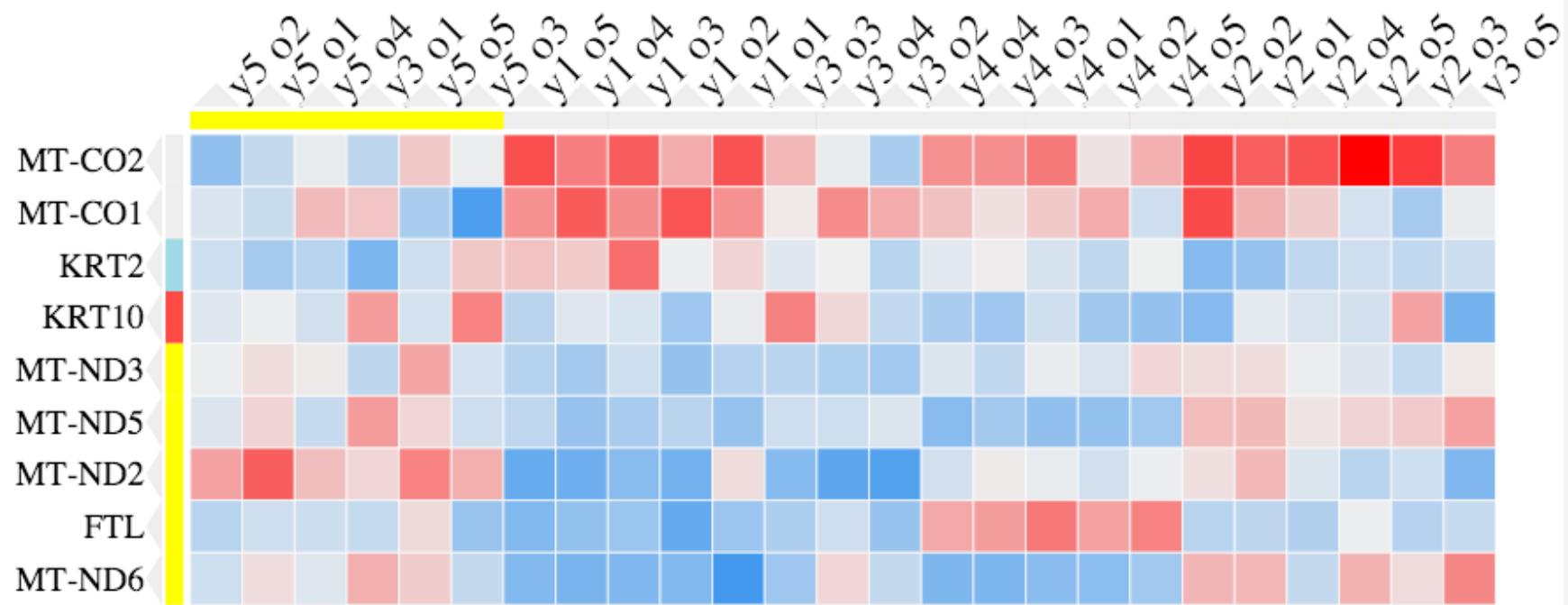
The protective barrier lipid layer lessens, leading to less efficiency in retaining moisture and more potential for sensitivity and dehydration. Skin shows wrinkles, fine lines and pigmentation.

10 donors

SKIN		
Donors	ID	SEX
GTEX-11P82-0008-SM-5S2MS	Y1	M
GTEX-U8XE-0008-SM-4E3K4	Y2	M
GTEX-XQ3S-0008-SM-4GIDZ	Y3	M
GTEX-ZTX8-0008-SM-4YCDV	Y4	M
GTEX-ZVTK-0008-SM-57WDA	Y5	M
GTEX-11GS4-2726-SM-5A5LE	O1	M
GTEX-11TUW-2726-SM-5EQLC	O2	M
GTEX-11WQC-2526-SM-5CVLE	O3	M
GTEX-Y5V6-2426-SM-4VDSB	O4	M
GTEX-ZDXO-3126-SM-5IJDF	O5	M

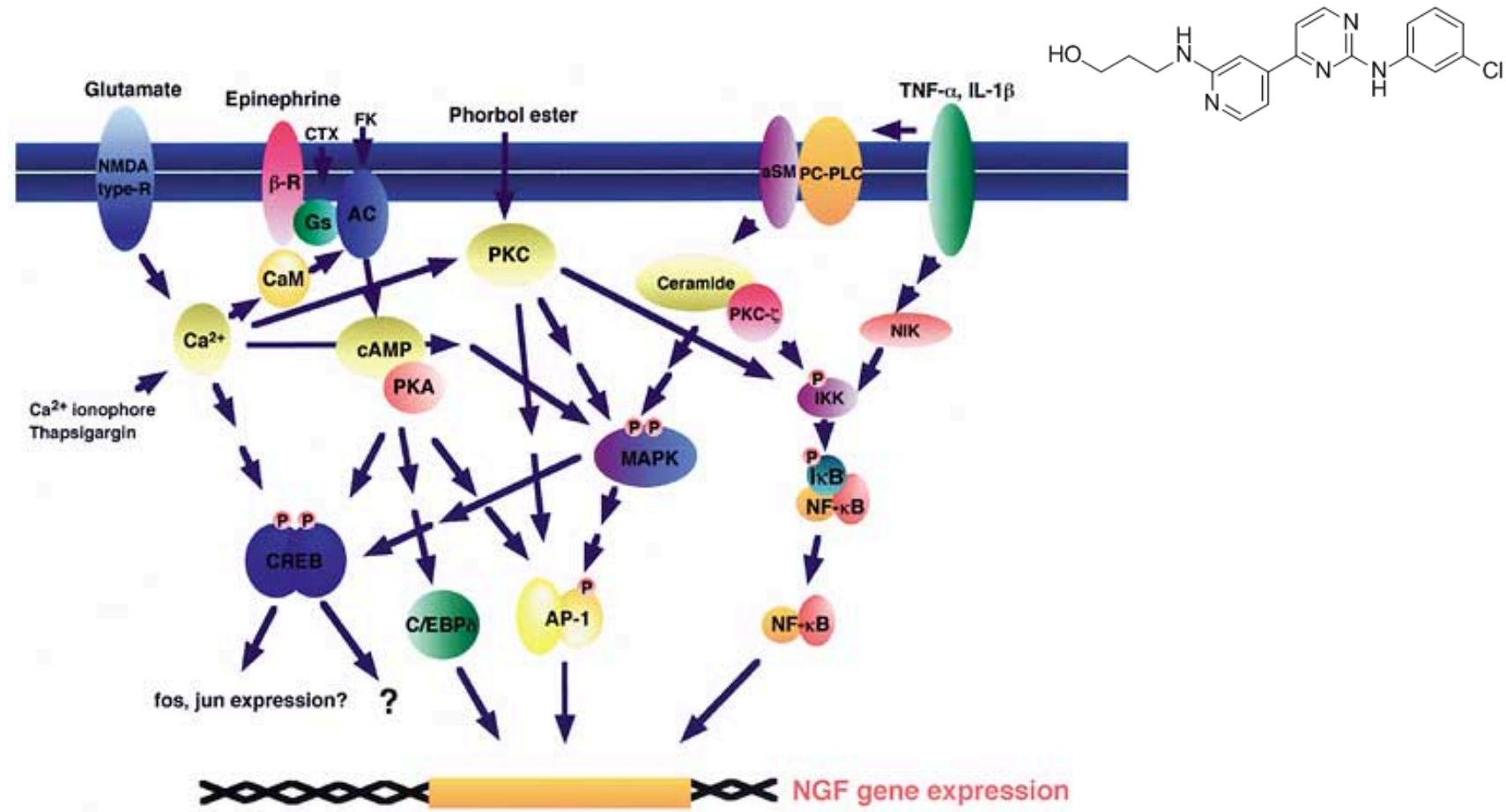


Skin 30%



73	dasatinib	11	JNK-9L
38	KIN001-043	11	K784-3131
27	CGP-60474	11	PHA-793887
24	NVP-AUY922	10	BRD-A10715913
24	geldanamycin	10	LDN-193189
22	SYK-inhibitor	10	PLX-4720
20	pelitinib	10	SB590885
16	trametinib	10	radicicol
15	PD-0325901	10	vemurafenib
14	BI-2536	9	1478
14	T5212475	9	CHIR-99021
14	WH-4-025		
13	BRD-K60230970		
12	BRD-A28970875		
12	NP-004102		

CGP60474



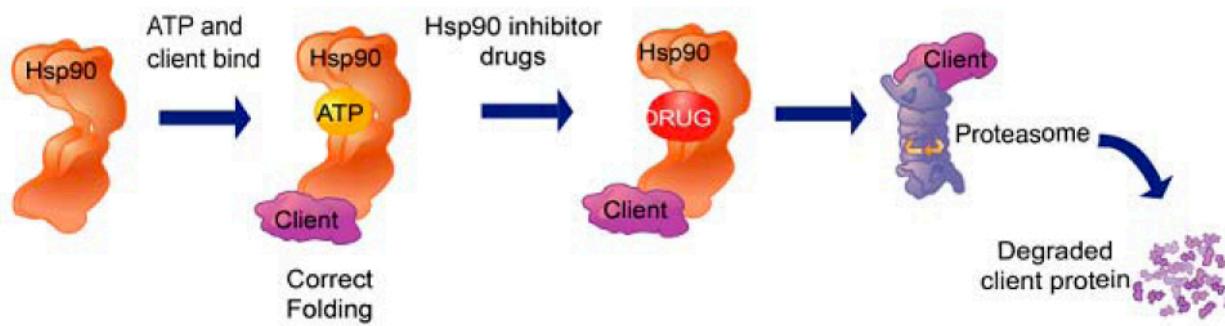


Figure 1. Mechanism of action of Hsp90 inhibitor drugs. Hsp90, when ATP bound, is involved in the correct folding and stabilization of Hsp90 client proteins. Hsp90 inhibitor drugs competitively bind to the ATP binding pocket and disrupt Hsp90 function such that client proteins are directed to the proteasome for degradation.

Dasatinib

Chronic myeloid leukemia

Oral dual BCR/ABL and Src family tyrosine kinase inhibitor

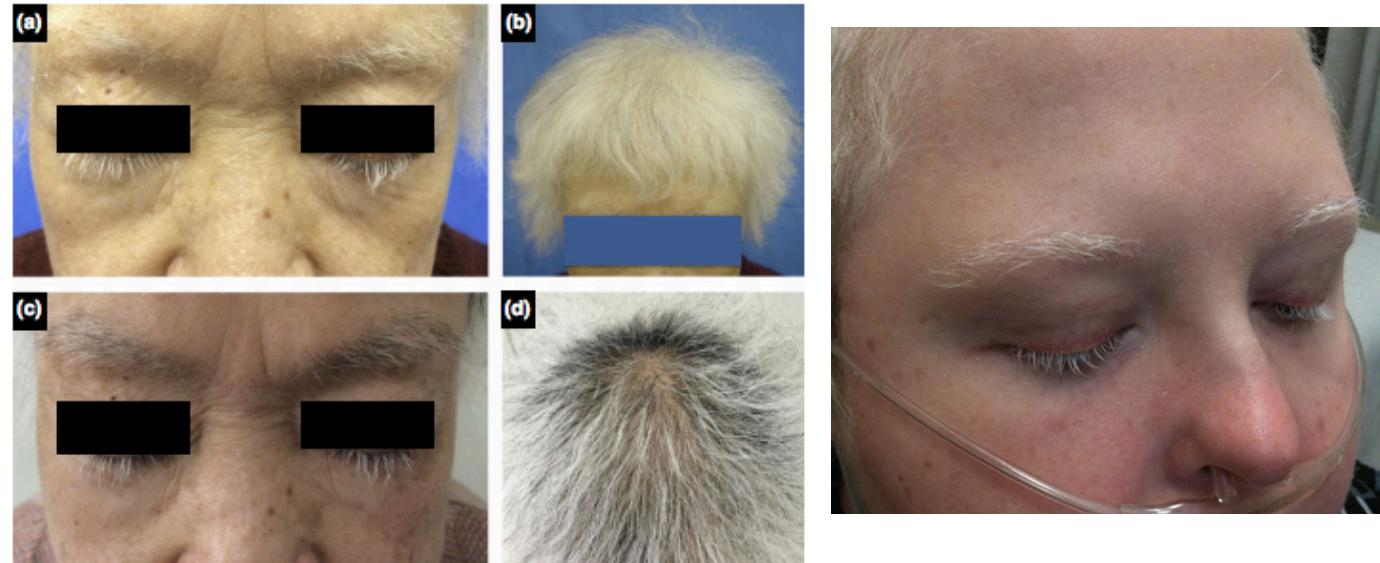


Figure 1. Depigmentation of the patient's (a) facial skin, eyebrows, eyelashes and (b) scalp hair is seen 12 months after initiating dasatinib therapy. Repigmentation of her (c) skin, eyebrows, eyelashes and (d) scalp hair is seen approximately 3 months after cessation of dasatinib.



**THANK YOU SO
MUCH!!!!**