

HOW MANY DRUG TARGETS DO WE NEED?

Alexander Kel



Fighting cancer



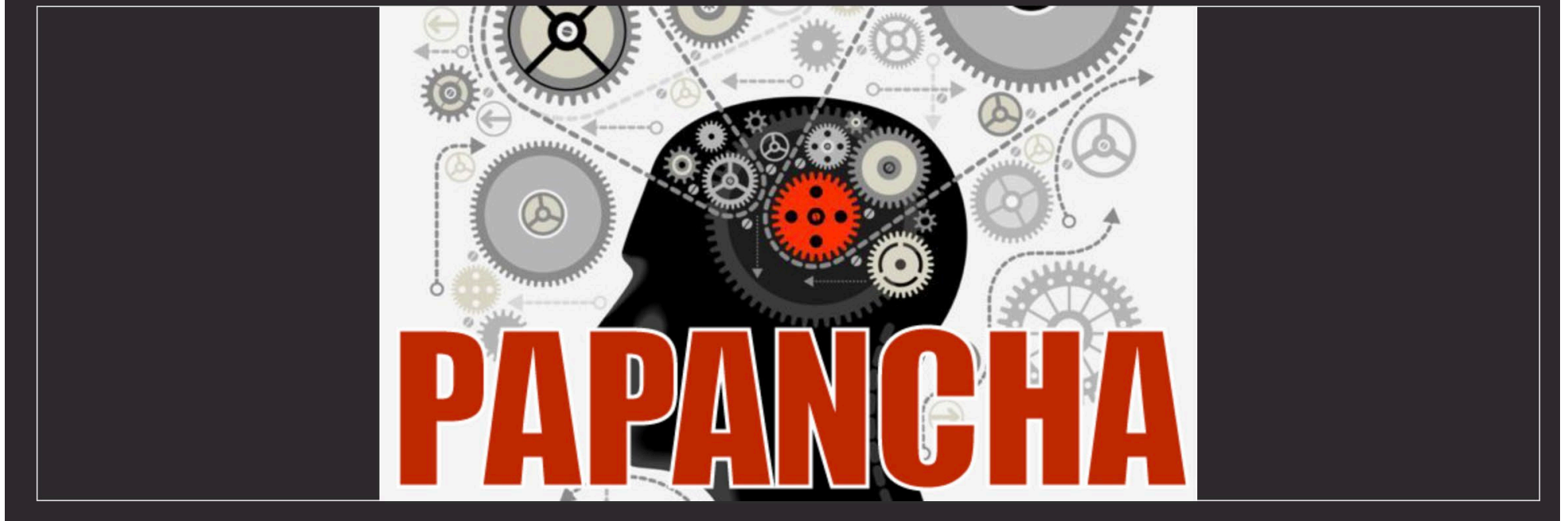
AI

English

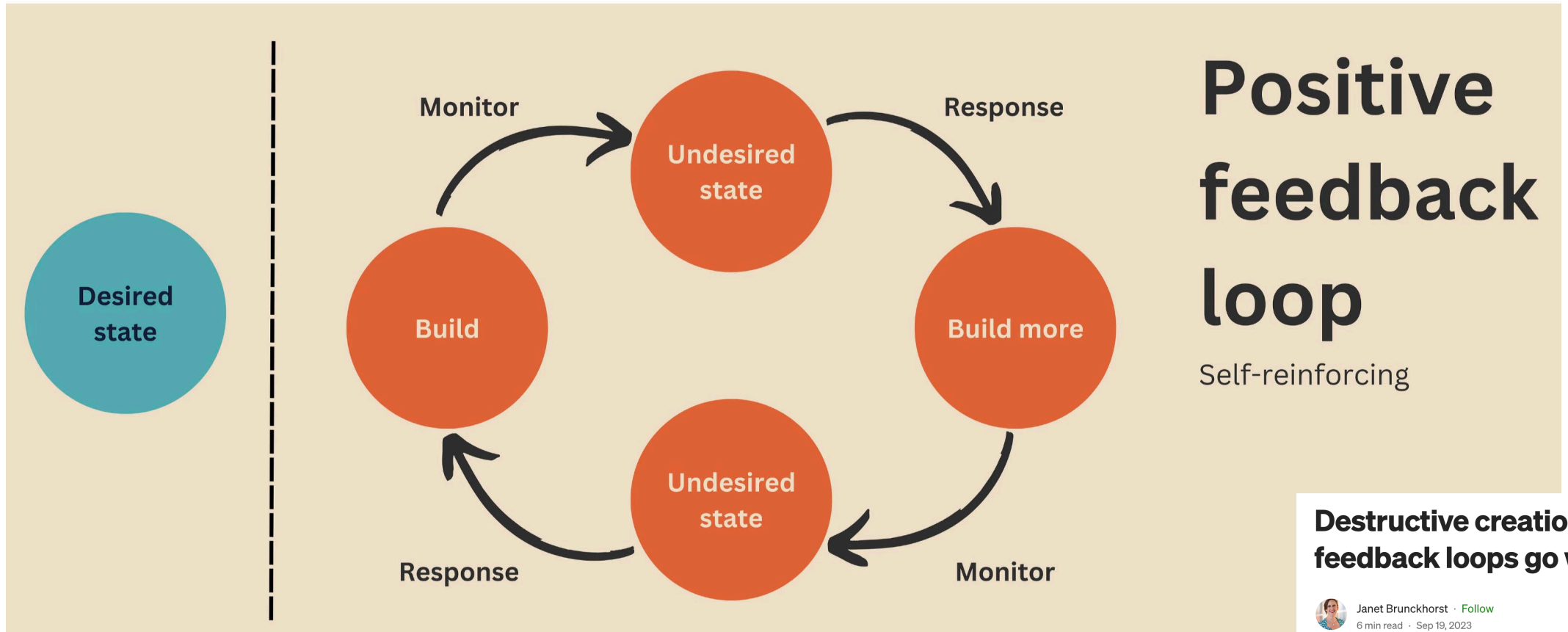
Conceptual proliferation

Sanskrit

प्रपञ्च (*prapañca*)



Suffering



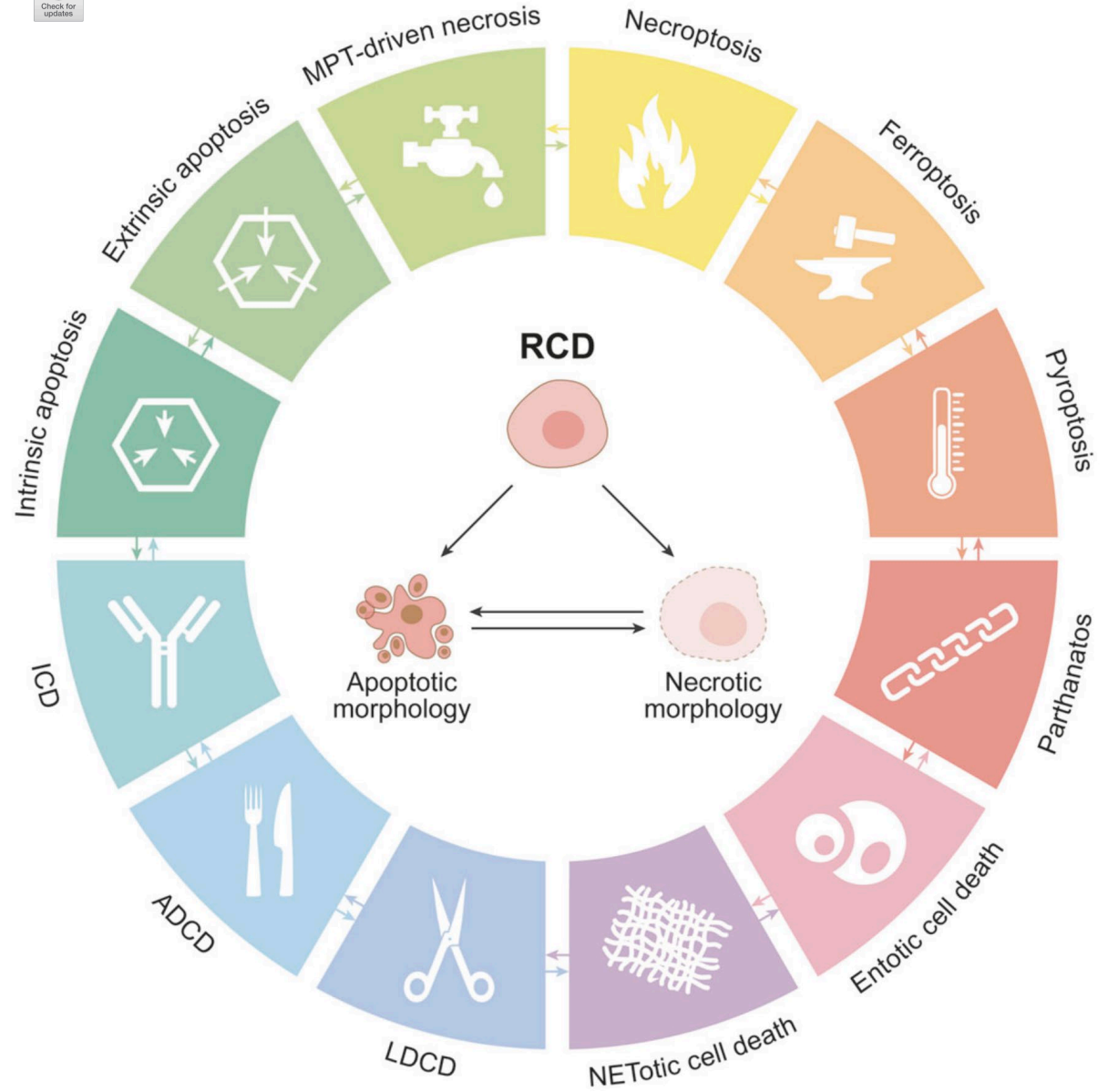
A positive feedback loop is self-reinforcing. **It will ultimately destabilize or even destroy a system, moving it toward chaos.** Colloquially, you might call positive feedback loops something like “downward spirals” or “vicious cycles”.

An example of a positive feedback loop from nature is melting sea ice: melting of sea ice leads to reduced reflection from the white surface, which leads to faster melting of sea ice, and so on.

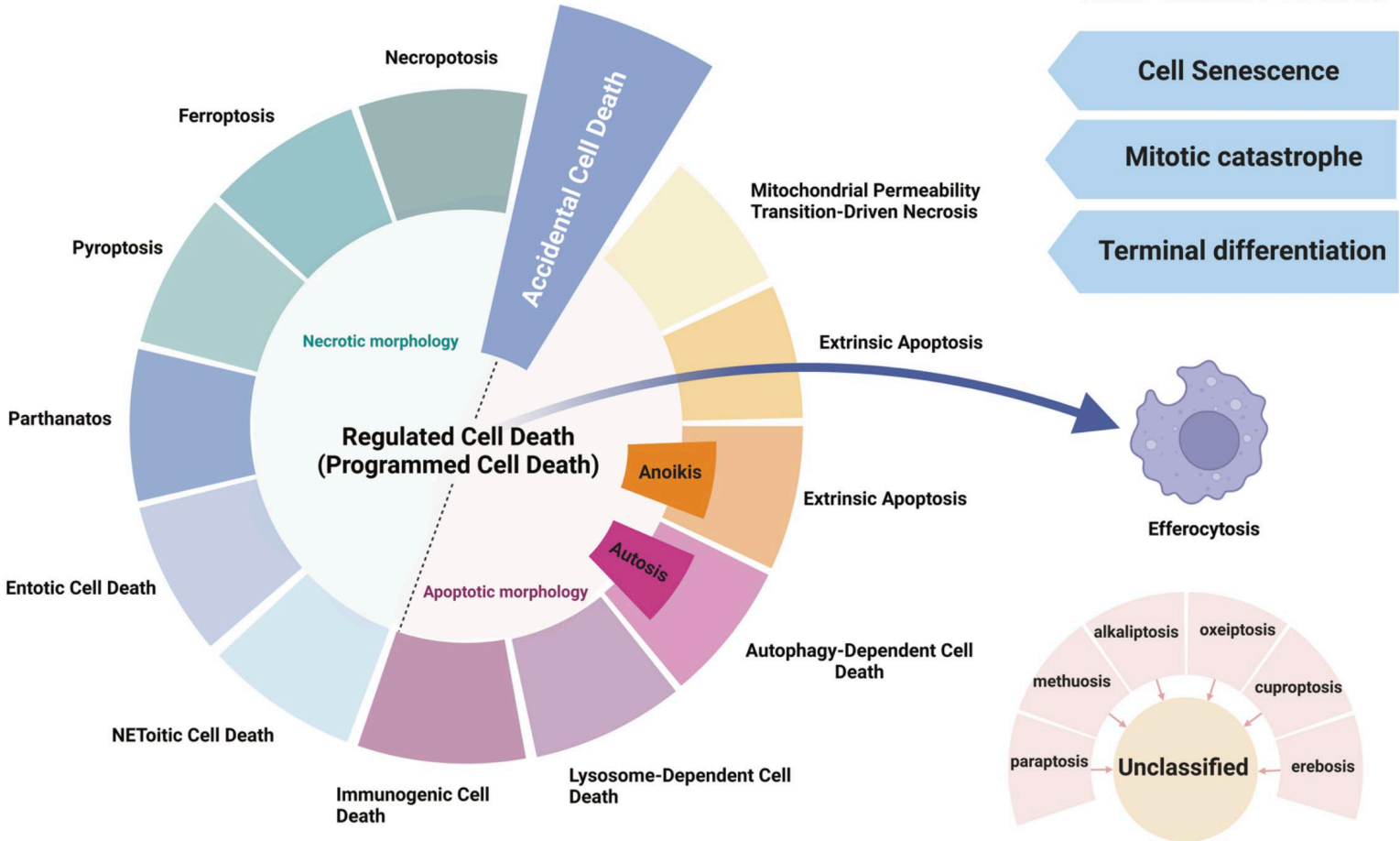


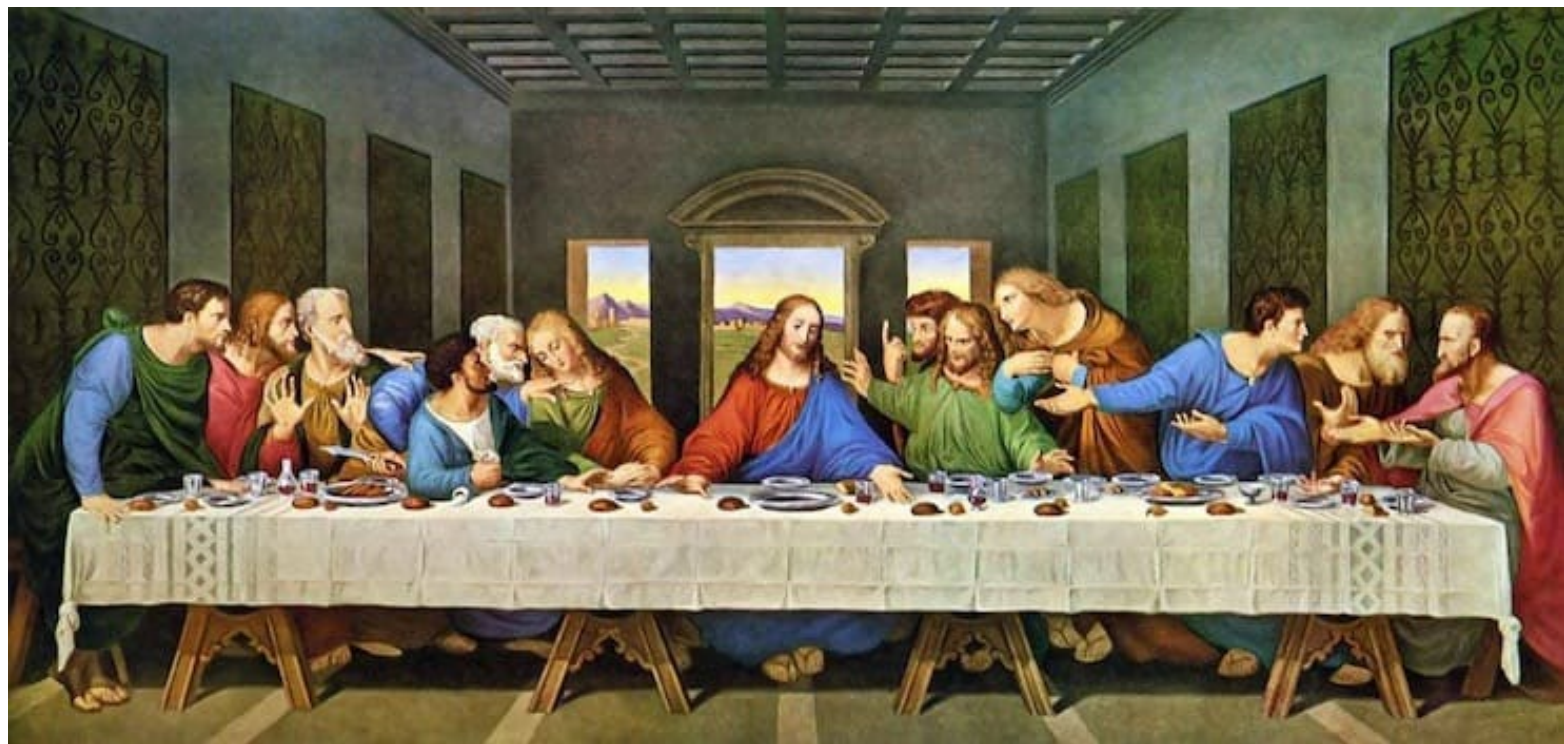
Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi^{1,2,3} · Ilio Vitale^{4,5} et al.



Classification of Cell Death



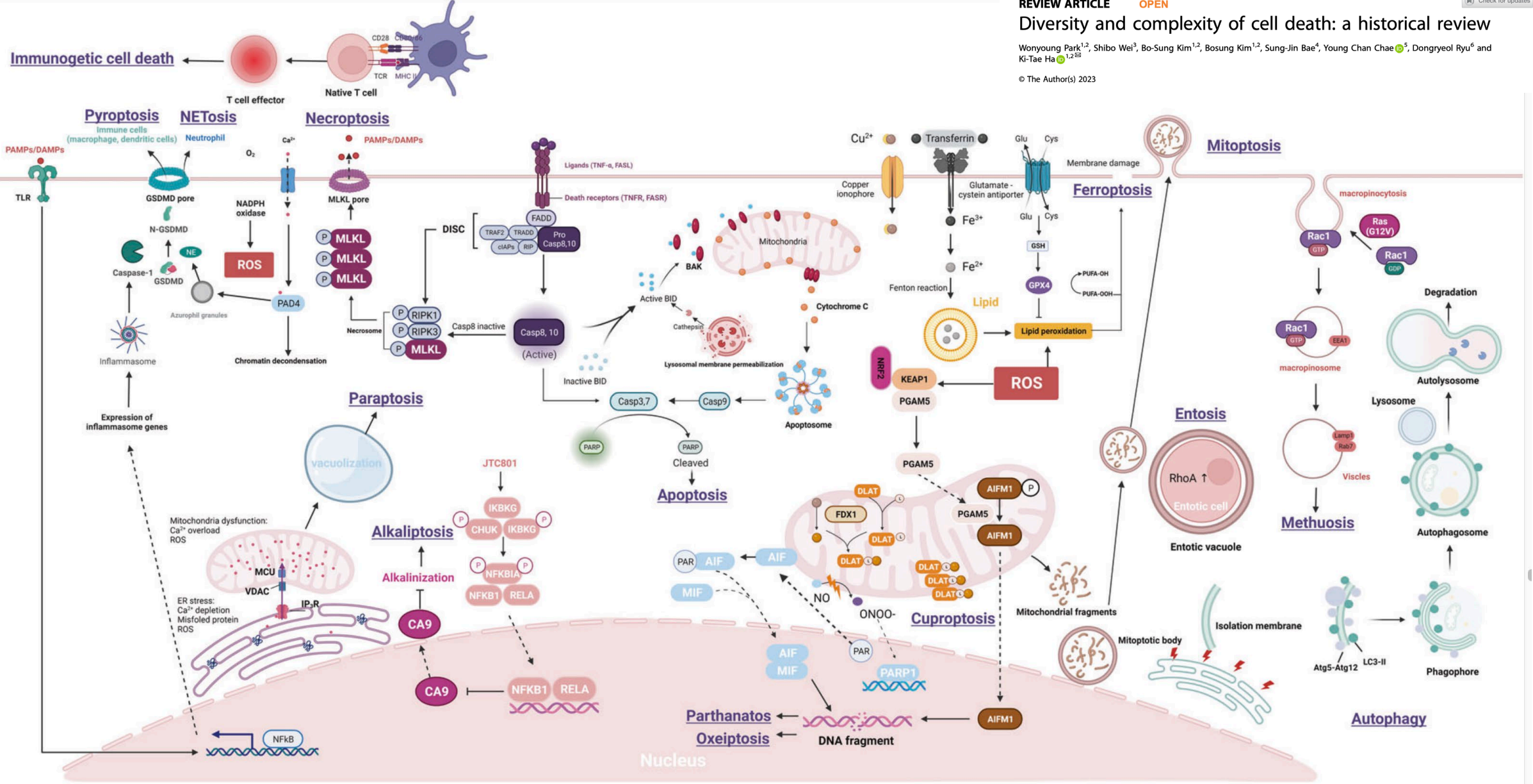


13

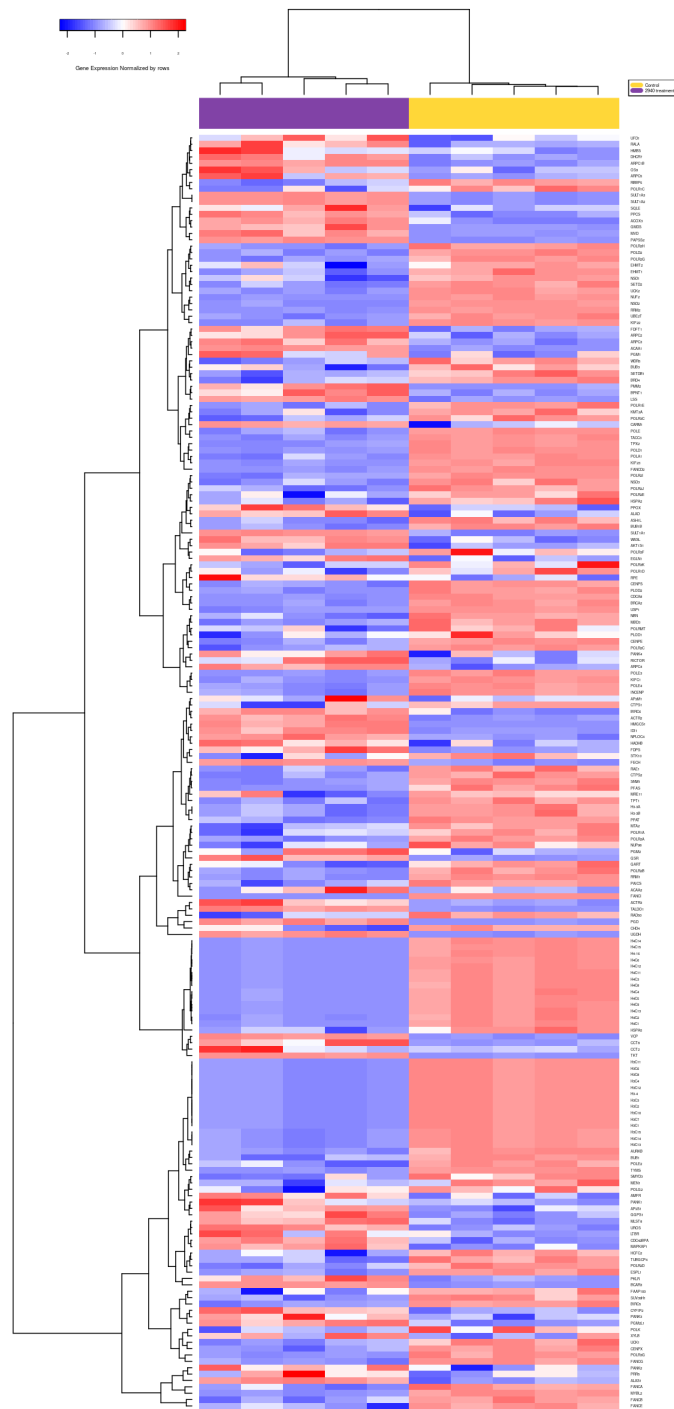
Diversity and complexity of cell death: a historical review

Wonyoung Park^{1,2}, Shibo Wei³, Bo-Sung Kim^{1,2}, Bosung Kim^{1,2}, Sung-Jin Bae⁴, Young Chan Chae⁵, Dongryeol Ryu⁶ and Ki-Tae Ha^{1,2,6*}

© The Author(s) 2023

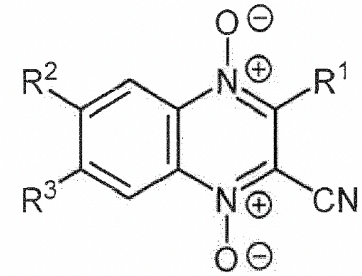


Cancer cell line
MCF-7



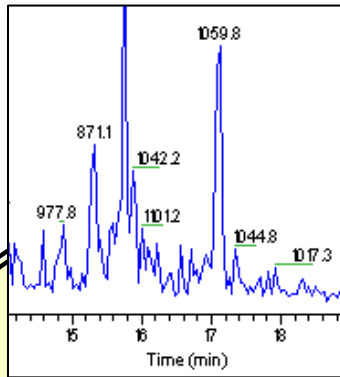
(54) **QUINOXALINE THIOREDOXIN REDUCTASE INHIBITORS**

(57) The present invention relates to novel compounds of formula (I):



These compounds are inhibitors of thioredoxin reductase TrxR1 and are useful in the treatment of various cancer diseases.

Proteomics

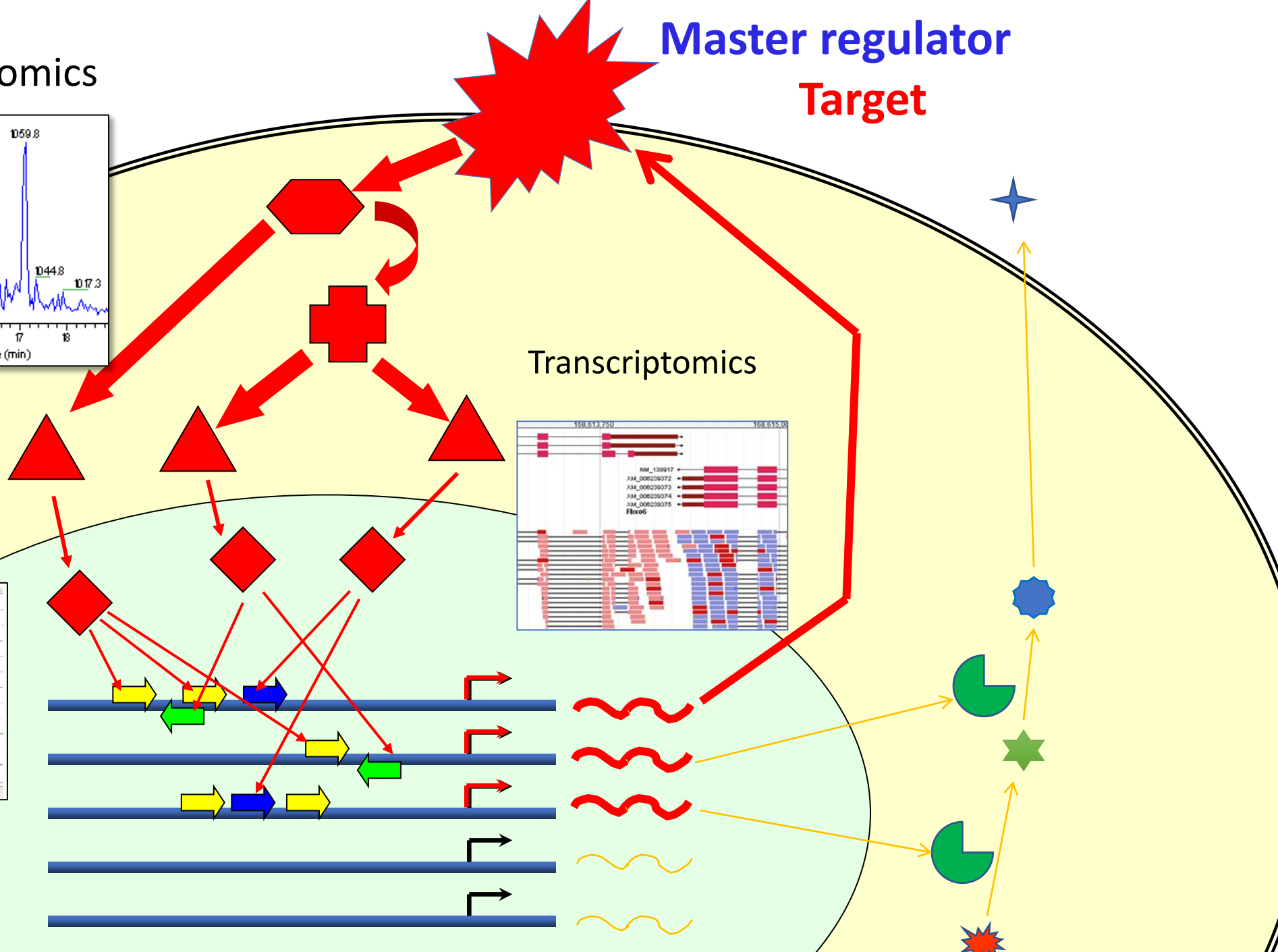
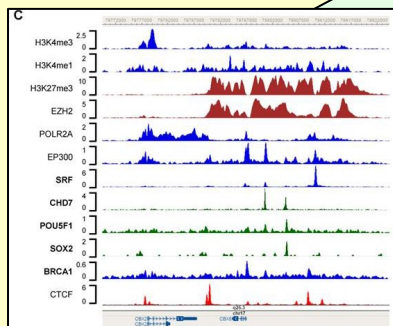


Master regulator
Target

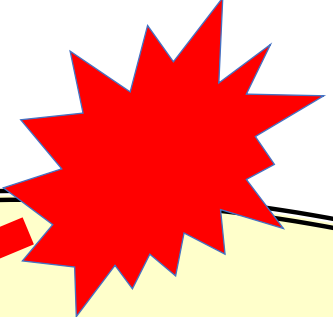
Transcriptomics



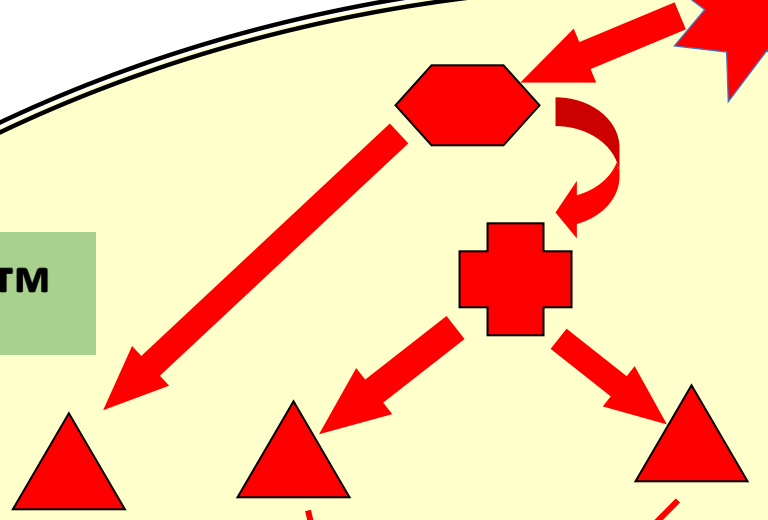
Epigenomics



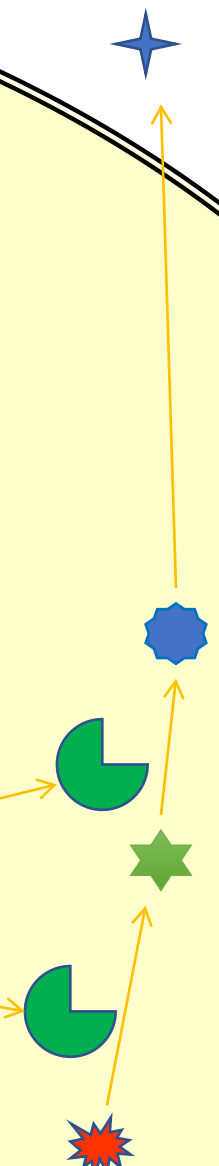
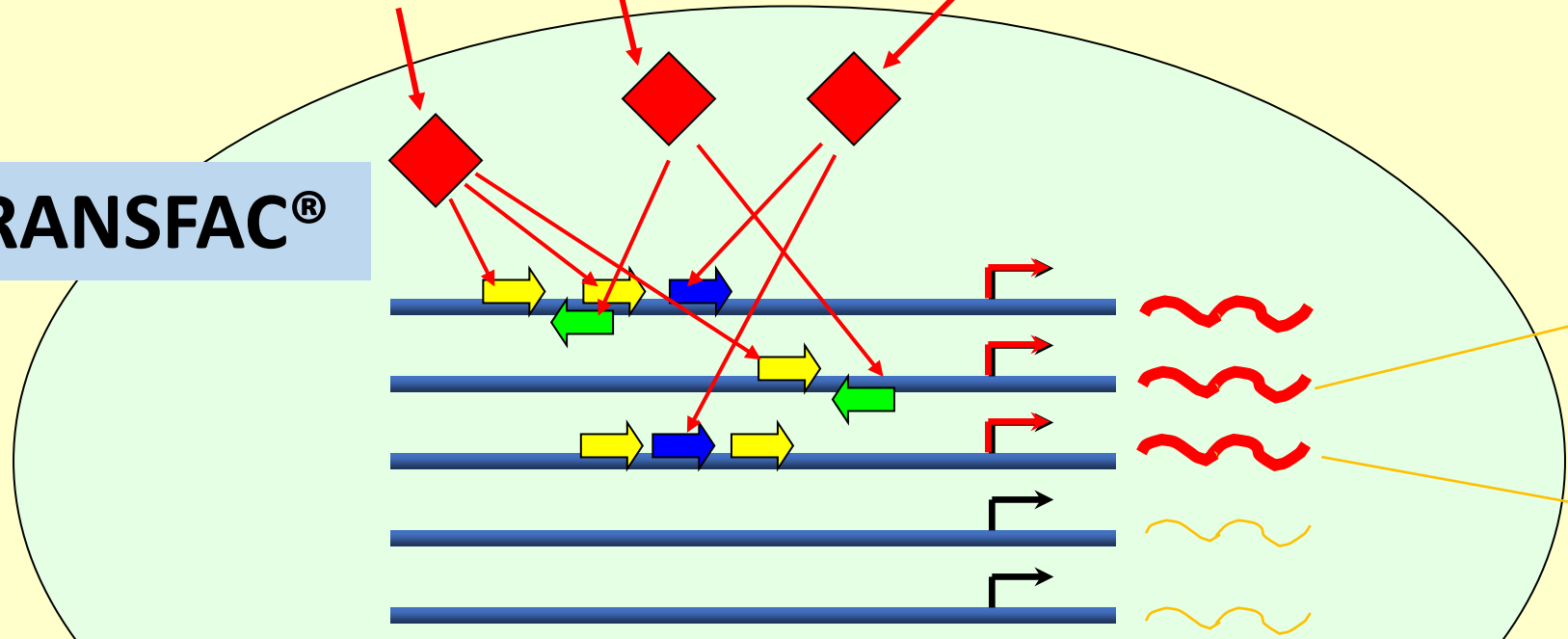
HumanPSD™



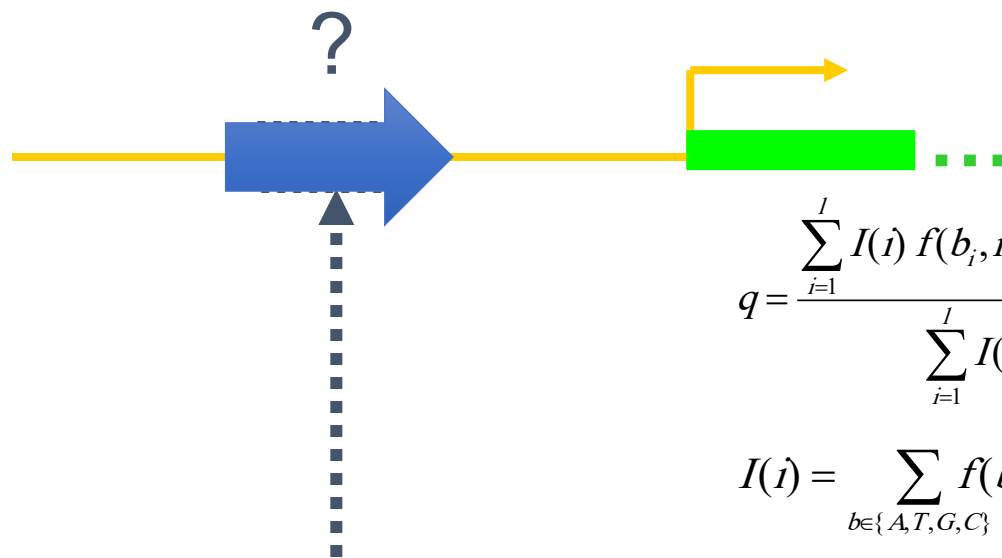
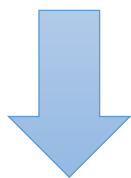
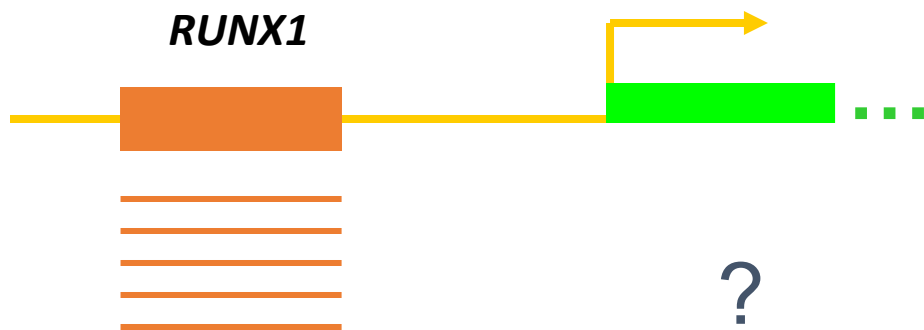
TRANSPATH™



TRANSFAC®



Search for new TF binding sites with PWMs



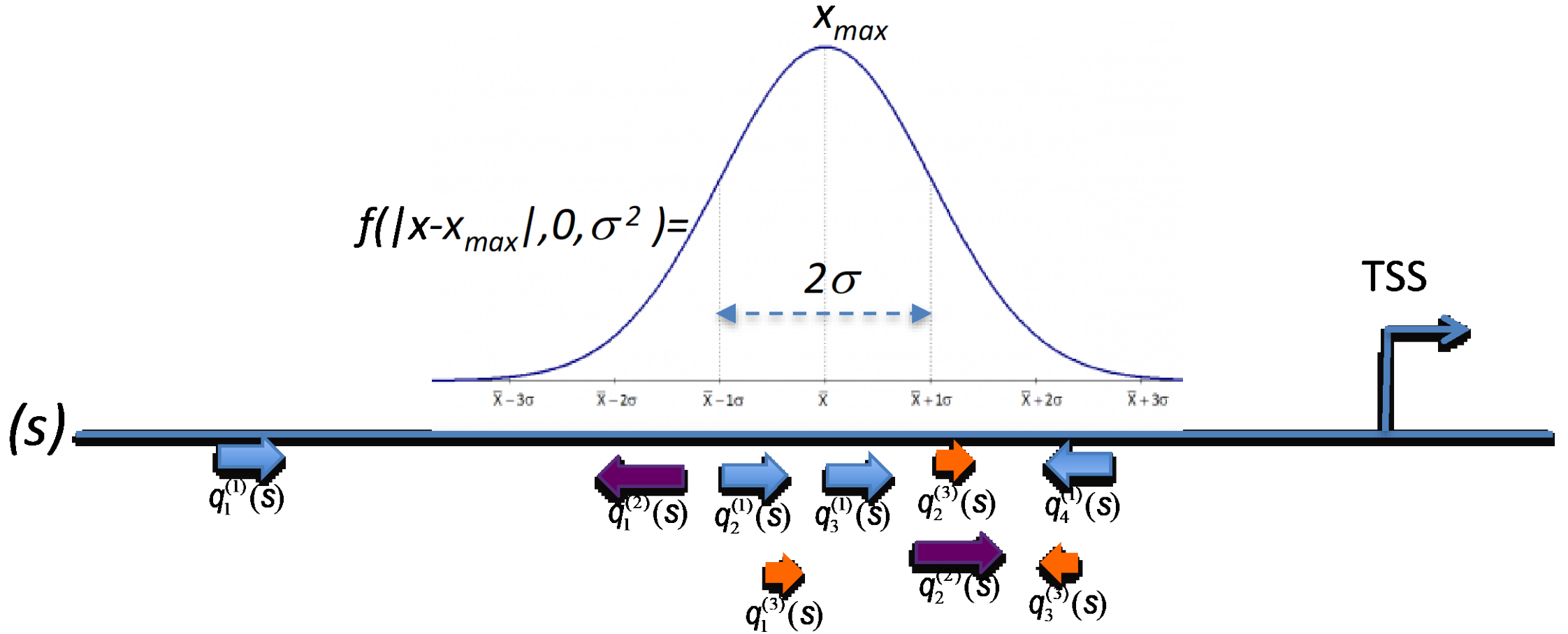
$$q = \frac{\sum_{i=1}^l I(i) f(b_i, i) - \sum_{i=1}^l I(i) f^{\min}(i)}{\sum_{i=1}^l I(i) f^{\max}(i)} \quad (1)$$

$$I(i) = \sum_{b \in \{A, T, G, C\}} f(b, i) \ln(4 f(b, i)) \quad (2)$$



TRANSFAC®

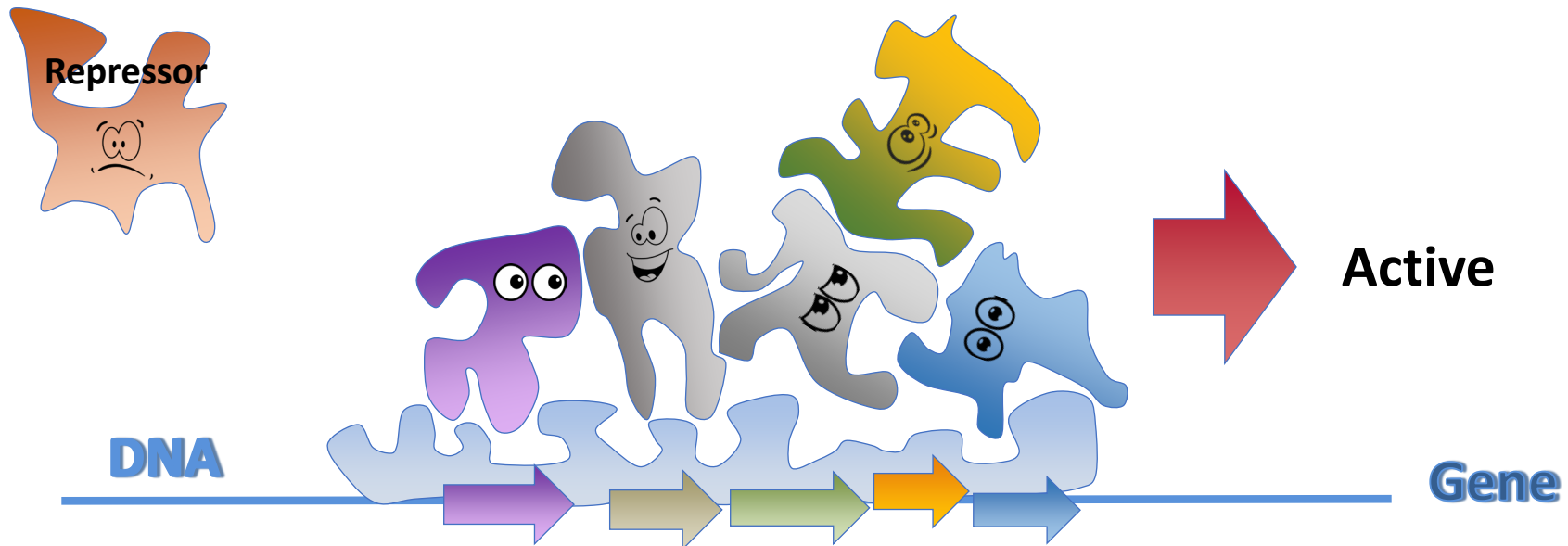
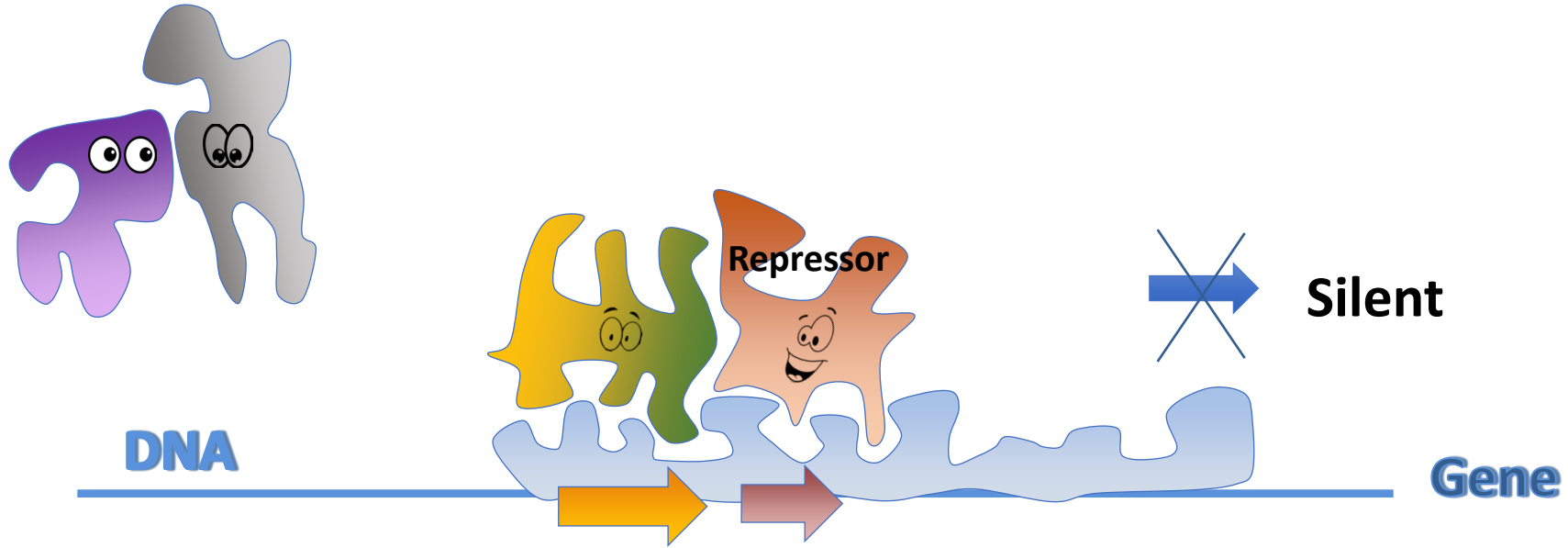
Composite model



V\$ASCL1_01 0.97; N=2	V\$HMGIY_Q6 0.96; N=2	V\$LEF1_05 0.78; N=3	V\$NKG25_08 0.97; N=2	V\$FRA1_Q6 1.00; N=2	V\$ZEB1_03 1.00; N=3
--------------------------	--------------------------	-------------------------	--------------------------	-------------------------	-------------------------

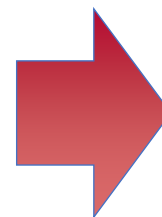
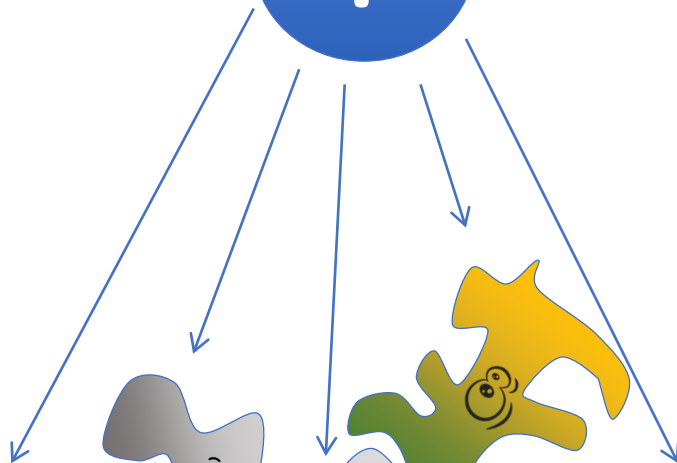
Module width: 148

It's a fuzzy puzzle!



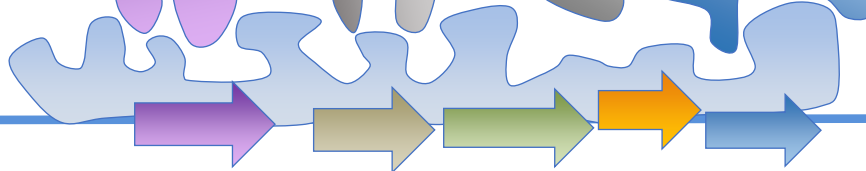


Master regulator ?



Active

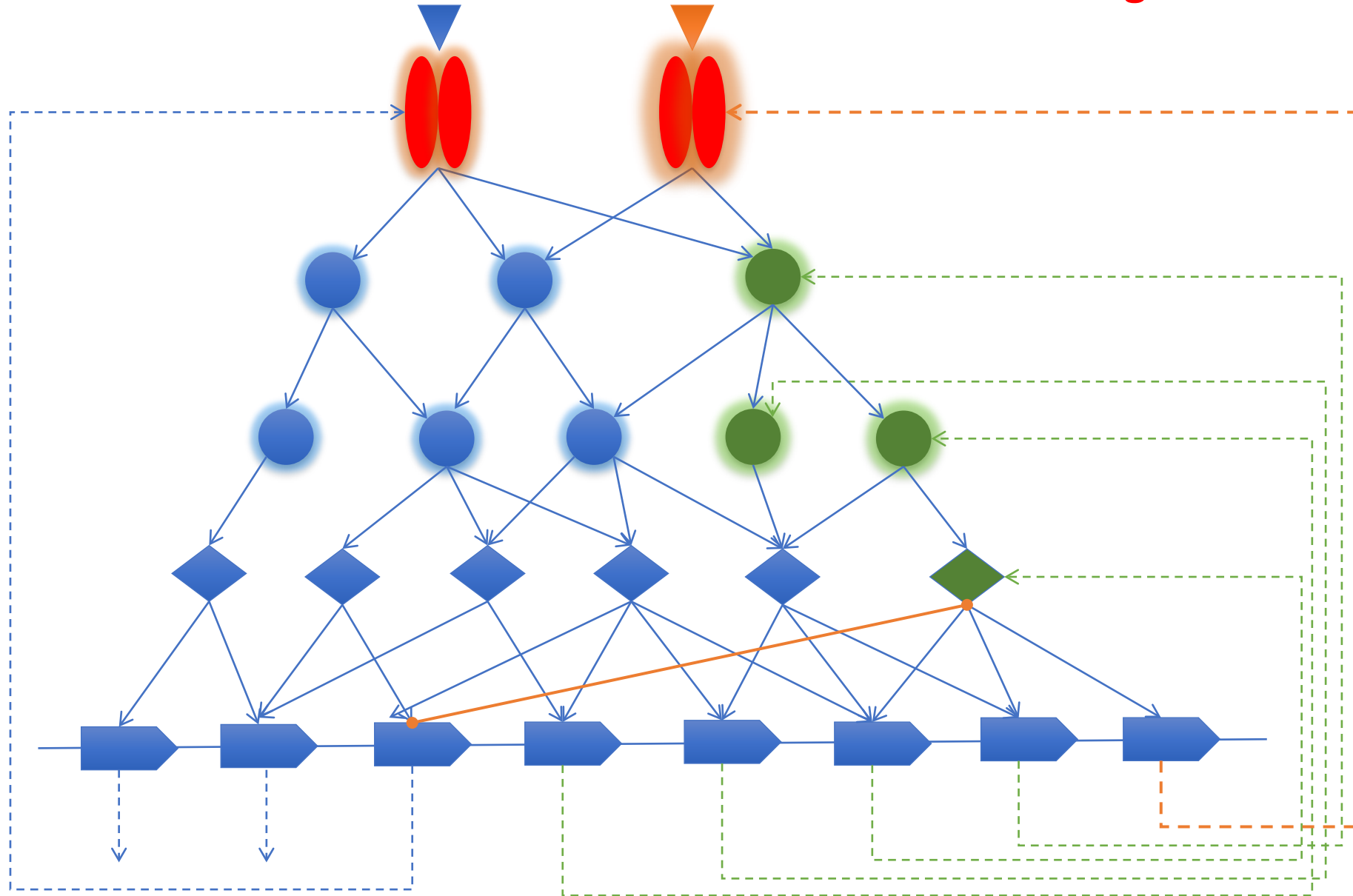
DNA



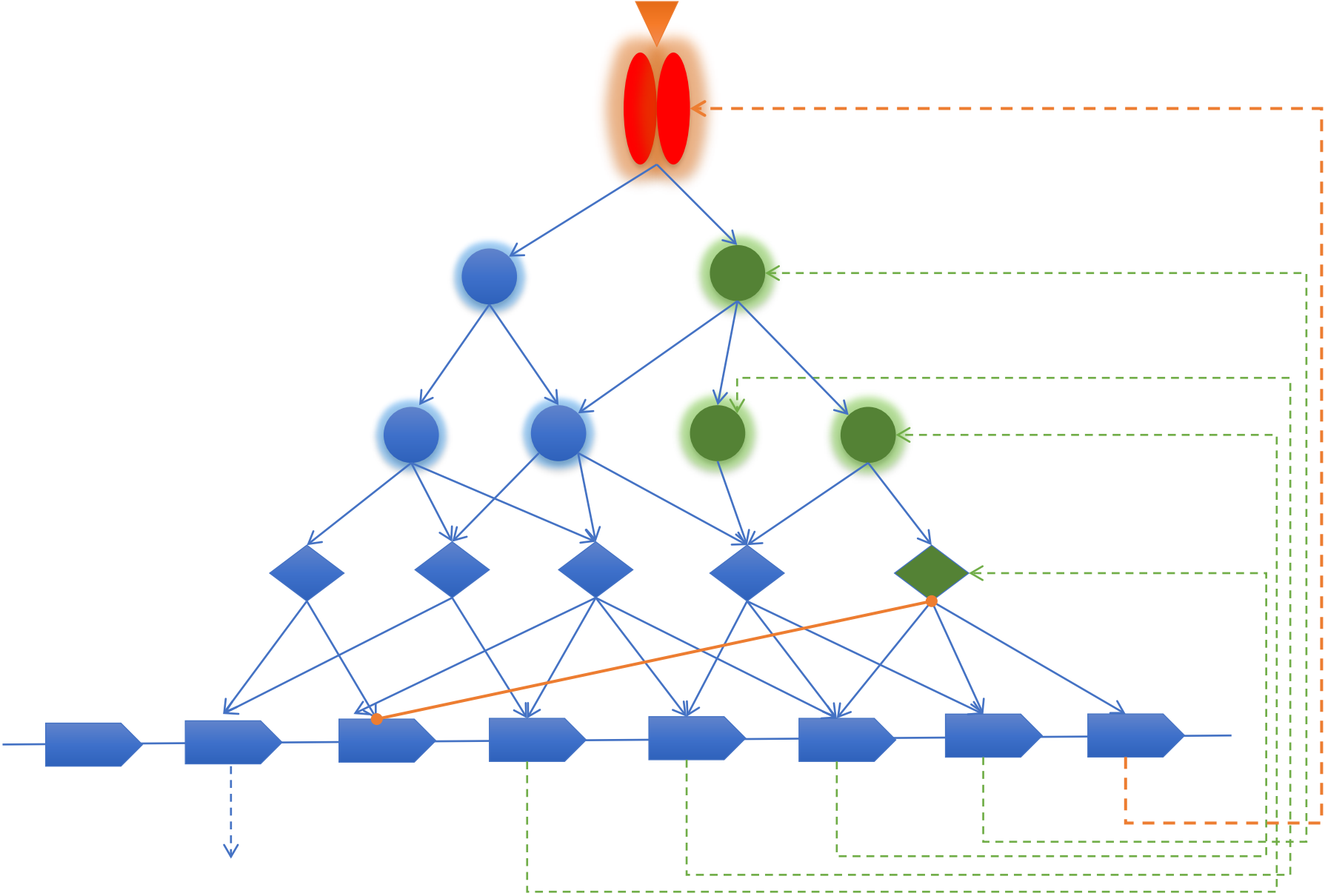
Gene

Master-regulator

New master-regulator



New master-regulator

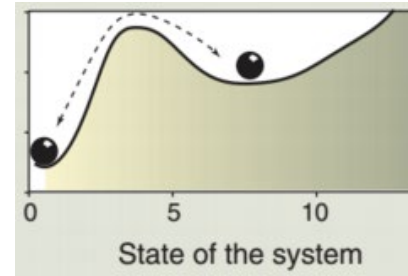
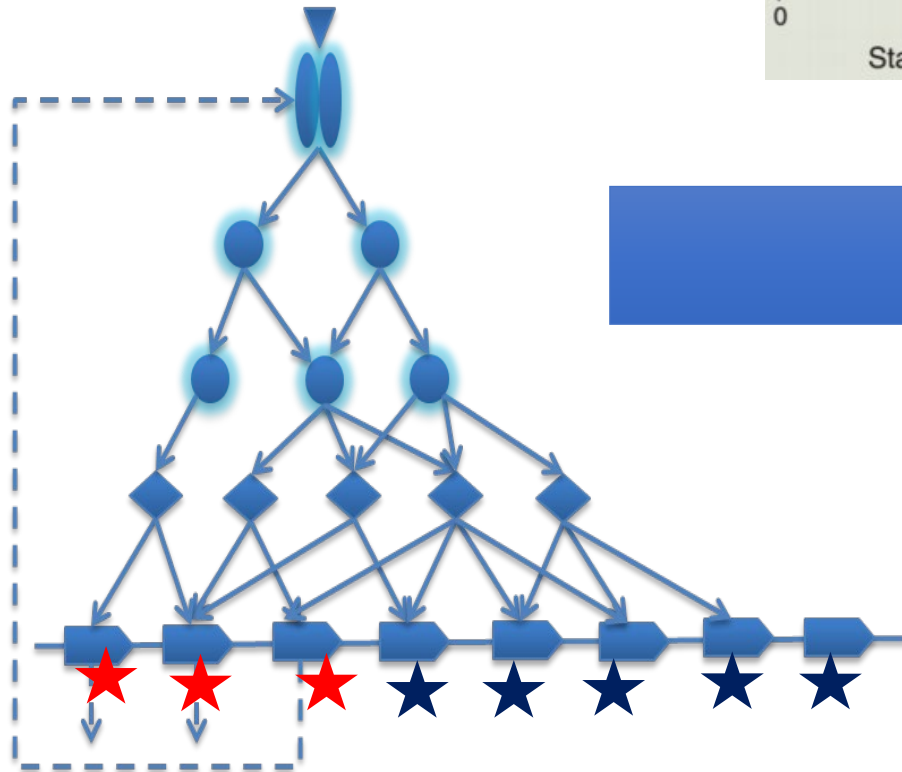


Walking pathways –

In cancer new rewired networks appear with multiple feedback loops

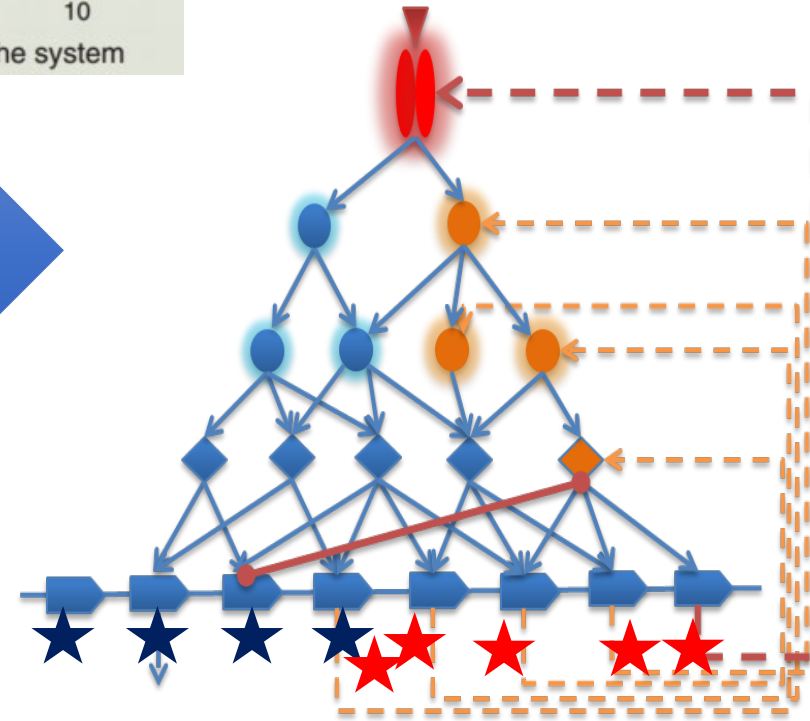
Healthy

Canonical pathways

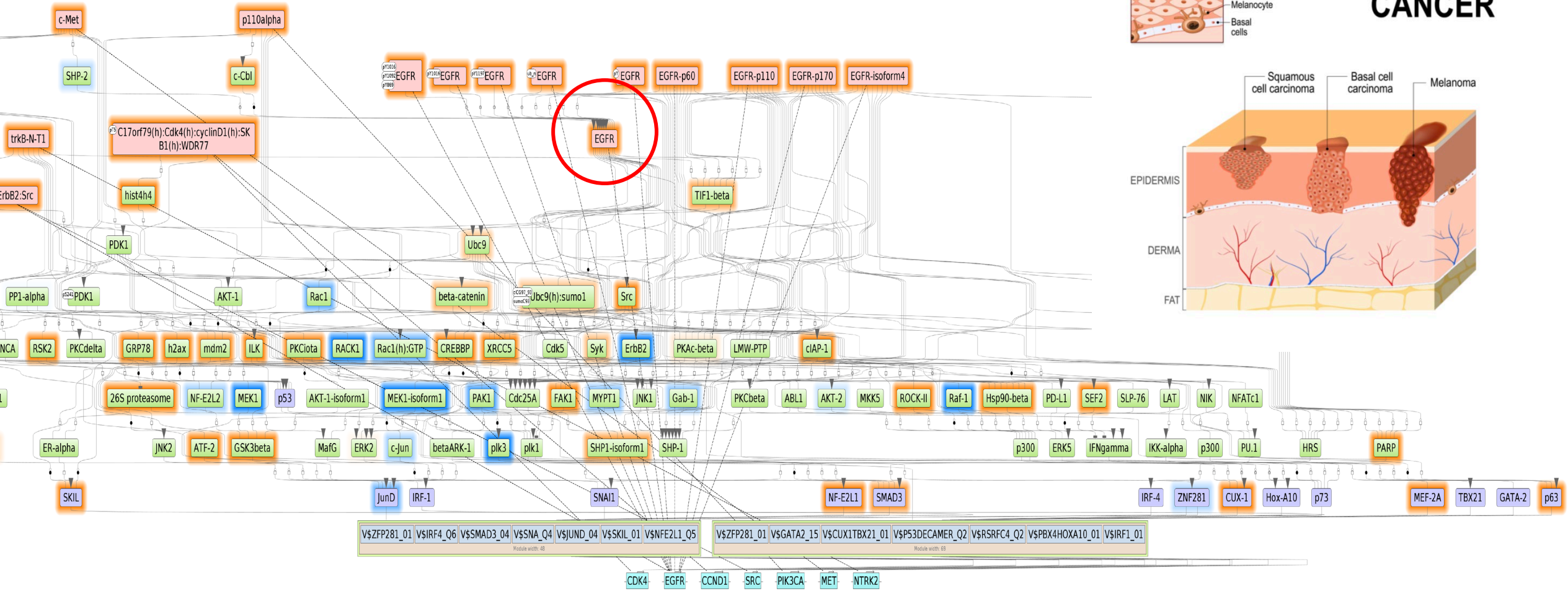


Cancer

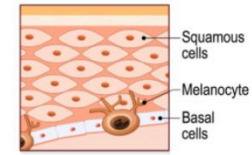
~~Canonical pathways~~



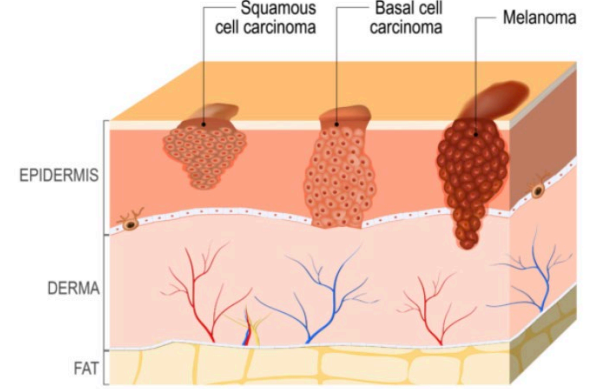
Master regulators of Squamous Cell Carcinoma



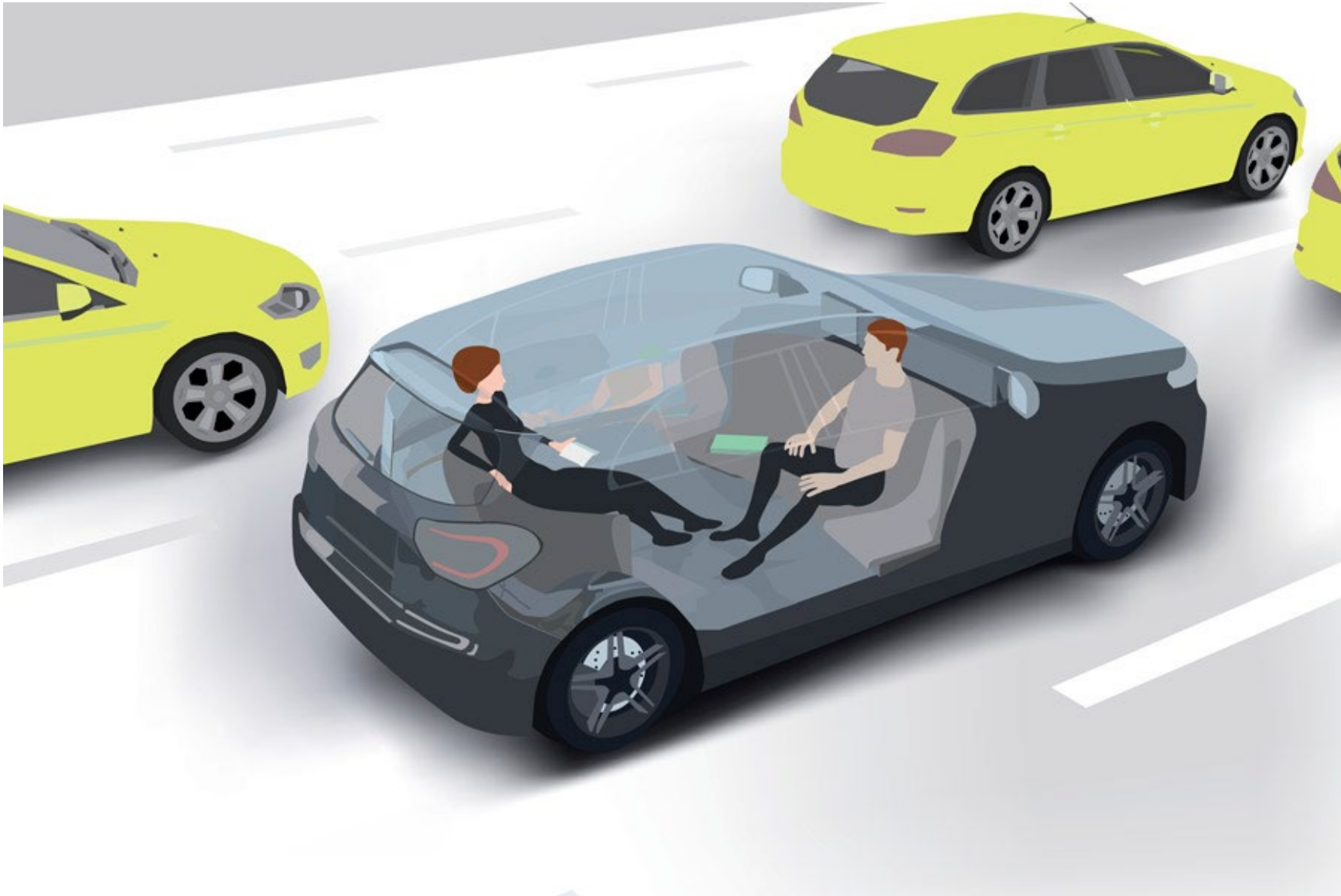
HEALTHY EPIDERMIS



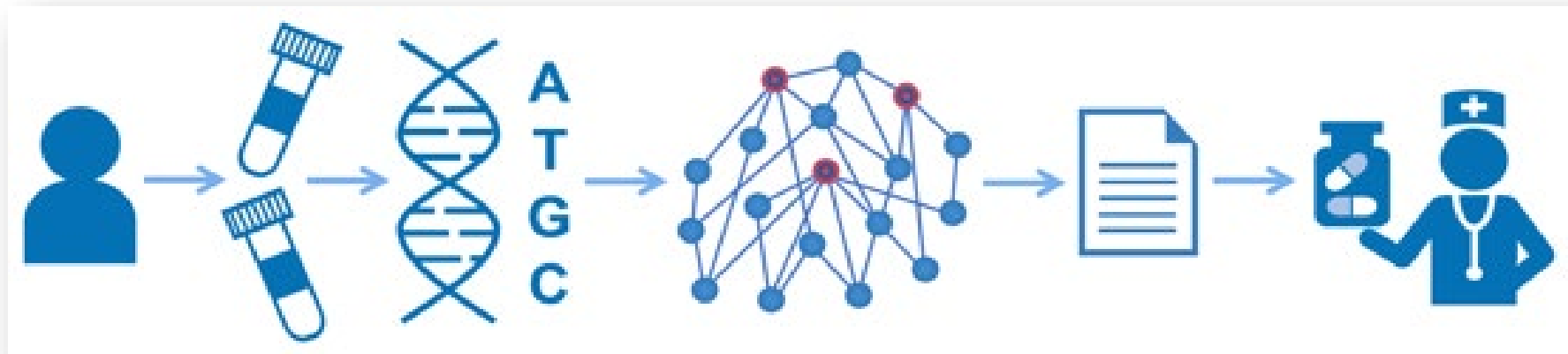
SKIN CANCER

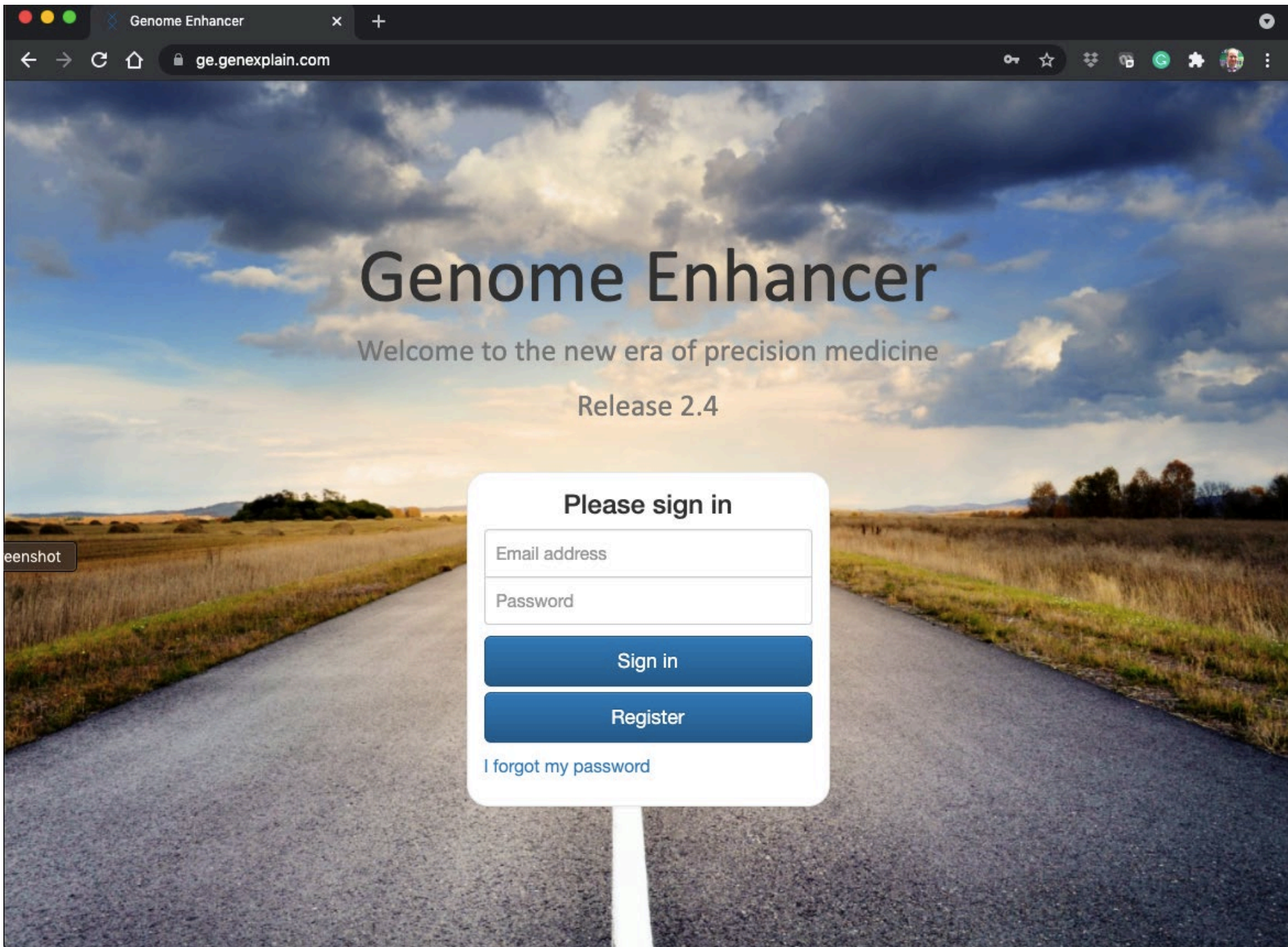


We would like AI to run the full data analysis completely automatic...



Genome Enhancer





Screenshot

Genome Enhancer

Welcome to the new era of precision medicine

Release 2.4

Please sign in

Sign in

Register

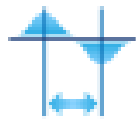
[I forgot my password](#)

Multi-omics data input

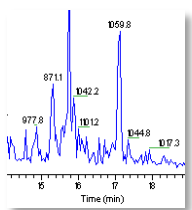
Transcriptomics



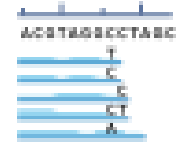
Epigenomics



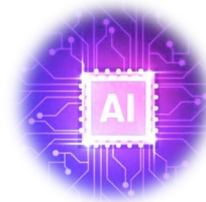
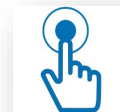
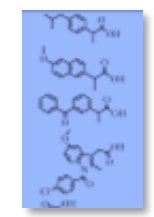
Proteomics



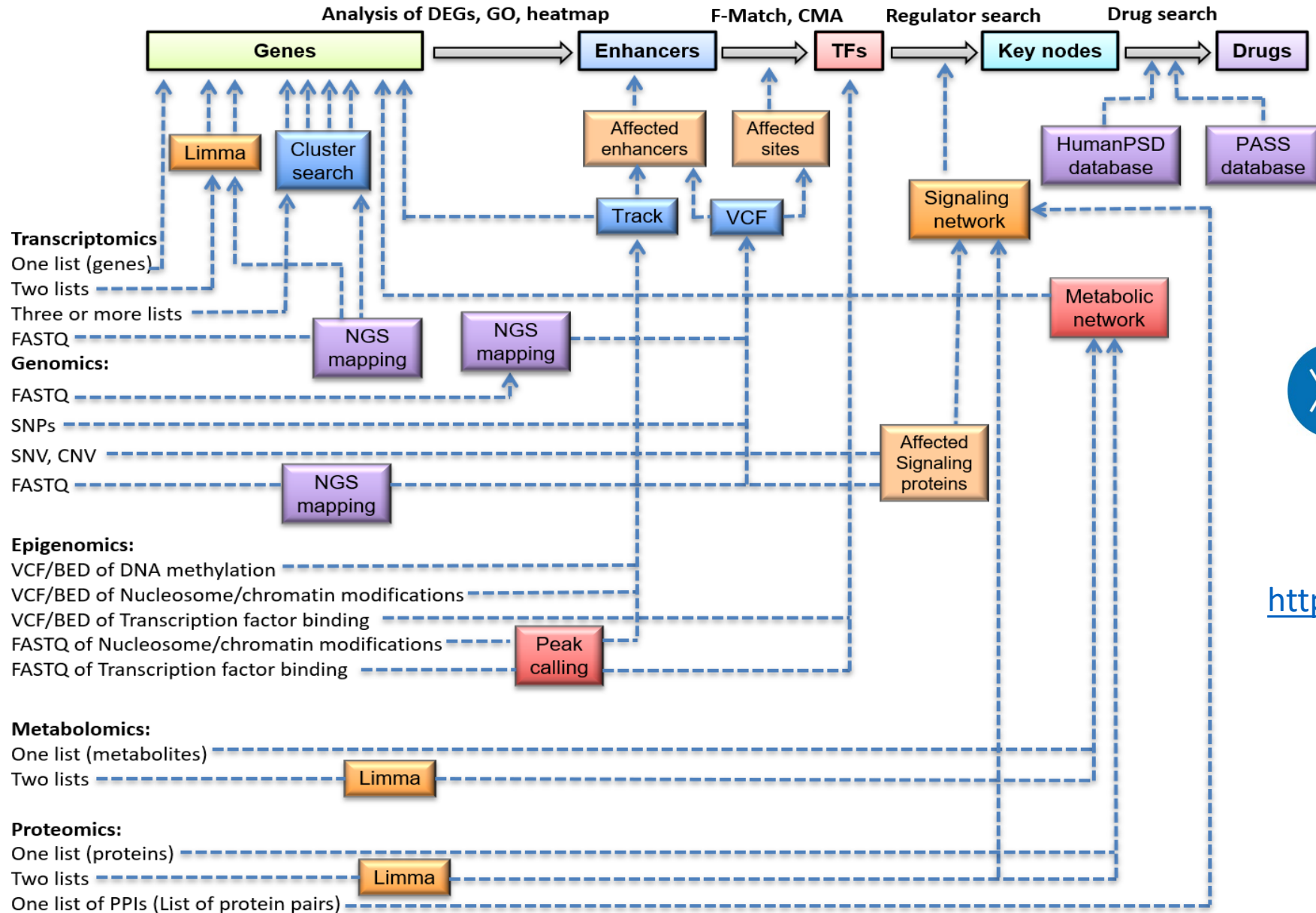
Genomics



Metabolomics



Overall analysis schema of Genome Enhancer pipeline



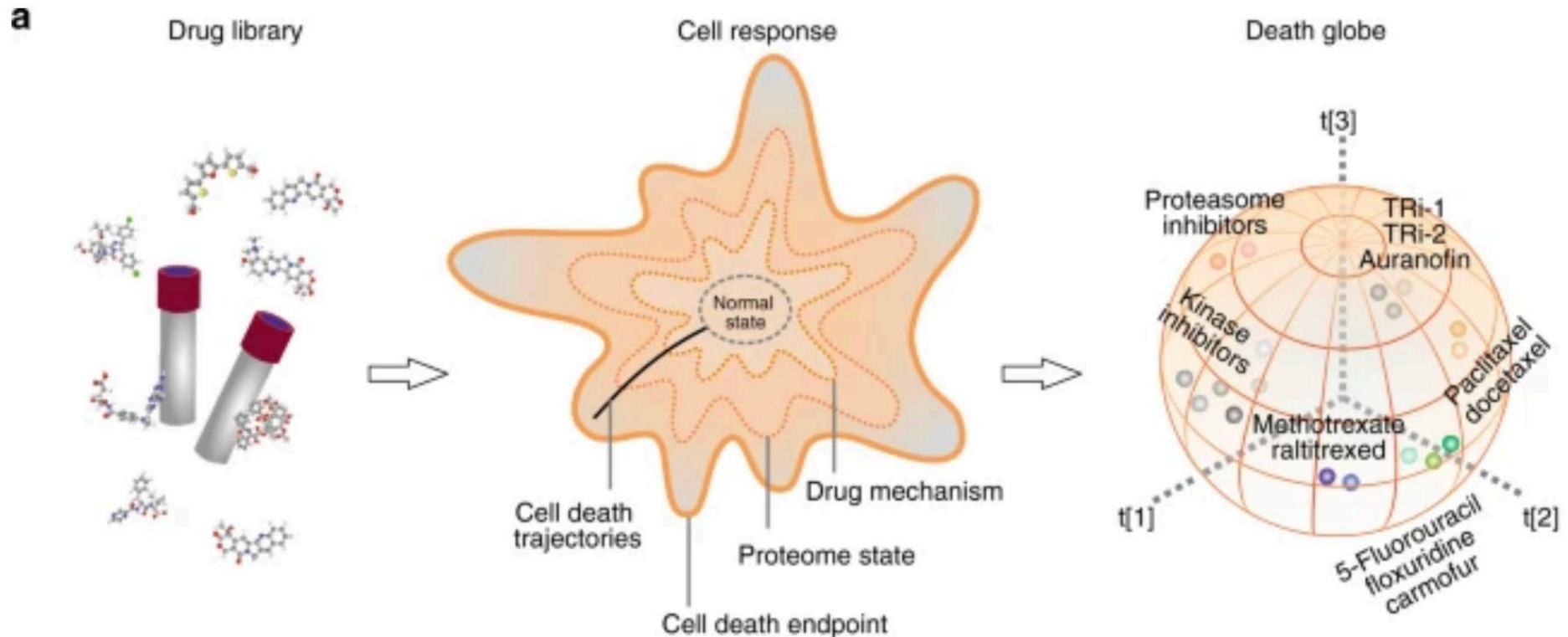
Full analysis description is available at <https://genexplain.com/genome-enhancer>

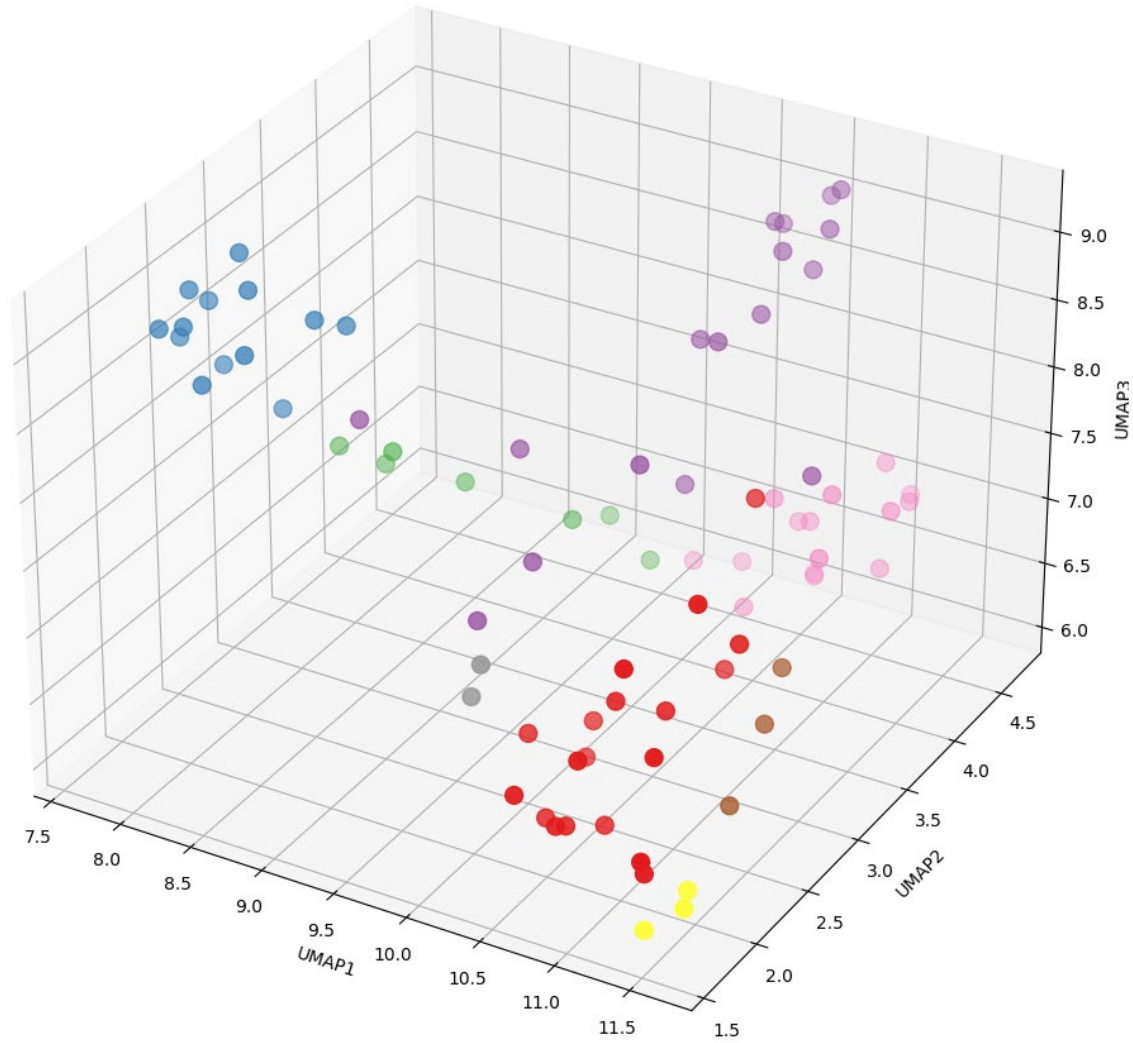
ProTargetMiner as a proteome signature library of anticancer molecules for functional discovery

[Amir Ata Saei](#), [Christian Michel Beusch](#), [Alexey Chernobrovkin](#), [Pierre Sabatier](#), [Bo Zhang](#), [Ülkü Güler Tokat](#), [Eleni Stergiou](#), [Massimiliano Gaetani](#), [Ákos Végvári](#) & [Roman A. Zubarev](#)

A collection of 56 compounds with LC50 below 50 μM was chosen to treat the cells (at LC50 concentrations) for 48 h in three replicates. With the biological effect (cell death) being of the same magnitude, the differences in the proteome states could be attributable to the differences in targets and MOAs.

The selected compounds belong to 19 different classes with versatile targets and MOAs





1)

Bosutinib
Enzalutamide
OSI-420
OSW-1
Pazopanib
Ponatinib
Temsirolimus
Vemurafenib
Vismodegib

2)

Methotrexate
Raltitrexed

3)

Auranofin
b-AP15
Bortezomib

4)

Axitinib
Bleomycin
Cabozantinib
Crizotinib
Doxorubicin
Epirubicin
Genistein
Nutlin

5)

Camptothecin
Idarubicin
Irinotecan
Teniposide
Topotecan

6)

2-methoxyestradiol
8-azaguanine
Afatinib
Apatinib
Azacitidine
Dasatinib
Docetaxel
Etoposide
Fludarabine
Gefitinib
Lapatinib
Lomustine
Mitotane
Nilotinib
Oxaliplatin
Paclitaxel
RITA
Ruxolitinib
Sunitinib
TRi-1
TRi-2
Vincristine

7)

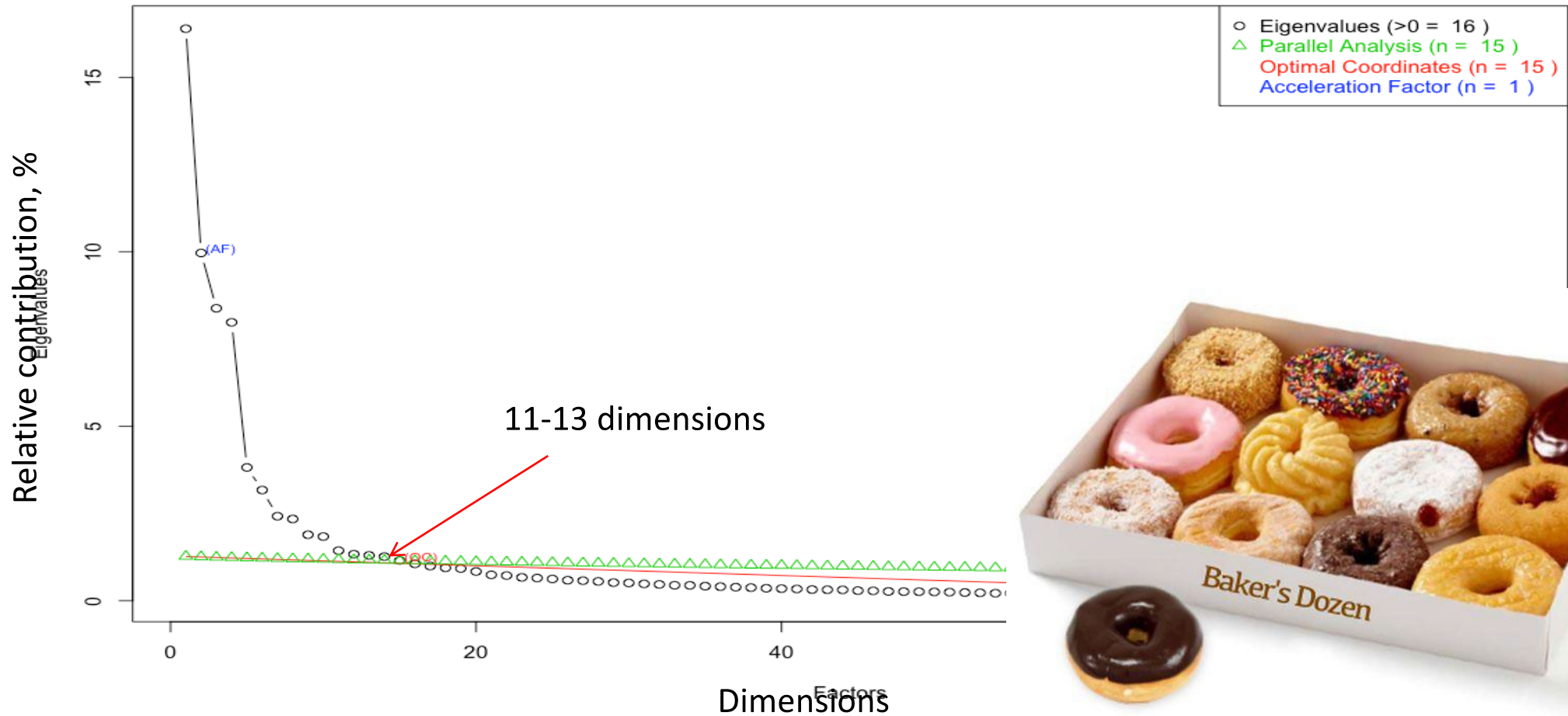
Everolimus
Regorafenib
Sorafenib

8)

5-fluorouracil
Carmofur
Floxuridine

ProTargetMiner: independent dimensions

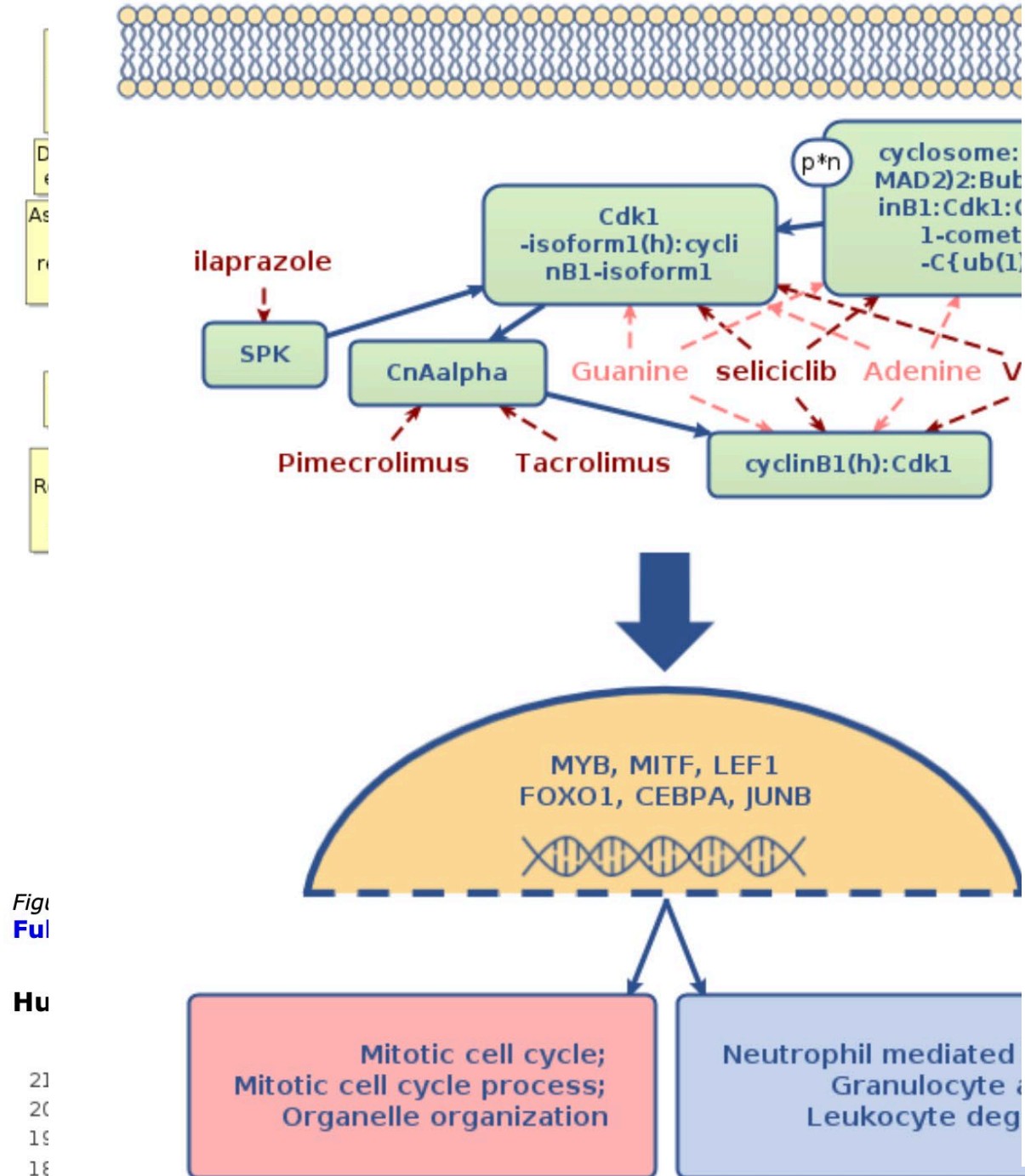
Non Graphical Solutions to Scree Test



Gene description	UniProt ID	ID	0.0	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0
cyclin dependent kinase inhibitor 1A	P38936	CDN1A	-6.71776	-2.54274	-2.7589	-1.89113	0.78327	0.03951	0.10672	-0.65994	1.12171	0.73564	-1.1489	0.28262	0.40526
ferredoxin reductase	P22570	ADRO	-4.84831	-3.14461	0.90517	-0.12392	0.6504	-0.95539	0.42728	-0.27265	0.23425	0.00445	-0.47115	0.06934	0.5528
cyclin D3	P30281	CCND3	-4.27616	-1.35253	-1.77641	-0.14039	-0.48123	0.18169	0.41496	0.15515	0.55012	0.03811	-0.13702	1.01853	0.48019
tumor protein p53 inducible protein 3	Q53FA7	QORX	-4.0781	-3.04711	1.52773	-0.9409	1.0147	-0.69369	-0.07911	-0.23578	0.2099	0.22718	-0.42647	-0.29831	0.06339
GM2 ganglioside activator	P17900	SAP3	-3.89386	0.4742	0.56136	-0.61055	-0.60819	0.21673	0.17415	-0.18978	-0.1127	0.5818	0.18433	0.66612	-0.11938
aldehyde dehydrogenase 3 family member A1	P30838	AL3A1	-3.46346	-1.93517	0.57744	0.15488	0.51692	-0.69978	0.27263	-0.06358	0.54375	-0.01895	-0.24192	0.38617	0.48712
retinol saturase	Q6NUM9	RETST	-3.45602	-0.11079	-0.02277	0.56648	1.1216	-0.6523	0.47834	-0.00584	-0.00839	0.01689	-0.22871	0.17291	0.20929
ISG15 ubiquitin like modifier	P05161	ISG15	-3.44174	-0.86203	-0.80653	-0.09544	0.98822	-0.61218	0.38777	-0.18338	-0.63773	0.65843	-0.38057	0.00881	-0.20995
apolipoprotein B mRNA editing enzyme catalytic subunit 3C	Q9NRW3	ABC3C	-3.31105	-1.43152	-0.1172	-0.31021	0.40477	-0.62832	0.2298	-0.02644	-0.27011	0.09338	-0.12171	0.33644	0.14304
tweety family member 3	Q9C0H2-2	TTYH3	-3.3083	-1.98603	1.29136	1.20735	-0.45074	-0.74074	0.40108	-0.49409	0.53751	0.18596	-0.42131	-0.05676	0.41174
galectin 3 binding protein	Q08380	LG3BP	-3.30432	0.78481	-0.51354	0.80121	0.12916	-0.20249	-0.13696	0.51126	-1.5475	0.14037	0.46105	-0.08528	-0.37475
sialic acid acetyltransferase	Q9HAT2	SIAE	-3.27895	-0.64528	1.26334	0.3737	0.522	-0.02861	0.7895	-0.05701	0.59655	-0.50014	0.33448	0.72912	-0.68829
Fas cell surface death receptor	P25445-6	TNR6	-3.21074	-3.9132	1.22782	-0.80143	0.82213	-0.73173	-0.25969	-0.31496	0.69161	0.0179	-0.76694	-0.4812	0.52847
vesicle associated membrane protein 8	Q9BV40	VAMP8	-3.13341	-0.79568	-0.07094	0.16346	0.45838	-0.4397	0.04053	0.46564	-0.53533	0.7034	-0.43848	-0.06591	0.17925
carboxymethylenebutenolidase homolog	Q96DG6	CMBL	-3.0879	-1.39734	0.91347	-0.67412	0.89214	-0.18543	-0.11458	-0.24912	0.24452	0.48519	-0.44272	-0.11514	0.02143
ribonucleotide reductase regulatory TP53 inducible subunit M2B	Q7LG56	RIR2B	-3.009	-2.30414	0.34167	-0.82028	0.47632	-0.51429	0.06976	-0.48735	0.35086	0.25516	-0.3361	-0.05478	0.15425
EPS8 like 2	Q9H6S3	ES8L2	-3.00707	-1.74905	0.55805	0.22149	0.76085	-1.04509	0.0797	0.20886	0.50428	0.19338	-0.3811	0.16304	0.25934
XPC complex subunit, DNA damage recognition and repair factor	Q01831	XPC	-2.90804	-1.26273	0.42362	0.57105	0.8116	-0.41067	0.33498	0.3583	-0.09473	-0.0364	-0.10575	-0.20473	0.16333
NAD synthetase 1	Q6IA69	NADE	-2.86049	0.38621	-0.36804	0.35504	0.18207	-0.6095	0.27844	-0.09442	0.5574	-0.32094	-0.03608	0.41742	0.26918
phospholipase D family member 3	Q8IV08	PLD3	-2.82663	0.26761	0.06756	0.45787	-0.01074	-0.20648	0.82921	-0.03474	-0.1711	0.51612	-0.57052	-0.40184	-0.03066
PBX homeobox interacting protein 1	Q96AQ6-2	PBIP1	-2.71269	1.23979	0.23822	0.11469	-0.46697	-0.13145	0.36363	-0.49658	0.22696	0.21145	0.38954	-0.27713	-0.21122
tripartite motif containing 3	O75382	TRIM3	-2.57502	-0.80234	-0.00299	0.11894	0.39687	-0.56307	0.45183	-0.19021	0.3407	-0.12	-0.18527	-0.02408	0.30677
stomatin	P27105	STOM	-2.52608	-0.85628	0.62988	-0.22787	-0.15514	-0.35522	0.25282	0.04006	-0.30531	0.28753	-0.04374	0.12043	0.08624
major vault protein	Q14764	MVP	-2.51314	0.98911	-1.4358	-0.46568	-0.73025	1.01275	-1.23309	0.55022	0.10428	0.53785	0.41825	-0.02991	-0.58742
adenylate kinase 1	P00568	KAD1	-2.47422	-1.16023	0.32014	-0.42879	0.67435	-0.38717	0.0063	-0.04081	0.22196	0.24937	0.01411	0.11255	0.37749
MICAL like 1	Q8N3F8	MILK1	-2.39636	-1.21341	-0.07729	0.08818	0.75265	-0.62939	0.26001	0.16362	0.31587	-0.14299	-0.1268	0.09342	0.38684
programmed cell death 4	Q53EL6-2	PDCD4	-2.37428	0.27981	-0.27825	0.462	-0.09973	0.27886	0.88386	-0.16984	-0.26785	0.41514	0.75117	-0.41729	-0.67889

Seq
3.
M/ We l
tal
ac
fac
ge
In tl
Gen
2) a
Tabl
See
alex
Data
Genc
Abs
In tl
cont:
pipel
path
regu
calle
drug
the i

GO (t
D
As
mito
mit
DNA
ce
DN
Hu
21
20
19
18



Drugs approved in clinical trials for Oncology



Table 12. Clinically approved (FDA, EMA, etc.) drugs for the clinically approved treatment candidates selected for the literature curation in HumanPSD™ database

[See full table](#) →

Name	Target names	Drug score	Disease activity score	Disease
Imatinib	STK10, RPS6KA3, MET, ABL1, PAK2, GSK3B, PRKCA... (more)	97	12	Phase 4 Gastrointestinal Tumors Leukemia Chronic
Sunitinib	STK10, RPS6KA3, MET, ABL1, PAK2, GSK3B, PRKCA... (more)	94	8	Phase 3 Adenocarcinoma Cell, Breast Breast Carcinoma
Erlotinib	STK10, RPS6KA3, MET, ABL1, PAK2, GSK3B, PRKCA... (more)	94	7	Phase 3 Neoplasia Carcinoma Adenocarcinoma Carcinoma Hepatocellular
Doxorubicin	MAPK14, TGM2, SP3, SRC, H2AX, TOP2A, TOP1	92	12	Phase 4 Abscess Neoplasia Lymphoma Carcinoma (more)
Tegafur	ITGA5, ITGB5, EGFR, ITGB1, MTOR, PTK2, FGF2	92	7	Phase 3 Adenocarcinoma Carcinoma Squamous Cholangiocarcinoma (more)

Fig
Full

Hu

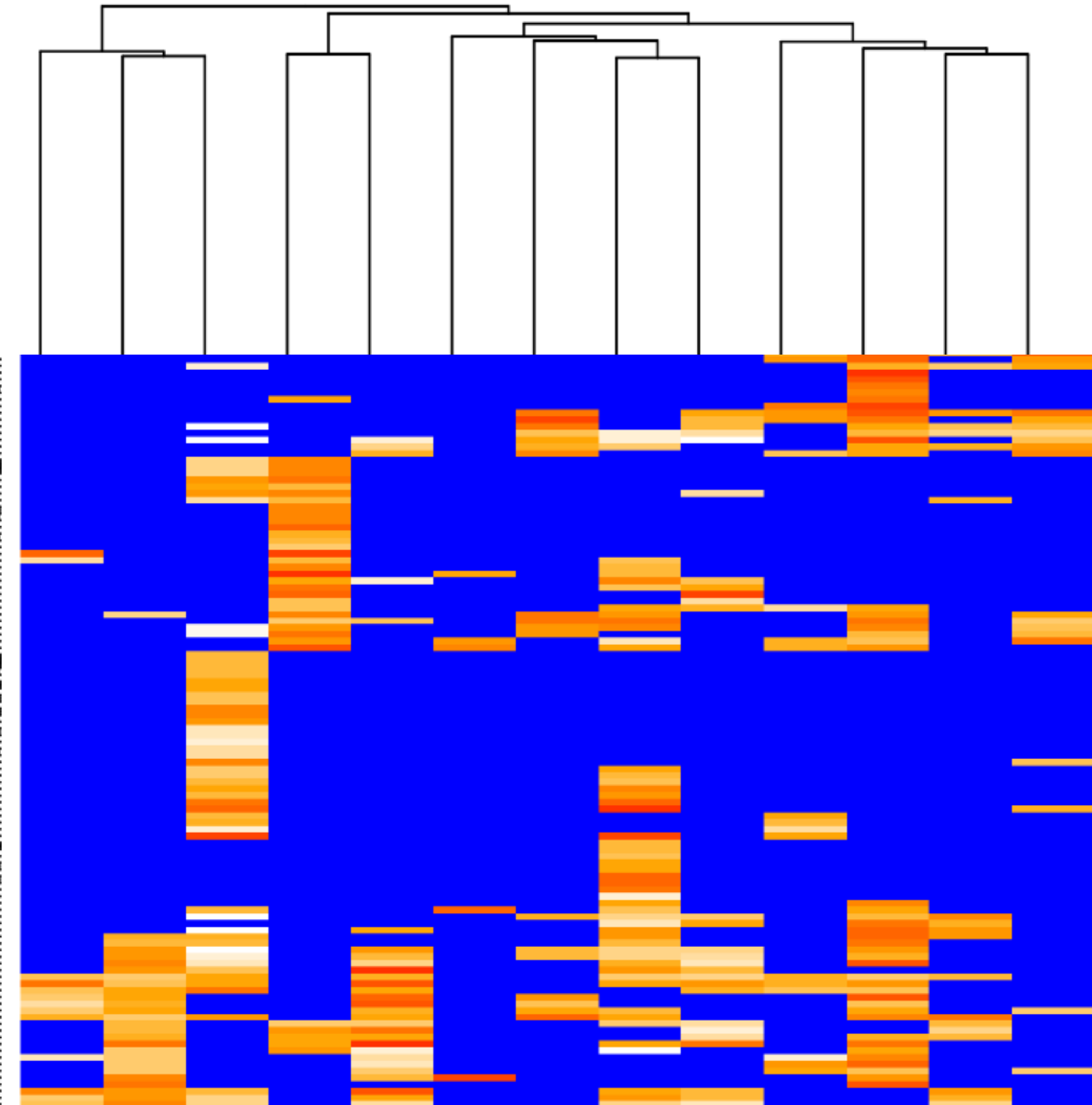
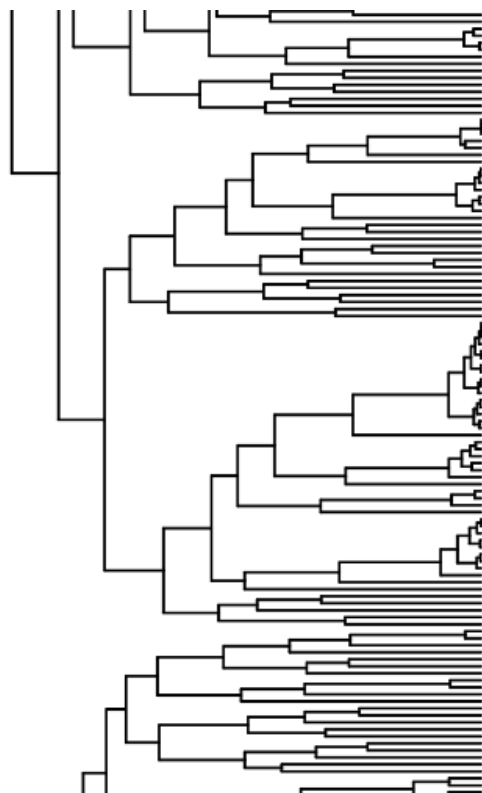
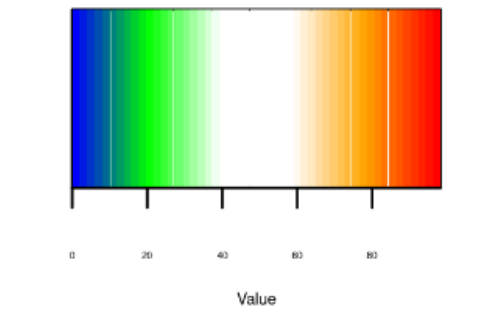
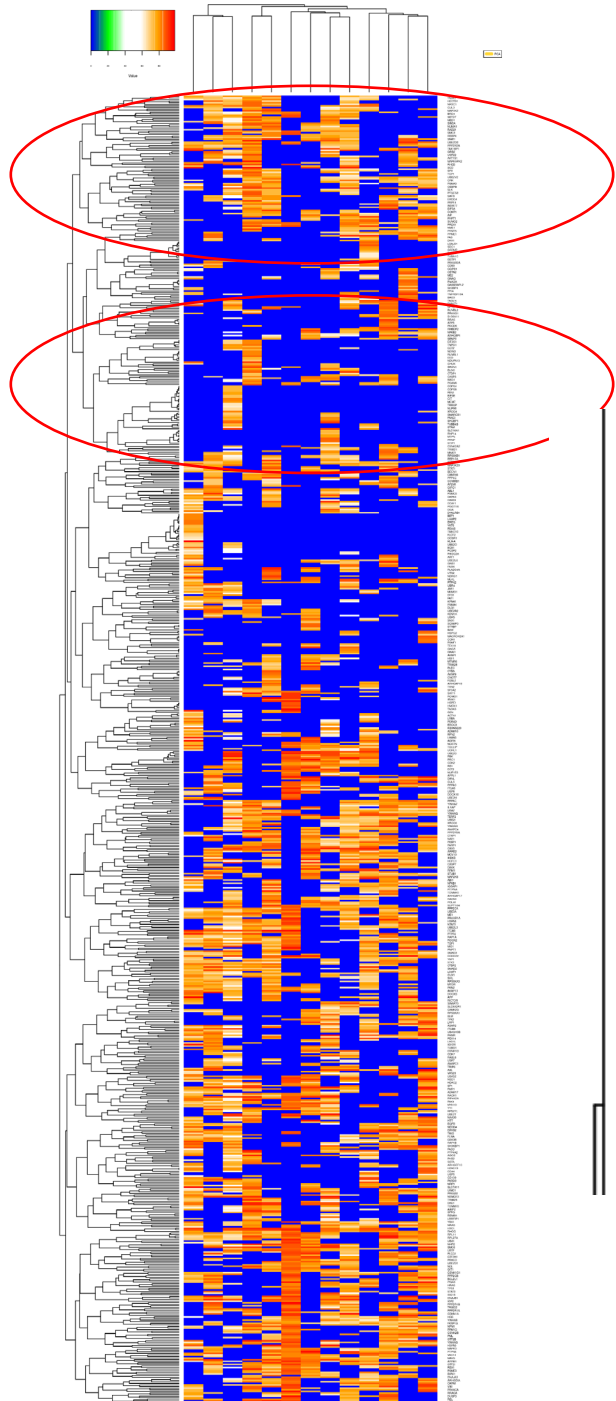
**HOW MANY DRUG TARGETS DO WE
NEED?**

826

First Previous Page 1 of 17 Next Last Showing 1 to 50 of 826 entries

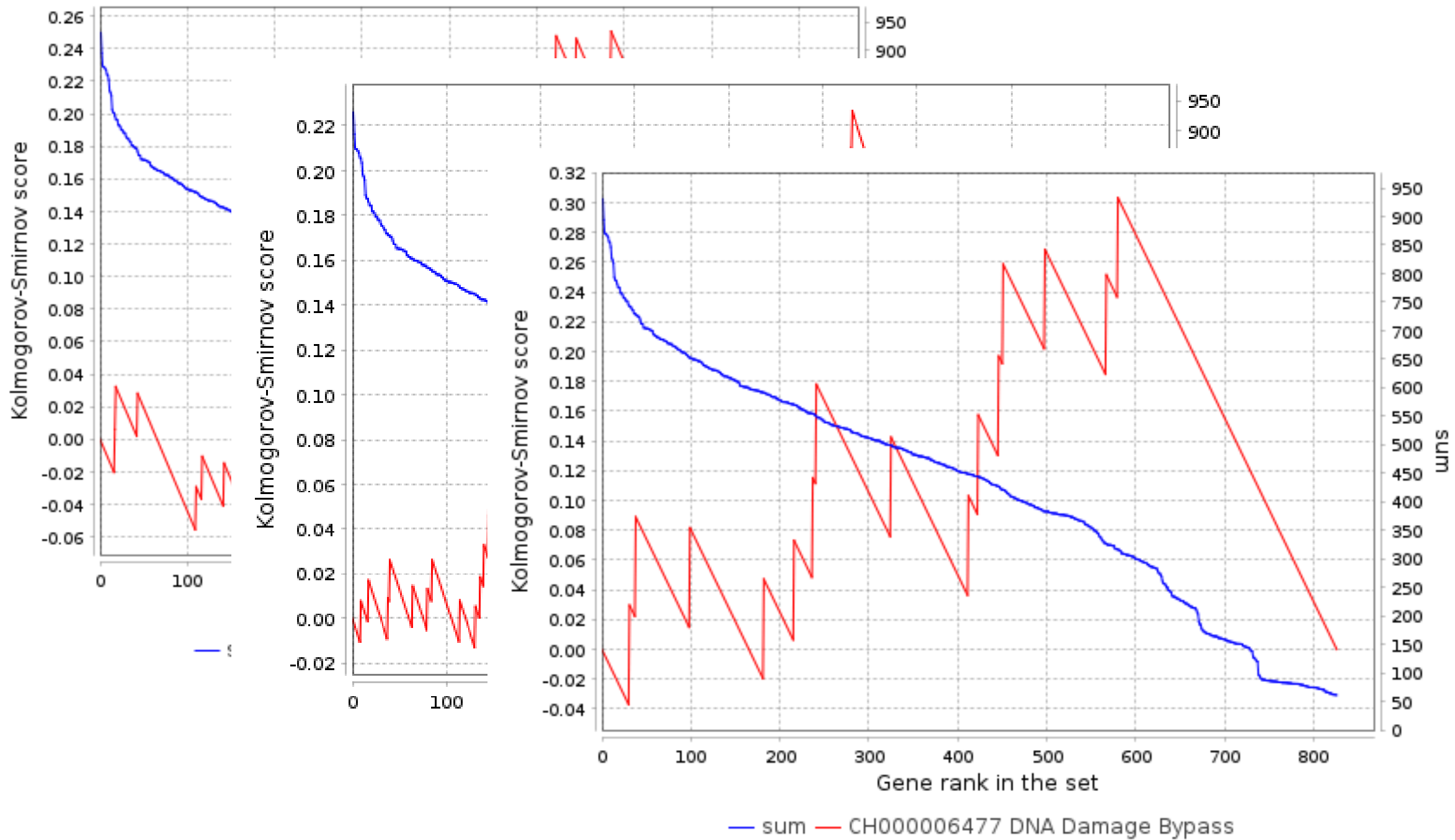
Show 50

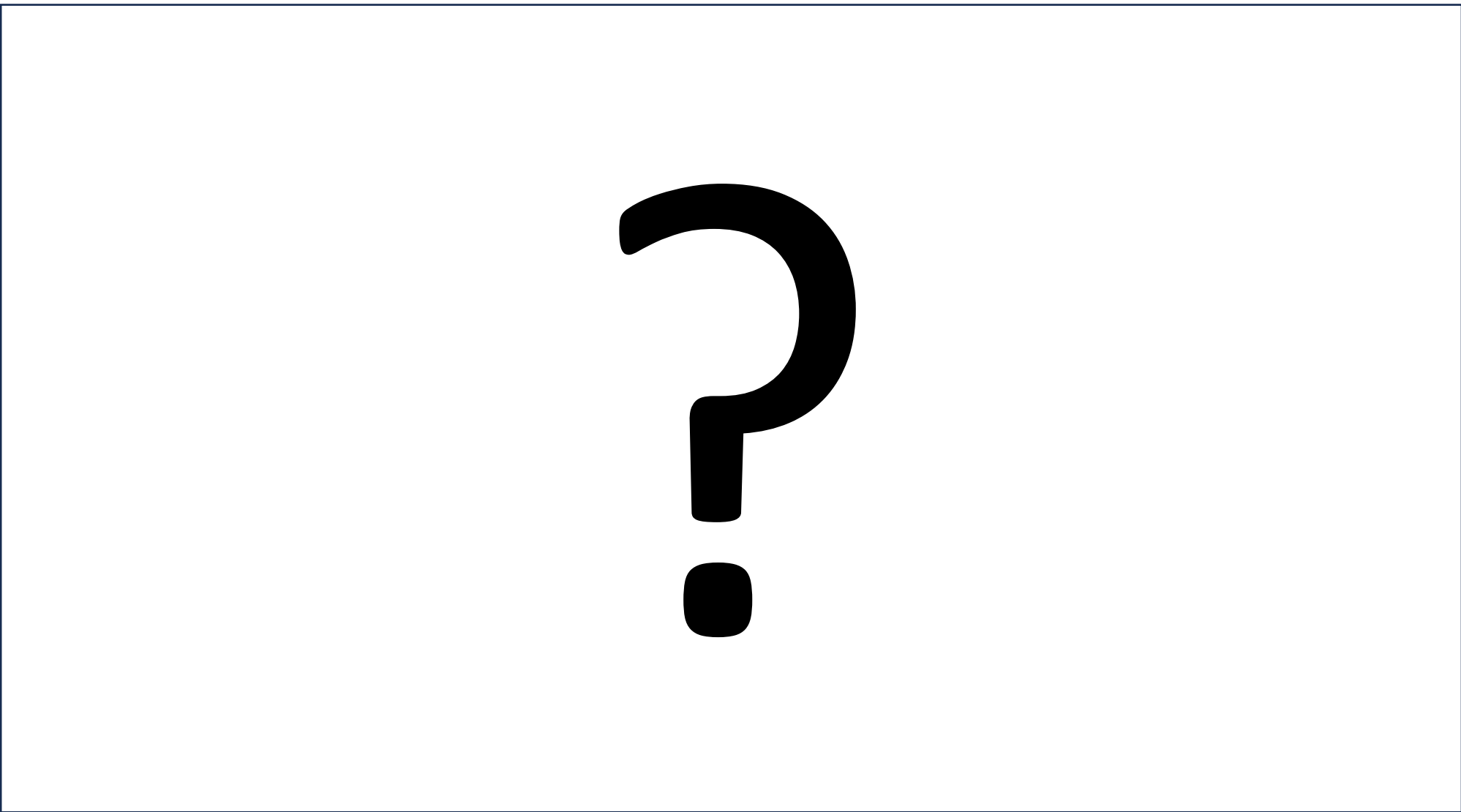
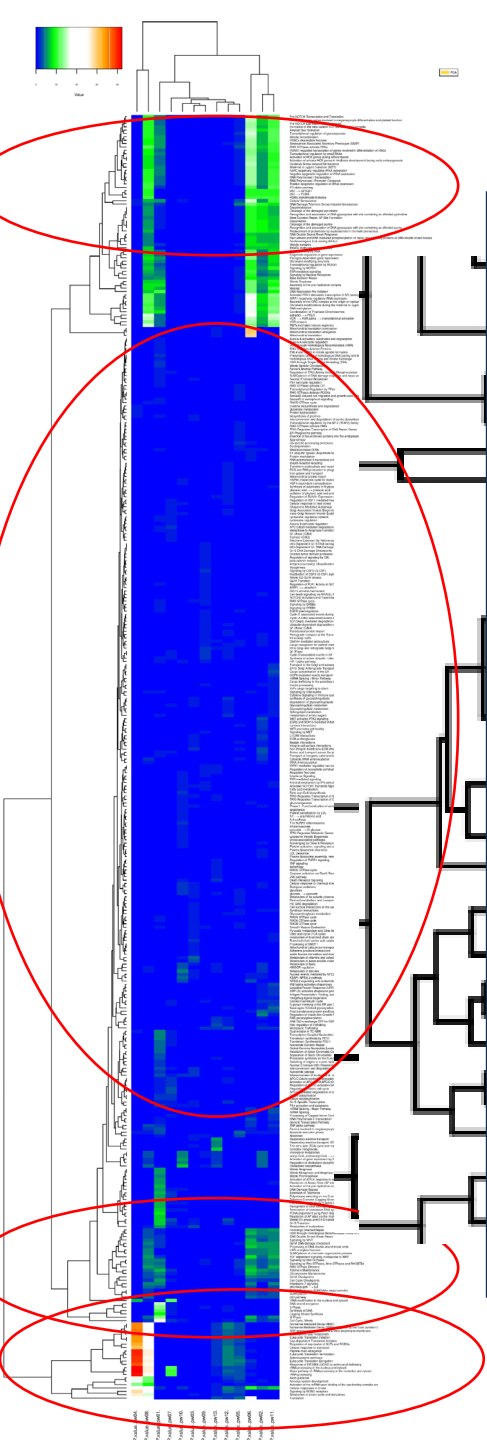
ID	Gene description	UniProt ID	ID	r01	r02	r03	r04	r05	r06	r07	r08	r09	r10	r11	r12	r13
MAD2L1	mitotic arrest deficient 2 like 1	Q13257	MD2L1	96.9875	0	67.2875	77.7125	0	76.5125	93.2	69.225	0	70.3375	79.625	0	0
PBK	PDZ binding kinase	Q96KB5	TOPK	95.6875	0	84.2375	71.8625	0	0	85.875	0	0	82.2875	0	87.4625	0
PRC1	protein regulator of cytokinesis 1	O43663-4	PRC1	94.3	0	73.0625	98.225	0	0	77.6625	0	0	83.1875	0	87.725	0
UBE2C	ubiquitin conjugating enzyme E2 C	O00762	UBE2C	93.35	0	82.525	90.975	0	0	90.25	0	0	76.2125	0	92.55	0
CCNB1	cyclin B1	P14635	CCNB1	92.6375	0	81.8875	81.475	0	0	89.825	0	0	80.9875	0	86.2625	0
UBE2T	ubiquitin conjugating enzyme E2 T	Q9NPD8	UBE2T	92.05	0	0	81.0375	0	73.1375	93.8125	0	78.2875	0	0	92.1125	86.45
PPP3CA	protein phosphatase 3 catalytic subunit alpha	Q08209-2	PP2BA	91.075	76.775	89.9125	0	74.8125	74.7125	0	0	87.175	0	0	0	80.275
UBE2S	ubiquitin conjugating enzyme E2 S	Q16763	UBE2S	90.7875	0	0	0	0	86.55	80.575	0	0	0	0	92.6375	69.7
CBX5	chromobox 5	P45973	CBX5	90.5	0	93.0125	86.9375	78.3625	84.9375	95.075	0	71.325	91.7125	82.55	0	0
RACGAP1	Rac GTPase activating protein 1	Q9H0H5	RGAP1	90.425	0	79.8375	93.1875	0	0	0	84.4125	0	81.4125	76.7625	0	73.925
H3C1	H3 clustered histone 1	P68431	H31	90.2375	89.65	88.0875	0	78.475	91.1375	84.7375	89.1625	0	75.675	93.925	88.6375	0
H4C1	H4 clustered histone 1	P62805	H4	90	87.1625	87.1375	0	74.2125	89.6	85.1375	87.0625	0	79.1125	91.7125	92.7125	0
CCDC22	coiled-coil domain containing 22	O60826	CCD22	89.9125	83.7875	78.875	93.9125	79.4875	0	0	0	73.9375	0	84.9125	94.3875	96.1125
MID1	midline 1	O15344	TRI18	89.575	68.8875	79.625	0	0	0	0	0	85.8375	0	78.725	90.3625	78.0625
ITGB5	integrin subunit beta 5	P18084	ITB5	89.525	94.1625	81.7375	0	0	88.2125	0	0	88.025	0	94.75	95.0875	0
ITGB6	integrin subunit beta 6	P18564-2	ITB6	89.525	78.3625	73.5625	0	95.6	0	82.175	0	88.025	0	0	0	0
RHEB	Ras homolog, mTORC1 binding	Q15382	RHEB	89.45	89.4	0	0	0	90.1125	0	0	0	68.8625	0	90.8375	70.325
TOP2A	DNA topoisomerase II alpha	P11388	TOP2A	89.325	0	91.875	91.0125	0	0	88.475	0	0	86.9625	0	90.7125	0
TK1	thymidine kinase 1	P04183	KITH	89.275	0	78.3625	0	0	0	88.425	0	0	0	0	0	0
NSMCE1	NSE1 homolog, SMC5-SMC6 complex component	Q8WV22	NSE1	87.65	79.65	0	91.725	92.925	91.2125	93.1	0	90.125	77.35	0	0	0
NSMCE3	NSE3 homolog, SMC5-SMC6 complex component	Q96MG7	NSE3	87.65	79.65	0	0	92.925	91.2125	93.1	82.175	90.125	0	0	0	0
SMC5	structural maintenance of chromosomes 5	Q8IY18	SMC5	87.65	79.65	0	91.725	92.925	91.2125	93.1	0	90.125	0	74.525	86.5875	0
SMC6	structural maintenance of chromosomes 6	Q96SB8	SMC6	87.65	0	0	91.725	92.925	91.2125	93.1	82.175	90.125	77.35	0	86.5875	0



PCA

- S100A11
- RRAS
- ARF5
- PDGFB
- RHBDF2
- NFKB2
- ARHGAP1
- SENP3
- EIF2S1
- TNPO1
- CCT2
- NONO
- RUVBL1
- EED
- NDUFA13
- CHUK
- SRXN1
- ELOC
- CTOP1
- CASP3
- BAG4
- PGAM5
- COPFS4
- COPFS8
- FEN1
- EIF3E
- CIT
- MCM7
- TRRAP
- NUP98
- XRCC4
- SMARCB1
- FANCI
- SHCBP1
- TUBB4B
- STAM
- SLC16A1
- RNF14
- MTPN
- PRNP
- STIP1
- CSNK2A2
- TRIM21
- MNAT1
- RPS8KB1
- PPP1CA
- STRN
- MAP3K20
- STAT1
- BECN1
- CEKRN6
- PPP4C
- COMMD1
- AP2M1
- GIPC1
- ABL1

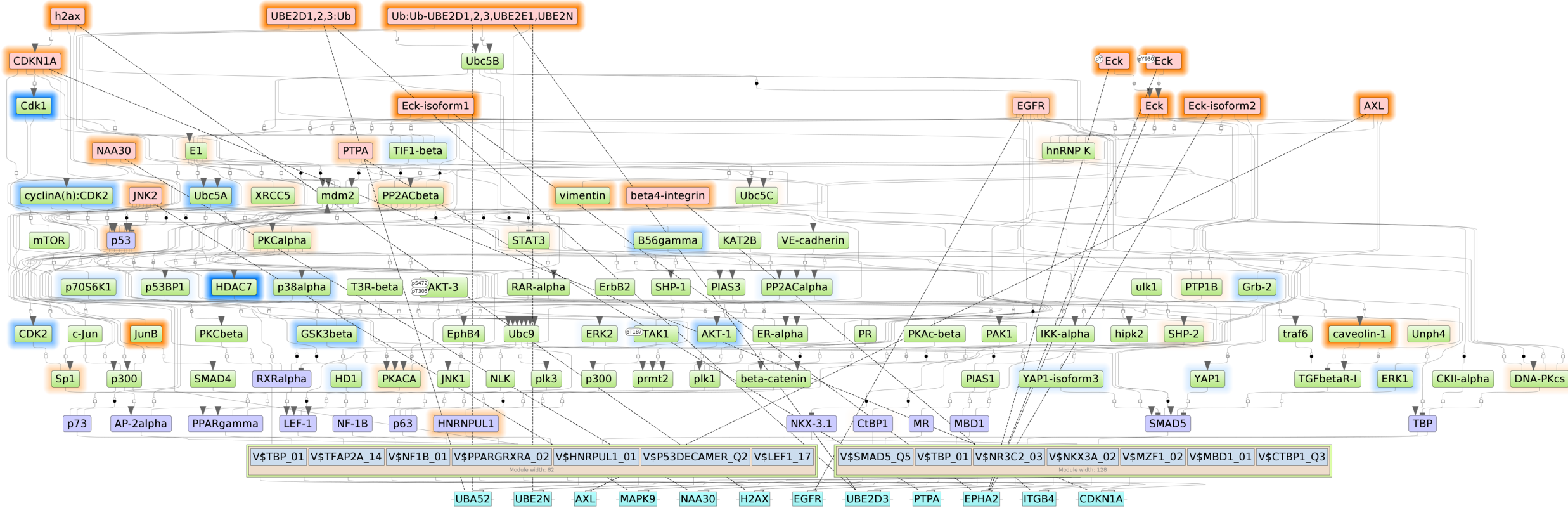




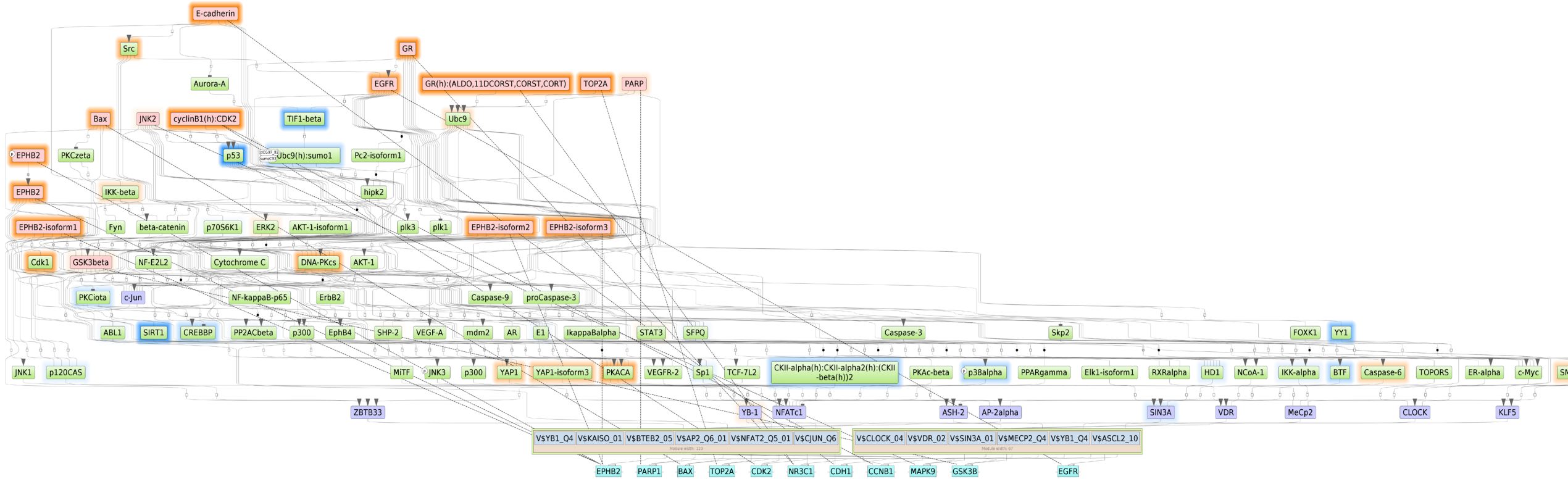
pw04.
pw08.
pw01.
pw07.
pw10.
pw03.
pw09.
pw13.
pw12.
pw05.
pw06.
pw02.
pw11.

ion
cence
se with
se with
n the m
on of re

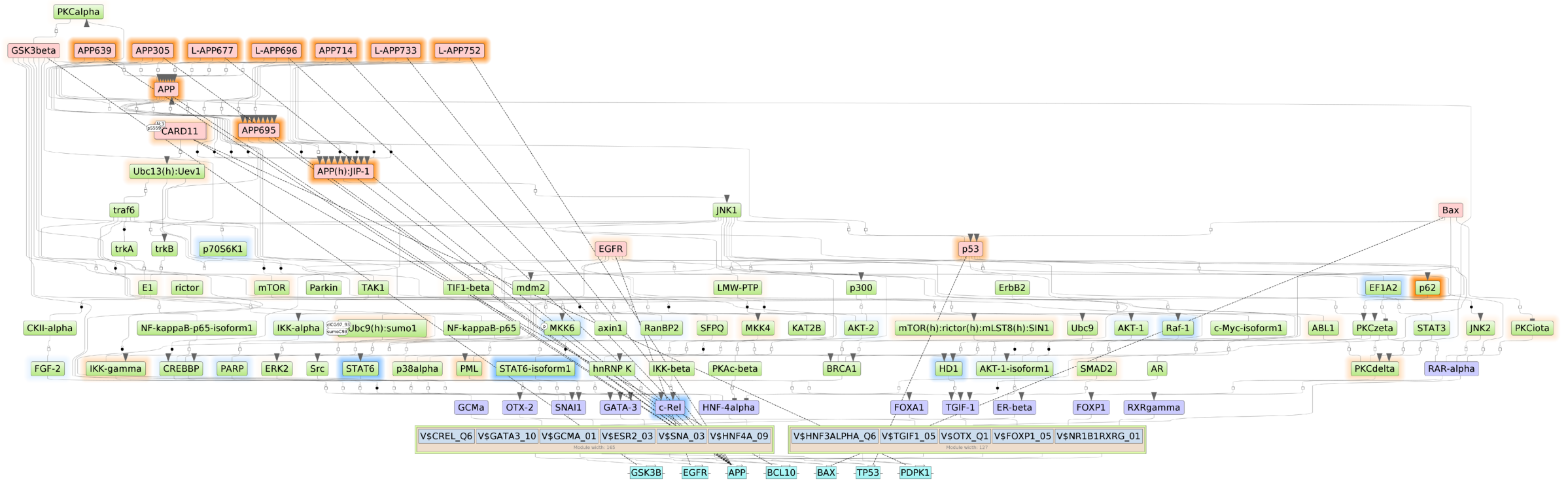
PCA5



PCA3



PCA13



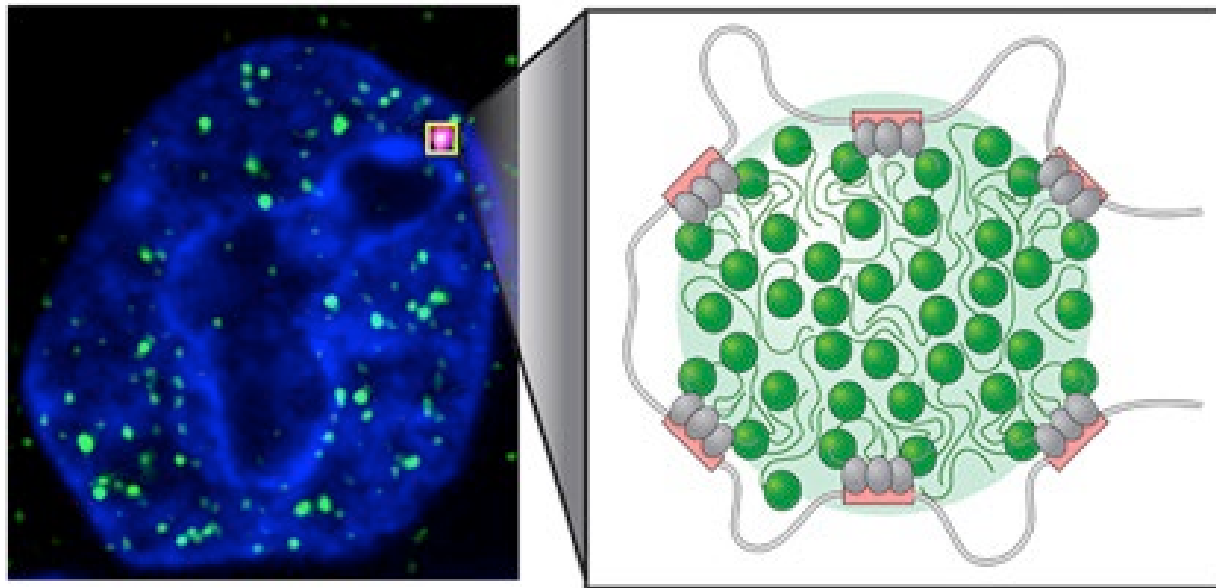


SCIENCEPHOTO LIBRARY



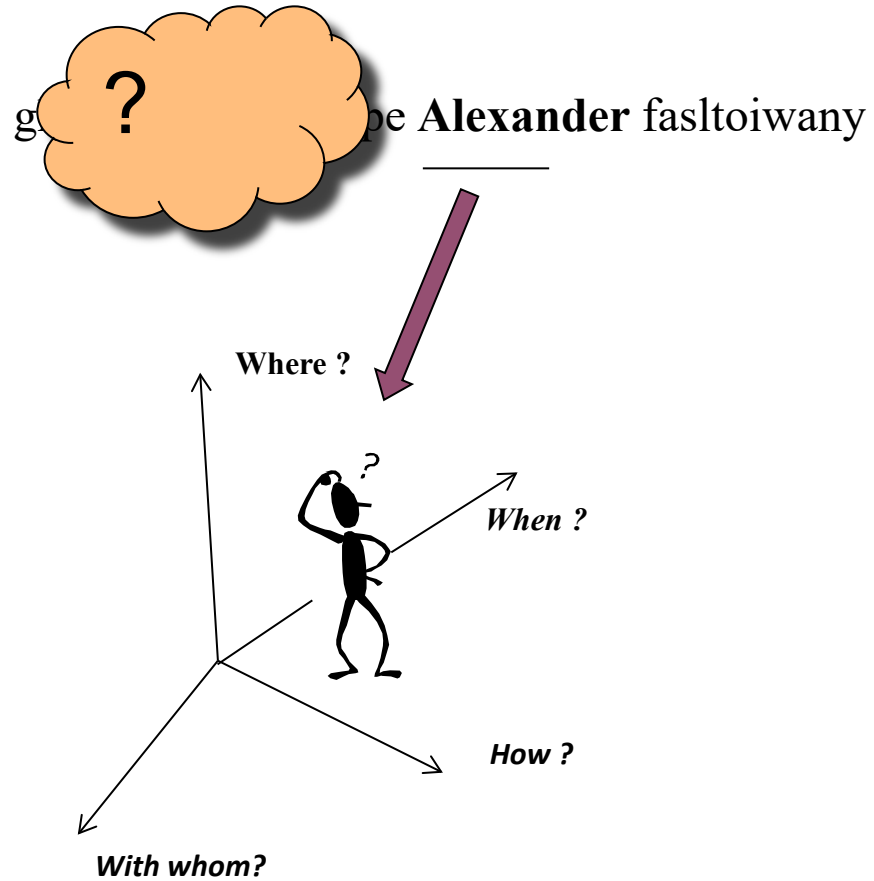
Phase-separated condensates

TFs have unstable and dynamic protein structure that promotes formation of such condensates.



Richard Young and colleagues at Massachusetts Institute of Technology (MIT).

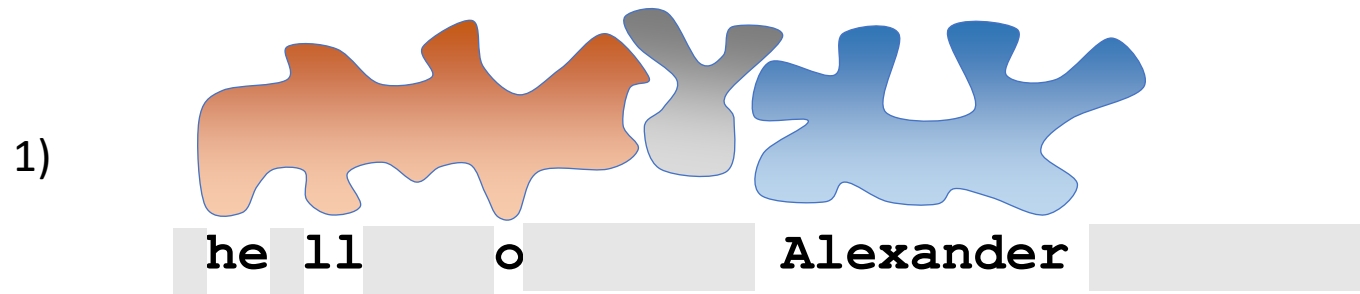
“Regulatory code”



Several regulatory messages could be written in the same sequence

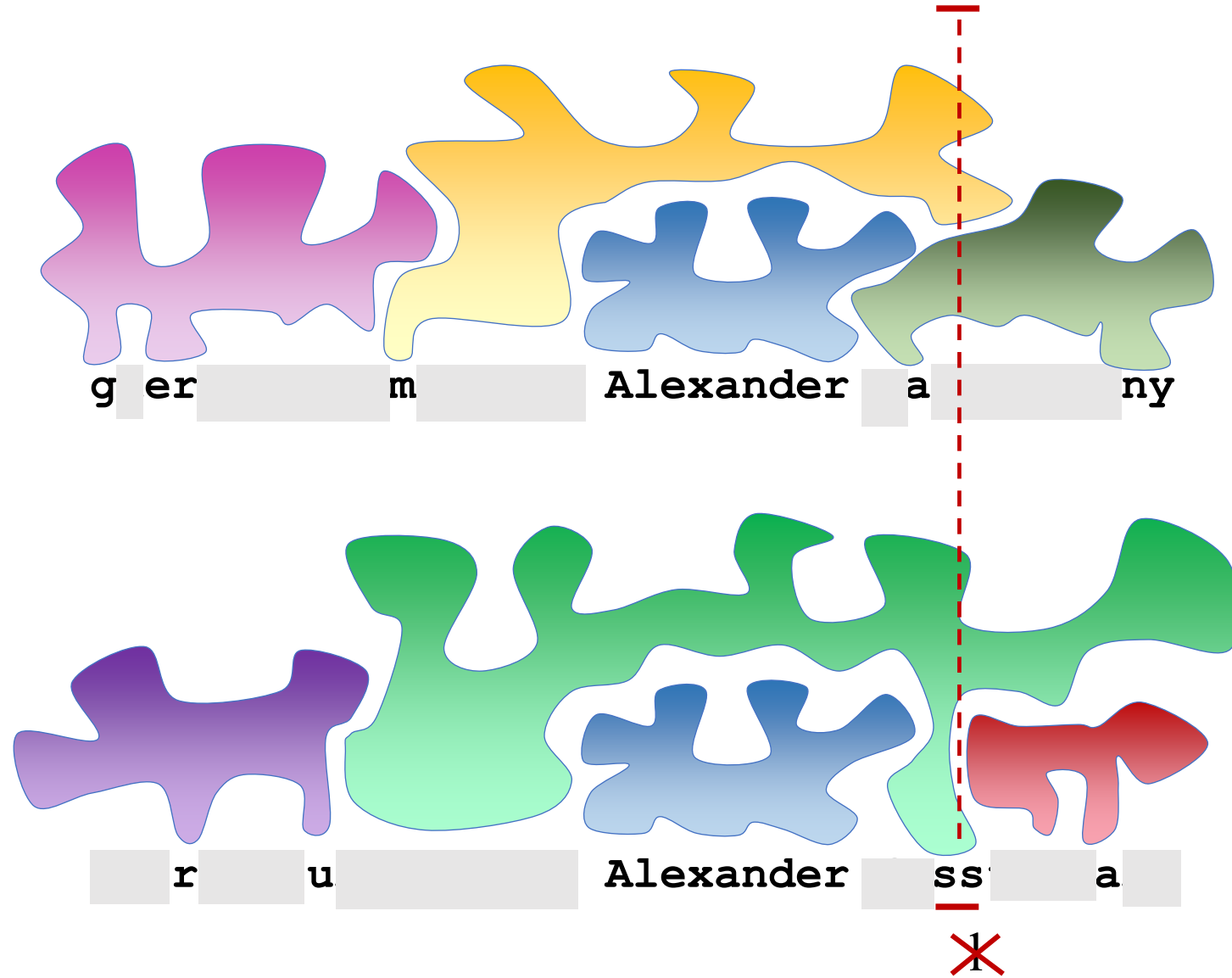
Reading of the messages depends on the cellular context

gherllojunomd-bype Alexander fasltoiwany

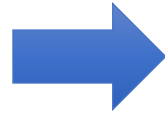


Even some messages which were not written

gherllojunomd-bype Alexander fasltoiwany

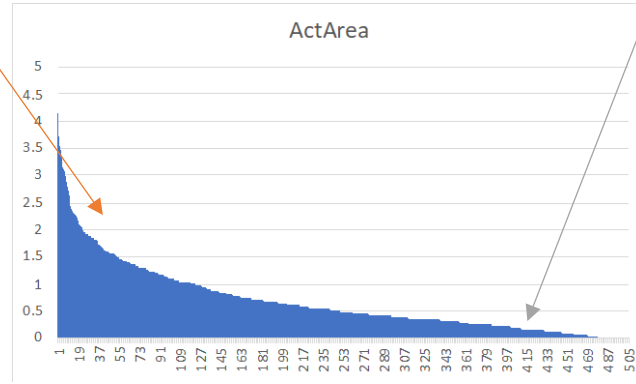


AI fighting ~~cancer~~



Sensitive

- Lapatinib_sensitive
- BT474_BREAST
- CALL3_LUNG
- CCK81_LARGE_INTESTINE
- HCC1954_BREAST
- HDQP1_BREAST
- KYSE140_OESOPHAGUS
- LS513_LARGE_INTESTINE
- MDAMB175VIL_BREAST
- MONOMAC1_HAE_D_TISSUE
- NCH1666_LUNG
- NCH2170_LUNG
- NCH3295_LUNG
- NCIN87_STOMACH
- NUG04_STOMACH
- SKBR3_BREAST
- SKMES1_LUNG
- TE11_OESOPHAGUS
- TE617T_SOFT_TISSUE
- WM963B_SKIN
- ZR7530_BREAST
- AU565_BREAST



Lapatinib sensitivity of 504 cancer cell lines RNA-seq data

Resistant

- Lapatinib_resistant
- A172_CENTRAL_N_S_SYSTEM
- AN3CA_ENDOMETRIUM
- BDMC_HAEMATOP_D_TISSUE
- C32_SKIN
- COLO679_SKIN
- COV318_OVARY
- COV504_OVARY
- GAMG_CENTRAL_N_S_SYSTEM
- HCC1187_BREAST
- HEC59_ENDOMETRIUM
- HS936T_SKIN
- JH6_LIVER
- KARPAS299_HAEM_D_TISSUE
- KNS60_CENTRAL_N_S_SYSTEM
- MESSA_SOFT_TISSUE
- MEWO_SKIN
- NCH228_LUNG
- NCH520_LUNG
- SUP14_HAEMATOP_D_TISSUE
- SW620_LARGE_INTESTINE
- TC71_BONE
- TCCSUP_URINARY_TRACT
- UMUC3_URINARY_TRACT
- YK61_CENTRAL_N_S_SYSTEM

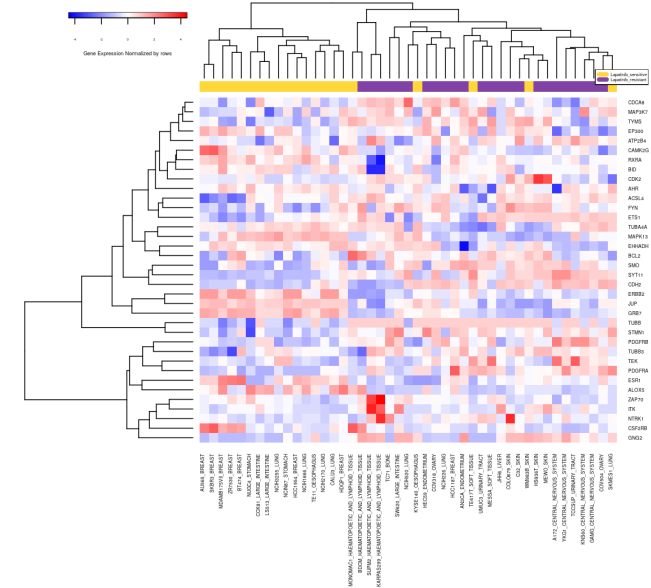


Table 12. FDA approved, promising treatment candidates in HumanPSD™ data. See full table →

Name	Target names	Drug rank
Lapatinib	EGFR, ERBB2	2
Pertuzumab	ERBB2	5
Afatinib	EGFR, ERBB2	26
Trastuzumab	EGFR, ERBB2	38
Vandetanib	VEGFA, EGFR	40

