

Genome Enhancer:

**Non-coding genome gives
clues to anti-cancer drug
treatment.**

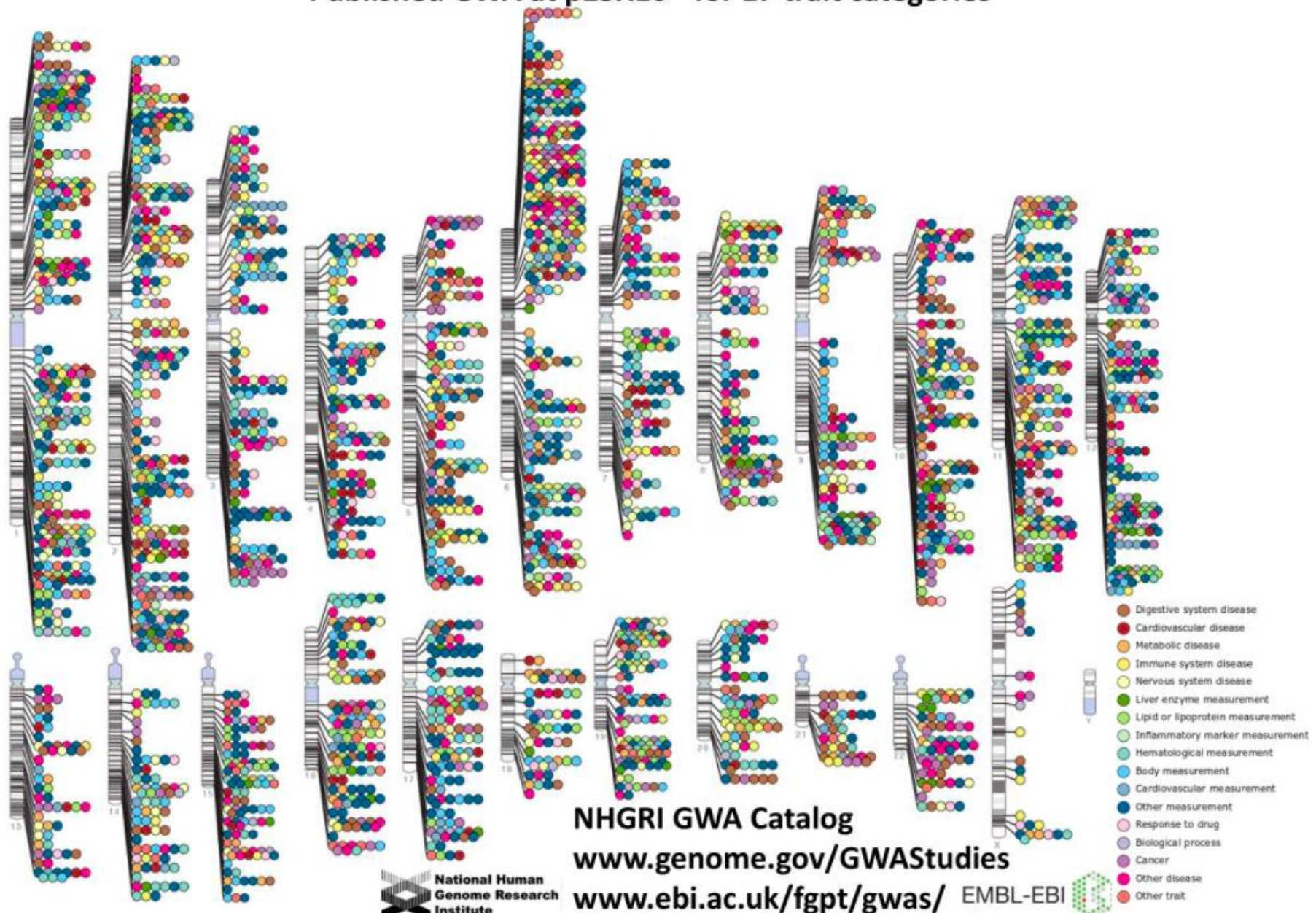
Alexander Kel

Wolfenbüttel



Published Genome-Wide Associations through 12/2012

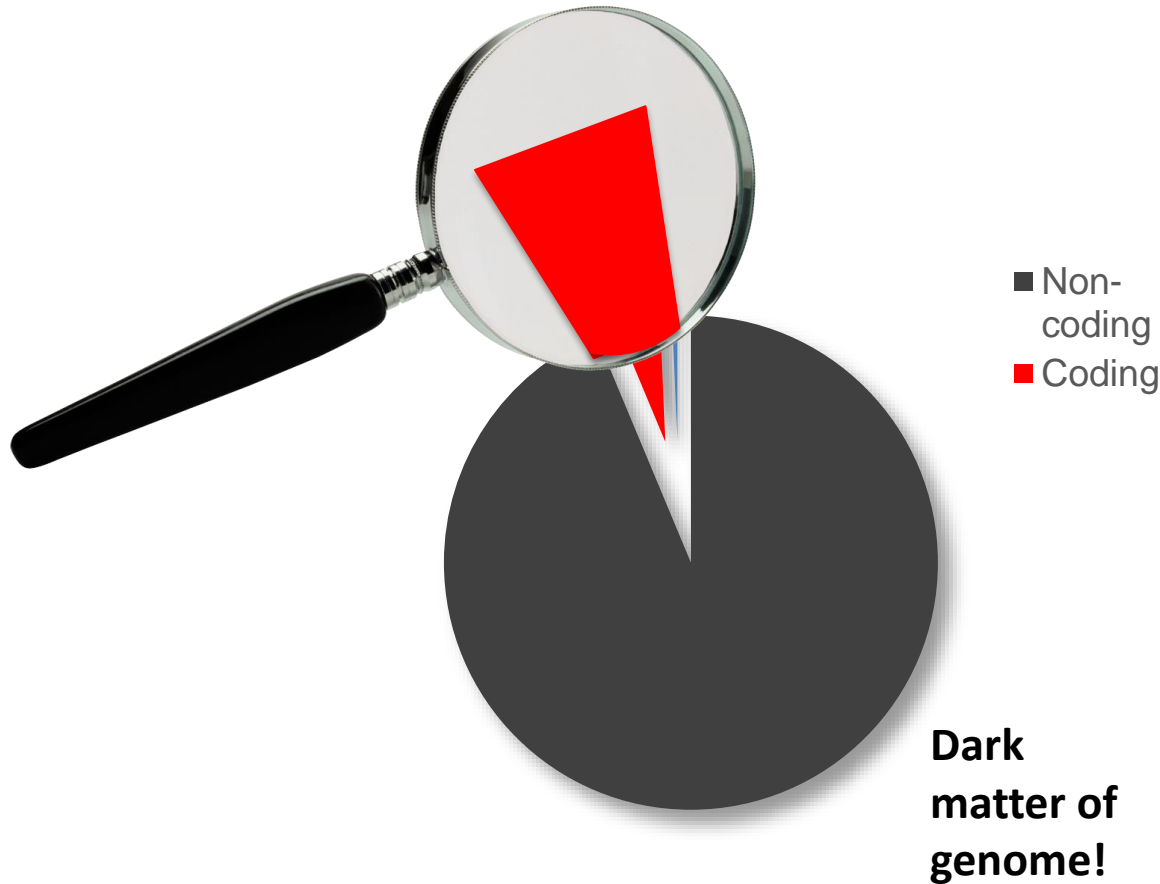
Published GWA at $p \leq 5 \times 10^{-8}$ for 17 trait categories



2020



95% of top disease associated mutations are
in non-coding regions.



Monsters are sleeping in our genome



Cancer is a dragon with many heads:



- Late detection
- Wrong drug
- Metastases
- Drug resistance

EGFR TKI resistance in NSCLC

Series [GSE121634](#)

Query DataSets for [GSE121634](#)

Status Public on Sep 03, 2020

Title Transcriptome profiling to determine molecular mechanisms of acquired EGFR TKI resistance

Organism [Homo sapiens](#)

Experiment type Expression profiling by high throughput sequencing

Summary The goal of this study was to compare the transcriptome (RNA-seq) of EGFR TKI sensitive NSCLC cells with that of cells with acquired resistance to erlotinib. HCC827 and HCC4006 cells were continuously cultured in erlotinib until erlotinib resistant (ER) variants emerged. All ER variants were negative for T790M. RNA from parental and ER cells was isolated for transcriptomic profiling. RNA-seq analysis reveals that EGFR TKI resistance is a mesenchymal gene expression signature.

Overall design RNA-seq on total RNA from EGFR mutant NSCLC cells with or without resistance

Contributor(s) [Heymach J](#)

Citation(s) Nilsson MB, Sun H, Robichaux J, Pfeifer M et al. A YAP/FOXM1 axis mediates EMT-associated EGFR inhibitor resistance and increased expression of assembly checkpoint components. *Sci Transl Med* 2020 Sep 2;12(507):eabg0001. PMID: [32878980](#)

Submission date Oct 22, 2018

Last update date Dec 03, 2020

Contact name Lixia Diao

E-mail(s) ldiao@mdanderson.org

Organization name University of Texas MD Anderson

Department Bioinformatics and Computational Biology

Street address 1400 Pressler Steet

City Houston

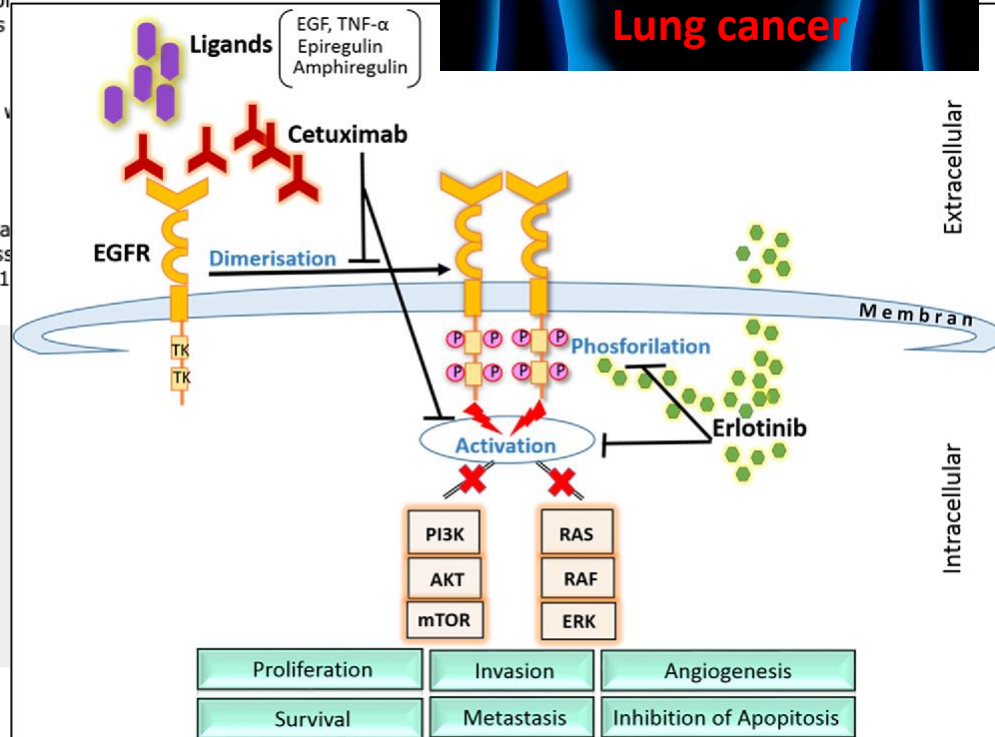
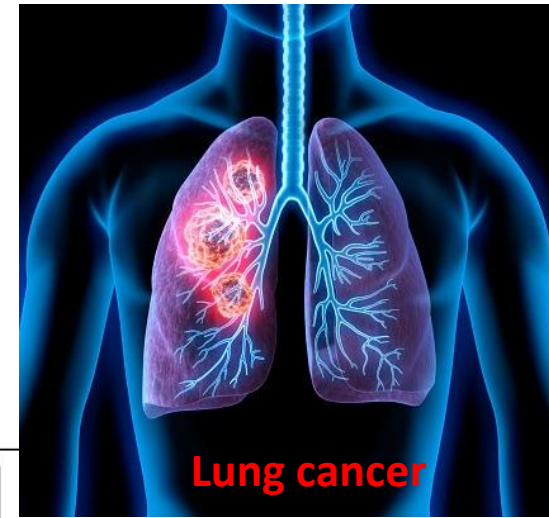
State/province TX

ZIP/Postal code 77030

Country USA

Platforms (1) [GPL20301](#) Illumina HiSeq 4000 (Homo sapiens)

Samples (30) [GSM3440791](#) 1_827Parental1
[GSM3440792](#) 2_827Parental2
[GSM3440793](#) 3_827Parental3
[GSM3440794](#) 4_827ER1_1
[GSM3440795](#) 5_827ER1_2



Published in *Advances in Therapy* 2015

Current Adjuvant Therapeutic Approaches for Pancreatic Cancer

Fusun Ozmen, Tevfik Tolga Şahin, M. Ozmen

**Erlotinib
resistant**

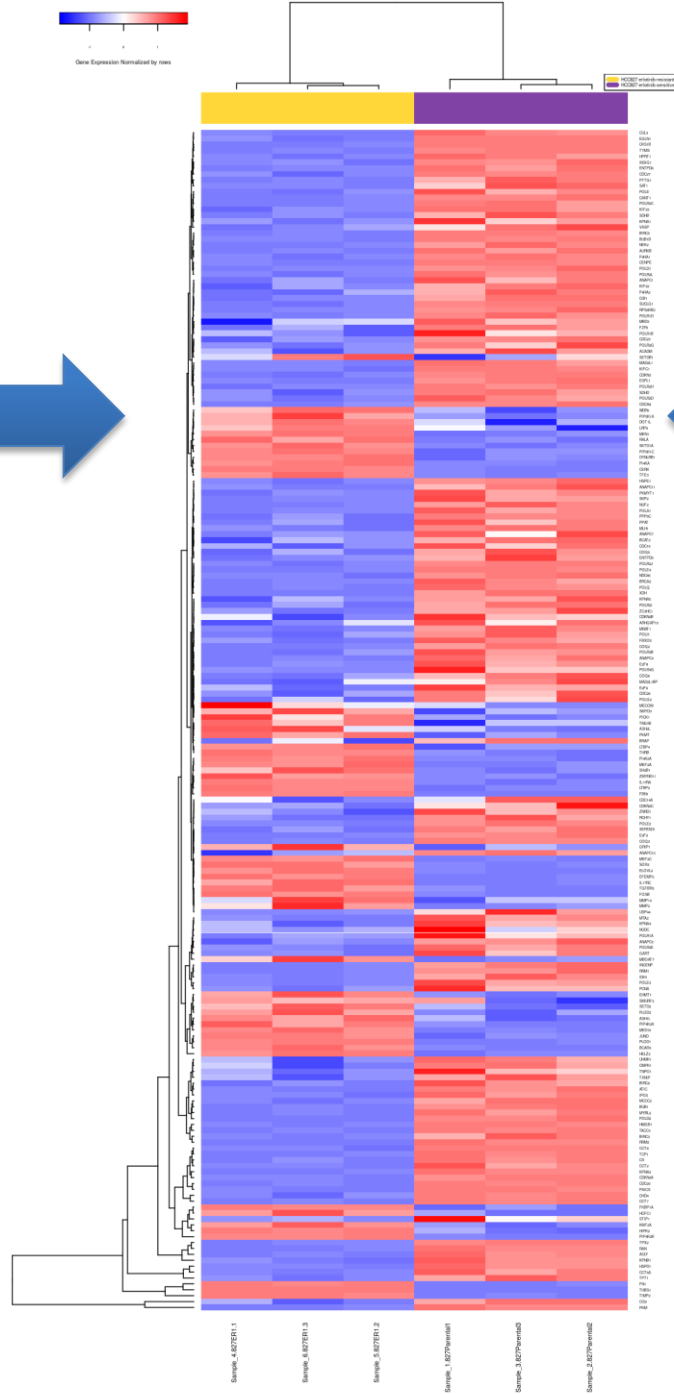


**Erlotinib
sensitive**



Up = 5495
Down = 5591

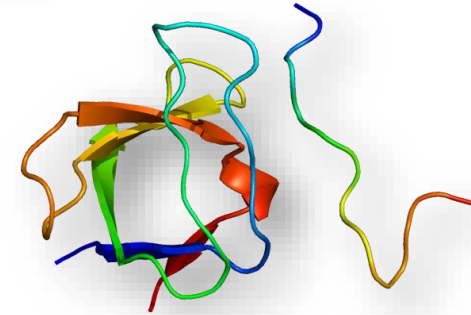
(
a
d
j
·
p
-
v



Introduction

Description

FYN oncogene related to SRC, FGR, YES, a protein tyrosine kinase that regulates activation of MAPK activity and apoptosis, aberrant expression is associated with Alzheimer disease, HIV infections, schizophrenia, renal cell carcinoma and several neoplasms



Disease details-all	Significance	Causal 6 associations	Correlative 48 associations	Preventative 4 associations	Negative 4 associations	Disease Mechanism 6 associations	Prognosis 4 associations	Therapeutic Target 4 associations
Schizophrenia	8 associations		7 associations		1 associations			

- Carcinoma, Hepatocellular
- Alzheimer Disease
- Stomach Neoplasms
- Lymphoproliferative Disorders
- HIV Infections
- Ovarian Neoplasms
- Asthma
- Breast Neoplasms
- Autoimmune Diseases
- Lupus Erythematosus, Systemic
- Polycystic Ovary Syndrome
- Dermatitis, Atopic
- Urinary Bladder Neoplasms
- Glioblastoma
- Uterine Cervical Neoplasms
- Carcinoma, Squamous Cell
- Lymphoma, Non-Hodgkin
- Alcoholism
- Head and Neck Neoplasms
- Carcinoma, Renal Cell
- Precursor Cell Lymphoblastic

2926 *Current Medicinal Chemistry*, 2011 Vol. 18, No. 19 Schenone et al.

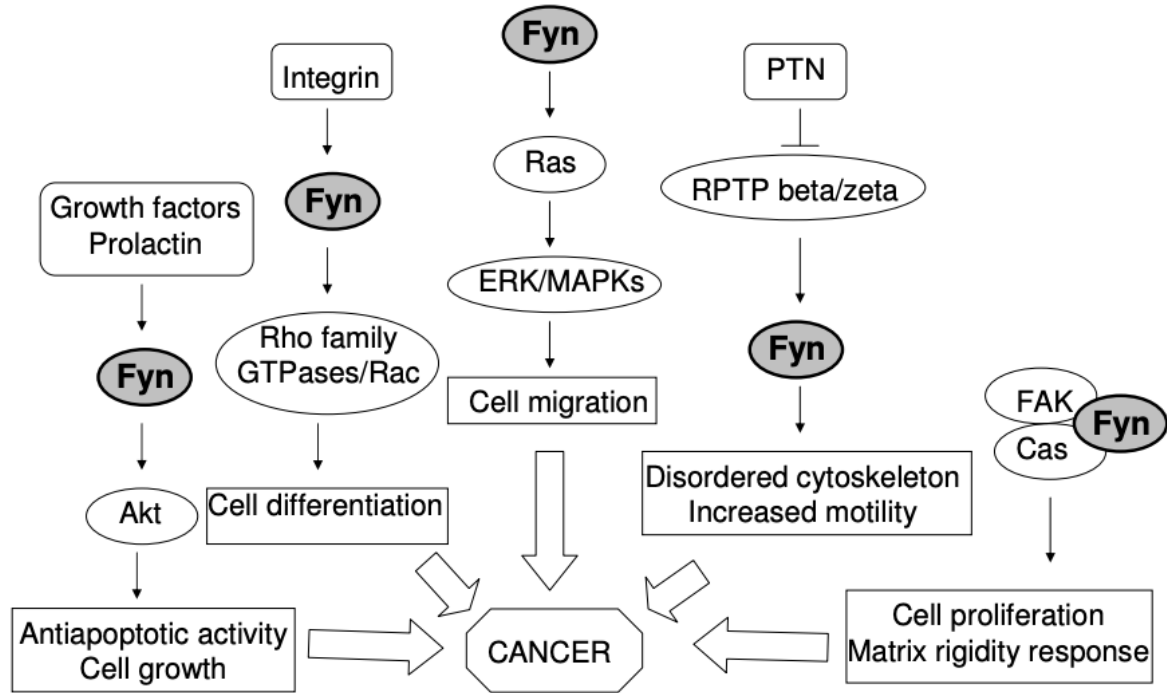
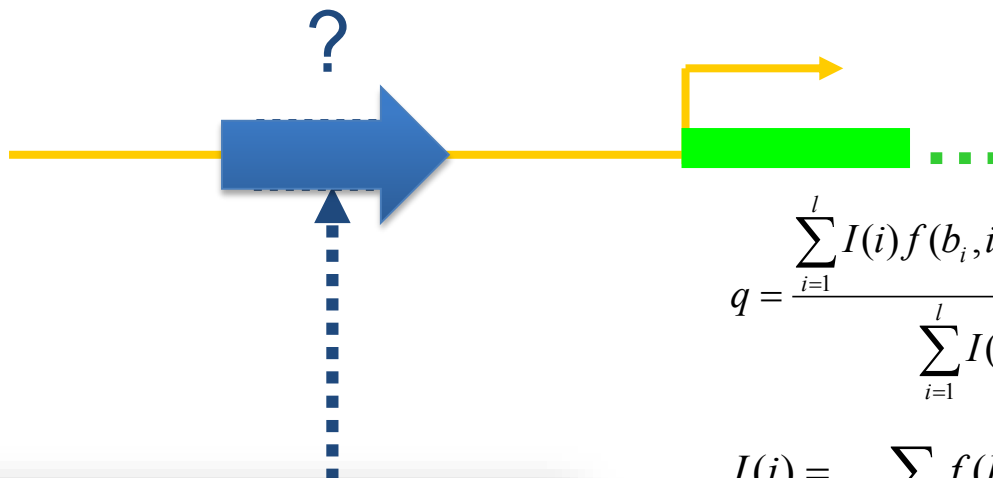
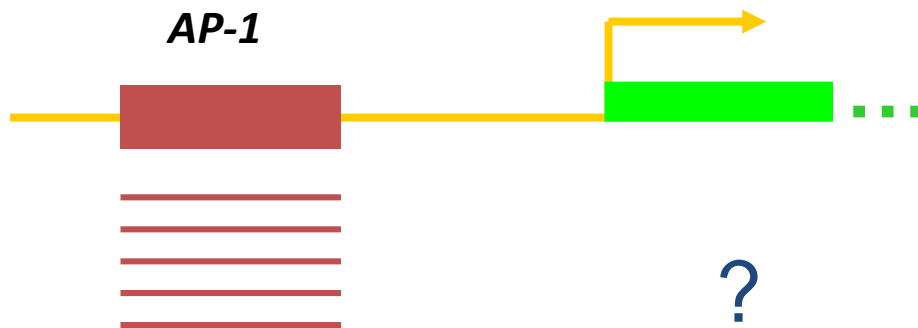


Fig. (4). Signalling pathways, involving Fyn, hyperactivated in cancer.

Search for new TF binding sites with PWMs



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

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

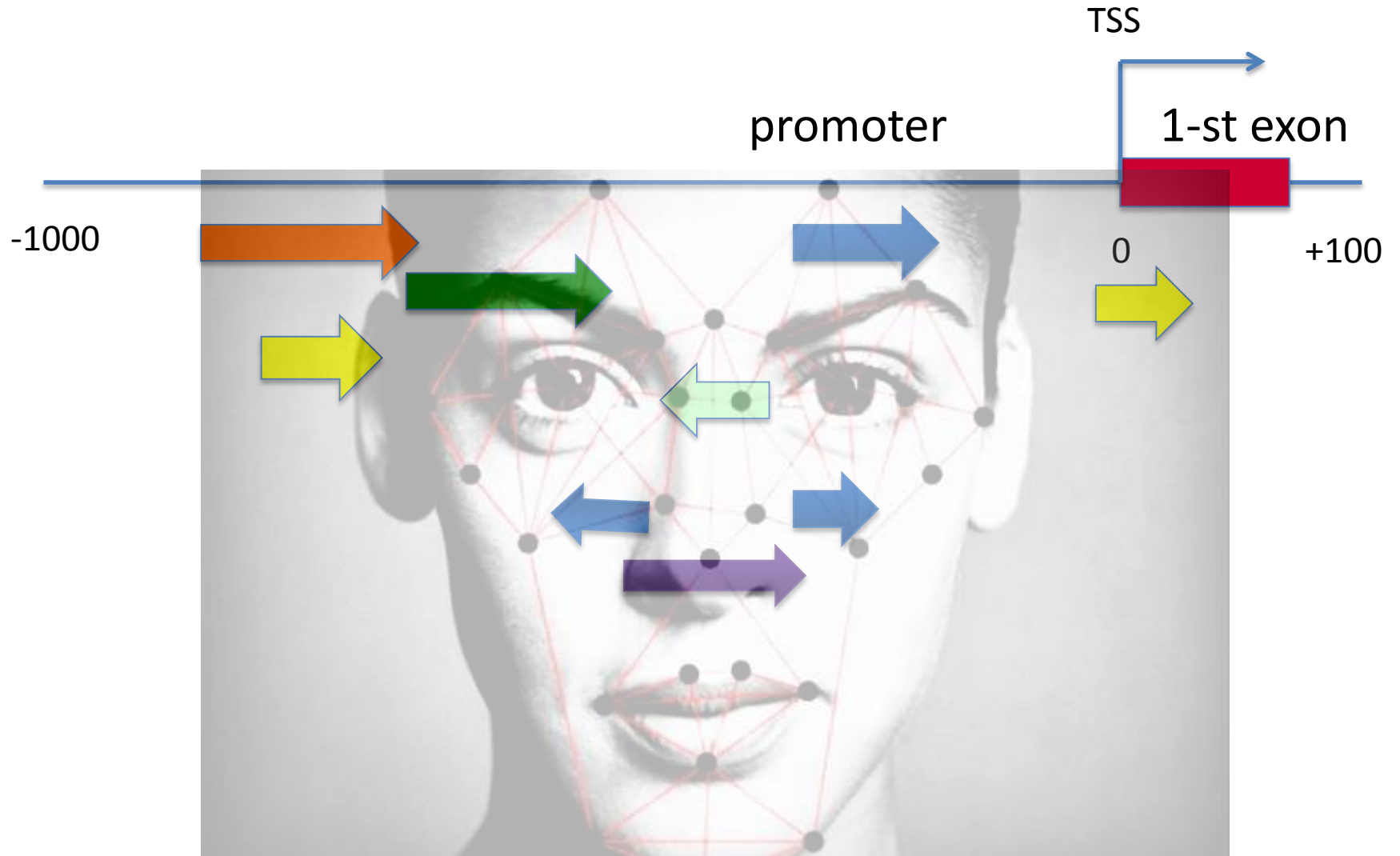
TRANSFAC[®],
 HOCOMOCO,
 JASPAR,
 FactorBook,
 UniPROBE,...

Logo



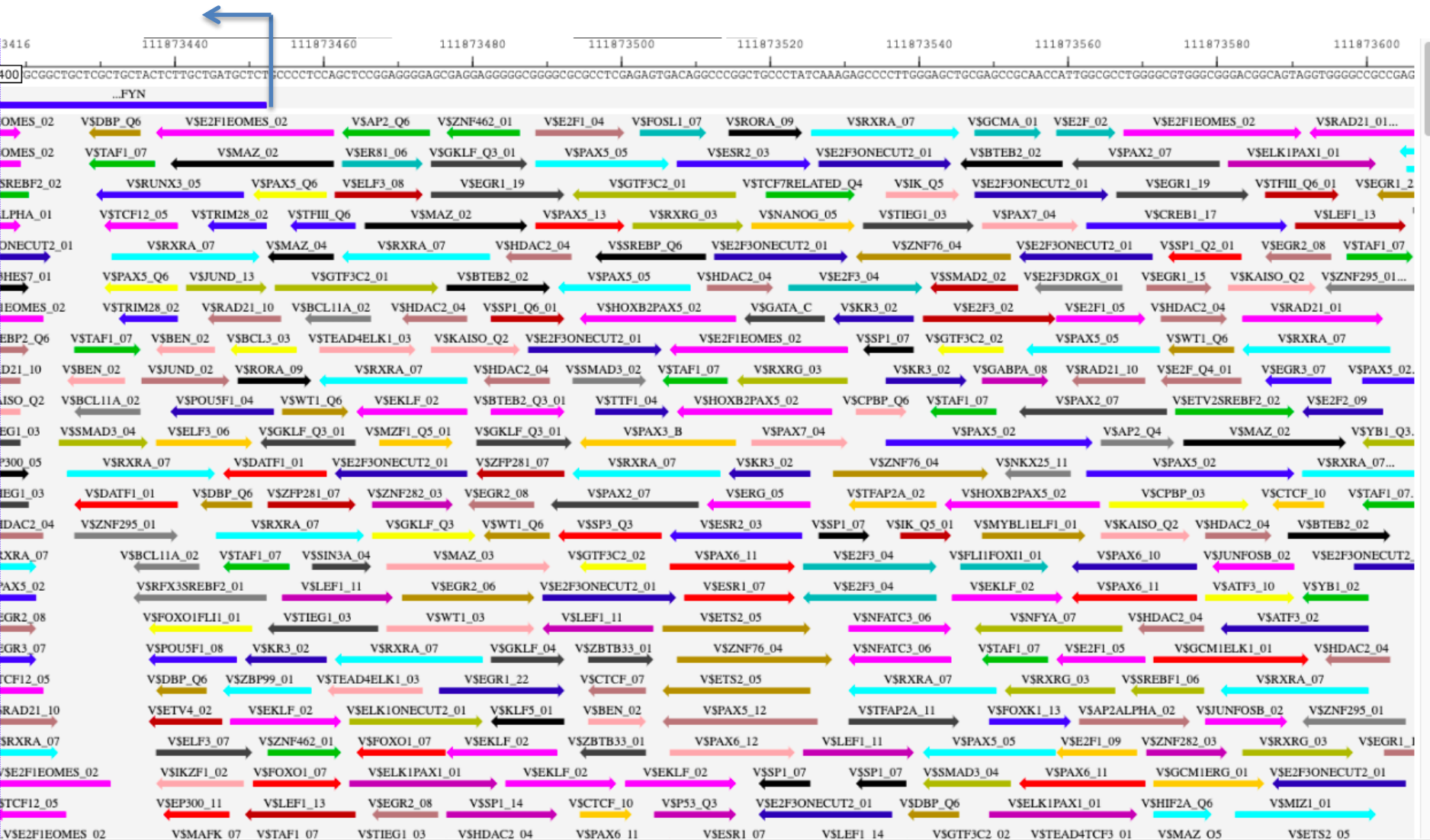
A	0.000	0.000	0.889	0.278	0.167	0.000	0.889
C	0.056	0.000	0.111	0.667	0.000	0.833	0.000
G	0.000	0.833	0.000	0.056	0.056	0.167	0.056
T	0.944	0.167	0.000	0.000	0.778	0.000	0.056

TF binding sites in promoters of a **Erlotinib-resistance genes**

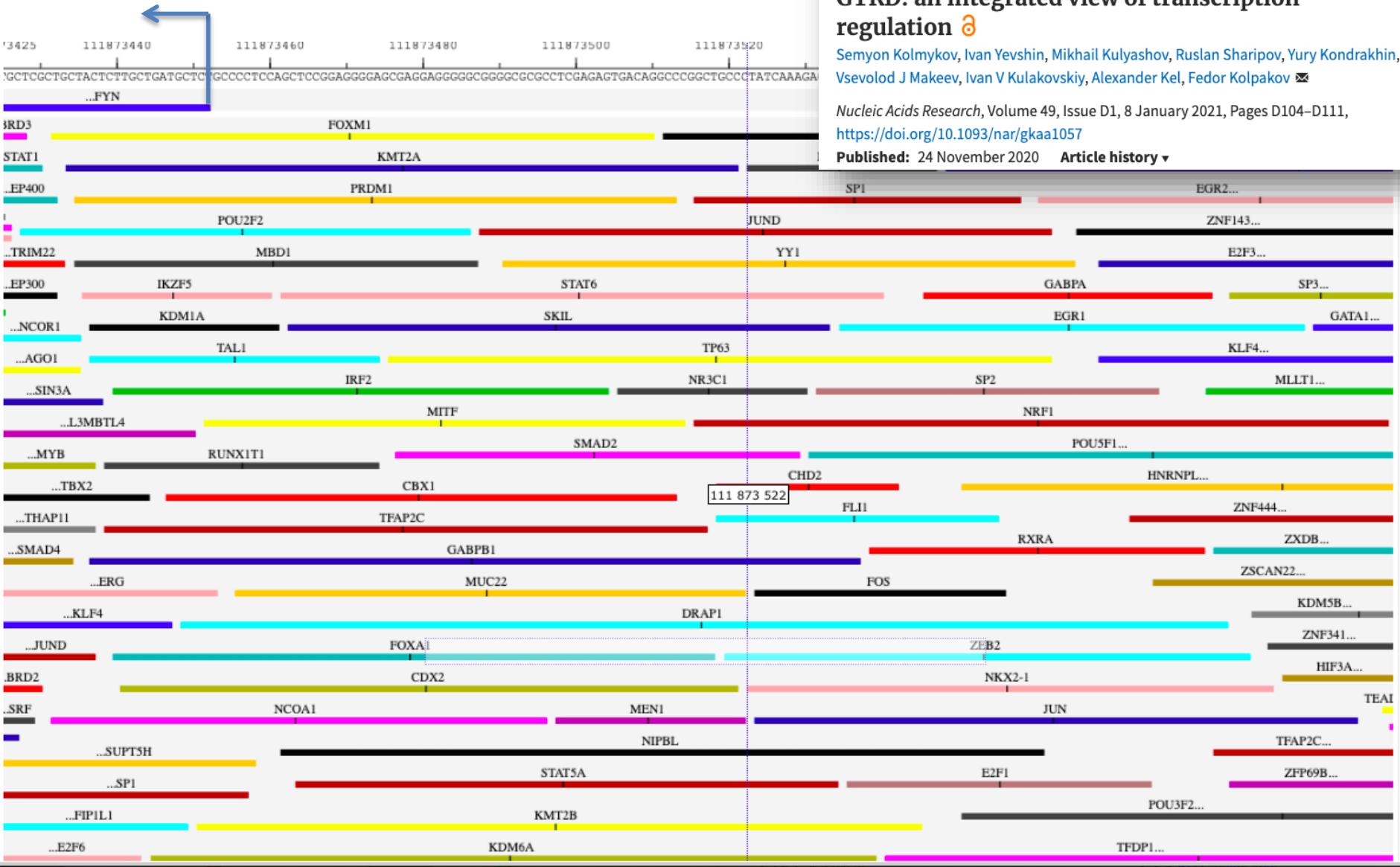


Promoter face

5260 TFs – the promoter face is too complicated !!!!



GTRD database – comprehensive ChIP-seq database



GTRD: an integrated view of transcription regulation

Semyon Kolmykov, Ivan Yevshin, Mikhail Kulyashov, Ruslan Sharipov, Yury Kondrakhin, Vsevolod J Makeev, Ivan V Kulakovskiy, Alexander Kel, Fedor Kolpakov

Nucleic Acids Research, Volume 49, Issue D1, 8 January 2021, Pages D104–D111, <https://doi.org/10.1093/nar/gkaa1057>

Published: 24 November 2020 Article history ▾

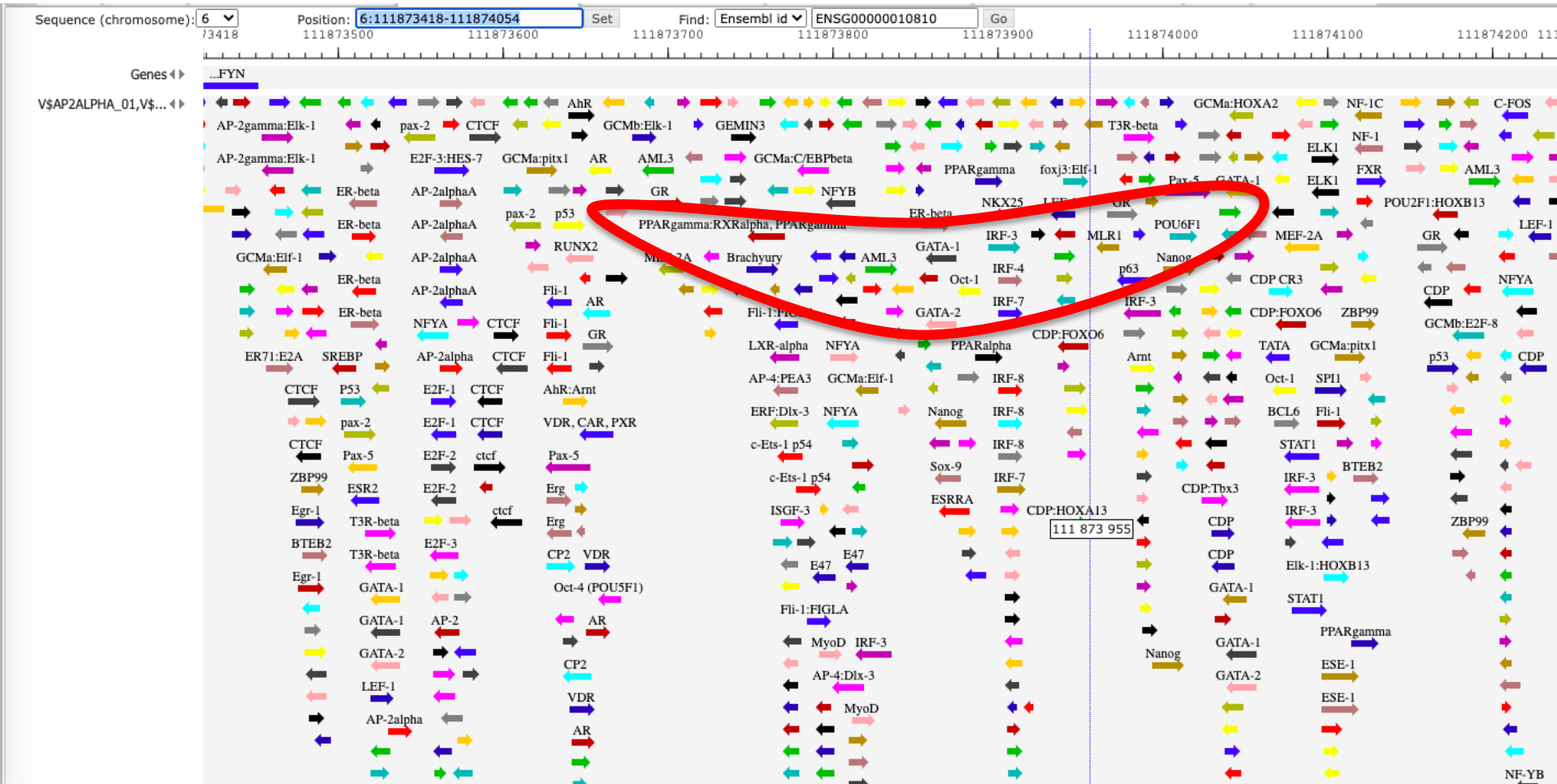
What is common
between all these
faces?



We need to search for Erlotinib-resistance promoter “smile”



Find a subset of TF sites out of all 5260 TFs



There are new AI methods available for recognition of human emotions:

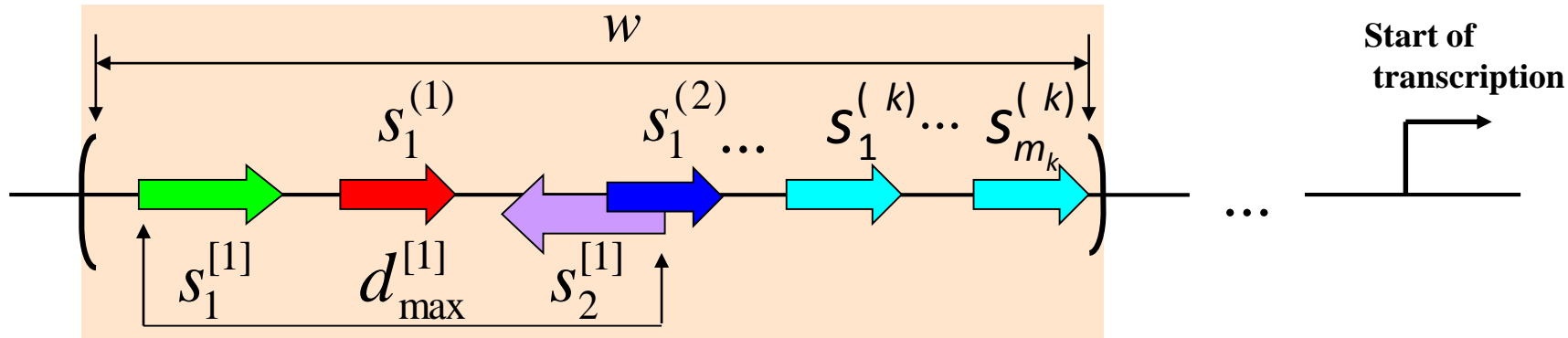
Emotion API - Emotion Detector | Microsoft Azure



We are going to use these algorithms for recognizing Erlotinib-resistance promoter “emotions” – promoter “smile”.

Composite Module Analyst (CMA)

Mathematical model



CM contains single elements as well as composite elements (site pairs)

$$d_{\max}^{[1]}$$

$$d_{\max}^{[1]}$$

...

$$d_{\max}^{[R]}$$

$$q_{\text{cut-off}}^{(1)}$$

$$q_{\text{cut-off}}^{(2)}$$

...

$$q_{\text{cut-off}}^{(k)}$$

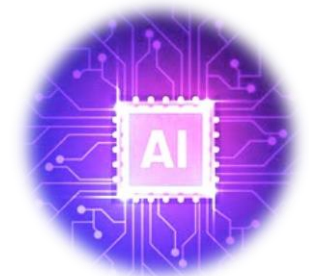
$$\phi^{(1)}$$

$$\phi^{(2)}$$

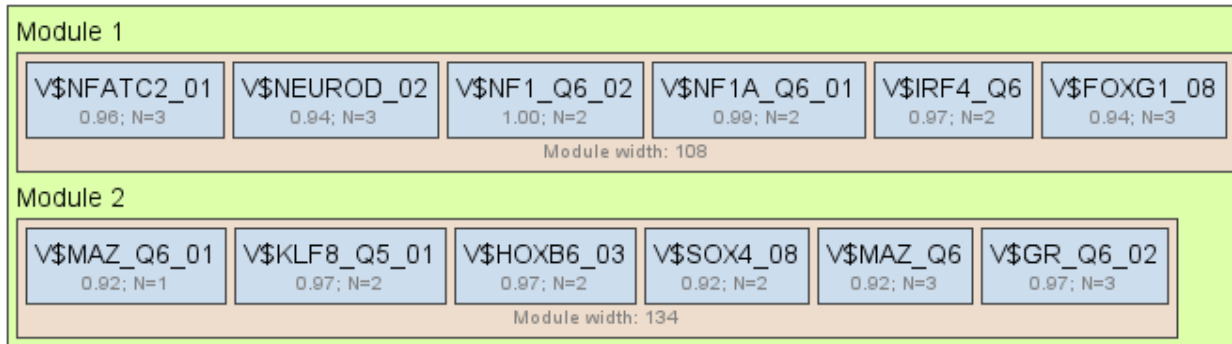
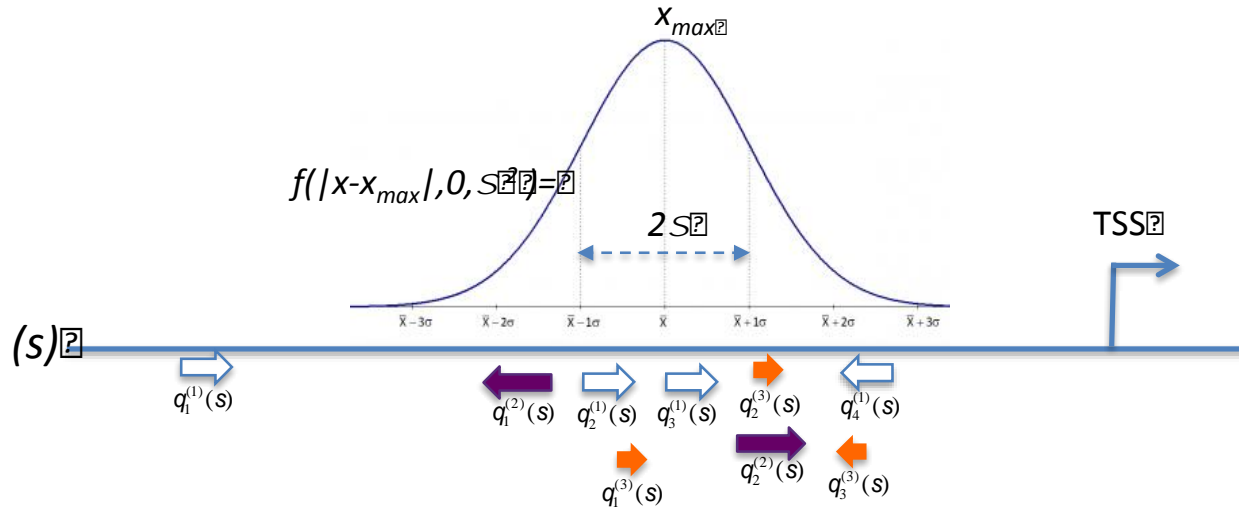
...

$$\phi^{(k)}$$

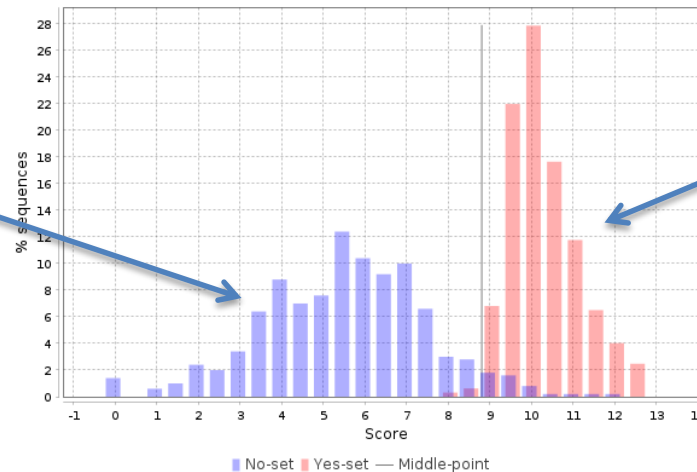
*Parameters of
the model to be estimated
by **Genetic Algorithm***



Composite model of the Erlotinib-resistance promoters



500
Non changed
genes



129 top
UP-regulated
genes
with TF
clusters

LogFC_FDR1000 X Model visualization on n... X

Showing 1 to 50 of 133 entries

ID	Ensembl IDs	Names	Model	Score	logFC	FDR
1264	ENSG00000114853	ZBTB47		11.05278	5.001867196	0.0
3108	ENSG00000008517	IL32		10.48934	6.948656666	0.0
3521	ENSG00000070404	FSTL3		10.88607	3.927192837	0.0
3739	ENSG00000158186	MRAS		11.18474	7.156590578	0.0
4250	ENSG00000185950	IRS2		10.78683	3.748762052	0.0
5957	ENSG00000011028	MRC2		11.08836	3.613094259	0.0
6260	ENSG00000144218	AFF3		10.73775	7.812936279	0.0
1251	ENSG00000091656	ZFHX4		11.02716	6.071772429	5.98E-308
1565	ENSG00000149596	JPH2		10.49592	8.188940644	3.64E-296
1230	ENSG00000125430	HS3ST3B1		10.59151	8.703748022	4.31E-296
308	ENSG00000101265	RASSF2		10.93977	2.251556386	4.97E-293
6158	ENSG00000169432	SCN9A		10.5899	3.588060268	8.4E-291
4215	ENSG00000049192	ADAMTS6		11.11227	4.997353096	4.59E-274
3756	ENSG0000010810	FYN		10.436	2.73740013	1.47E-268
5869	ENSG00000170485	NPAS2		10.97058	2.098625129	2.04E-241

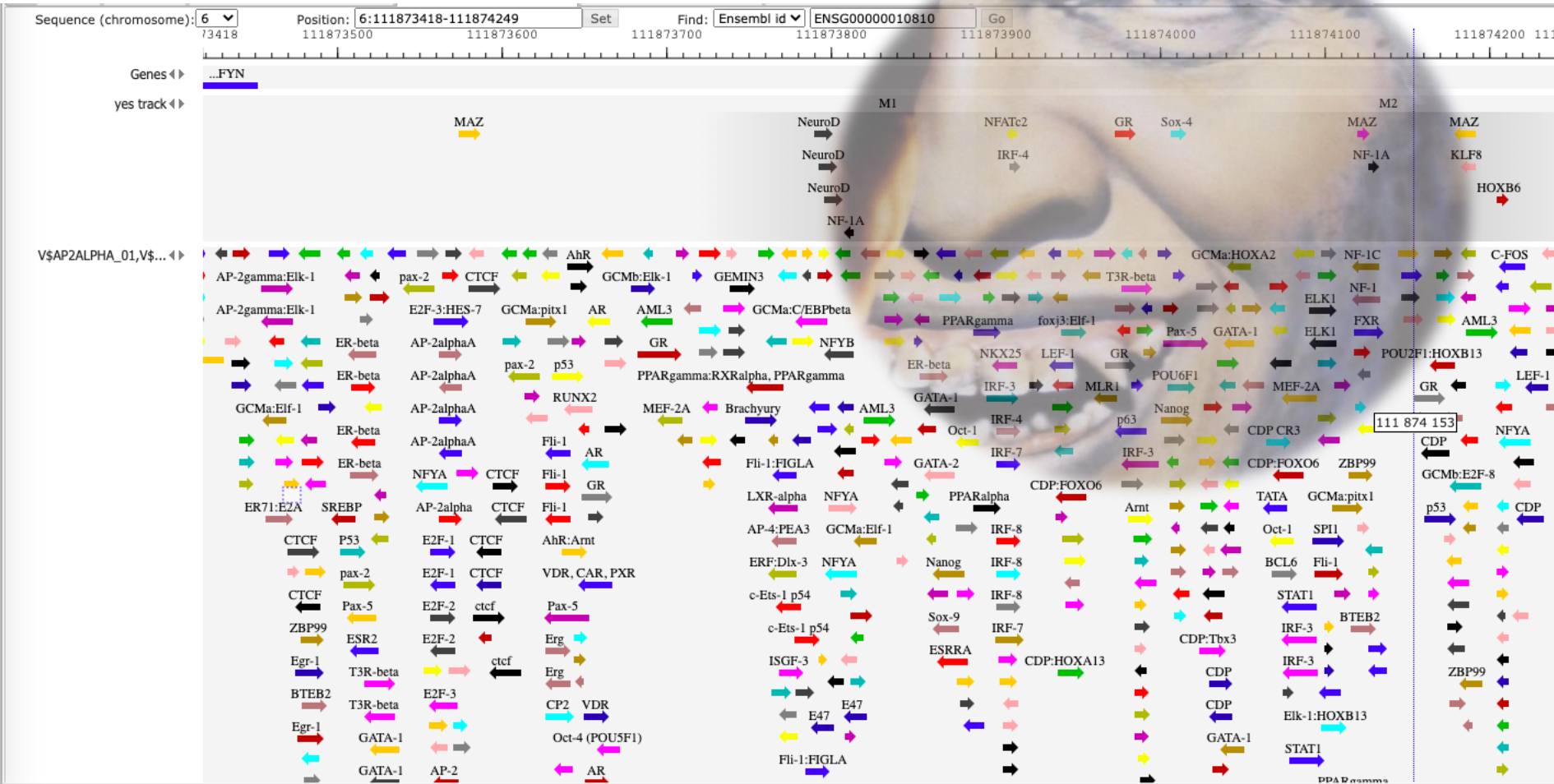
Search Info Default

Model V\$GR_Q6_02
Binding element: GR
Threshold: 0.9661
Matrix: V\$GR_Q6_02
Matrix length: 13

Filters Columns Genome browser Site colors My description Graph search Script Clipboard Tasks

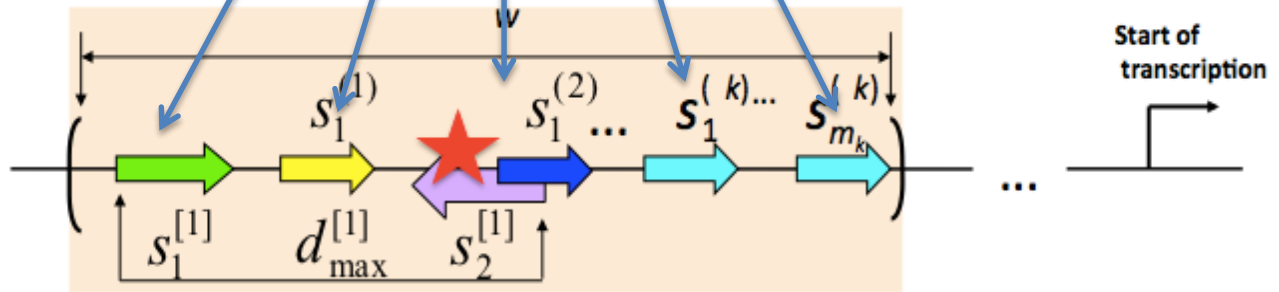
yes track

TF clusters in the promoter of **FYN** gene



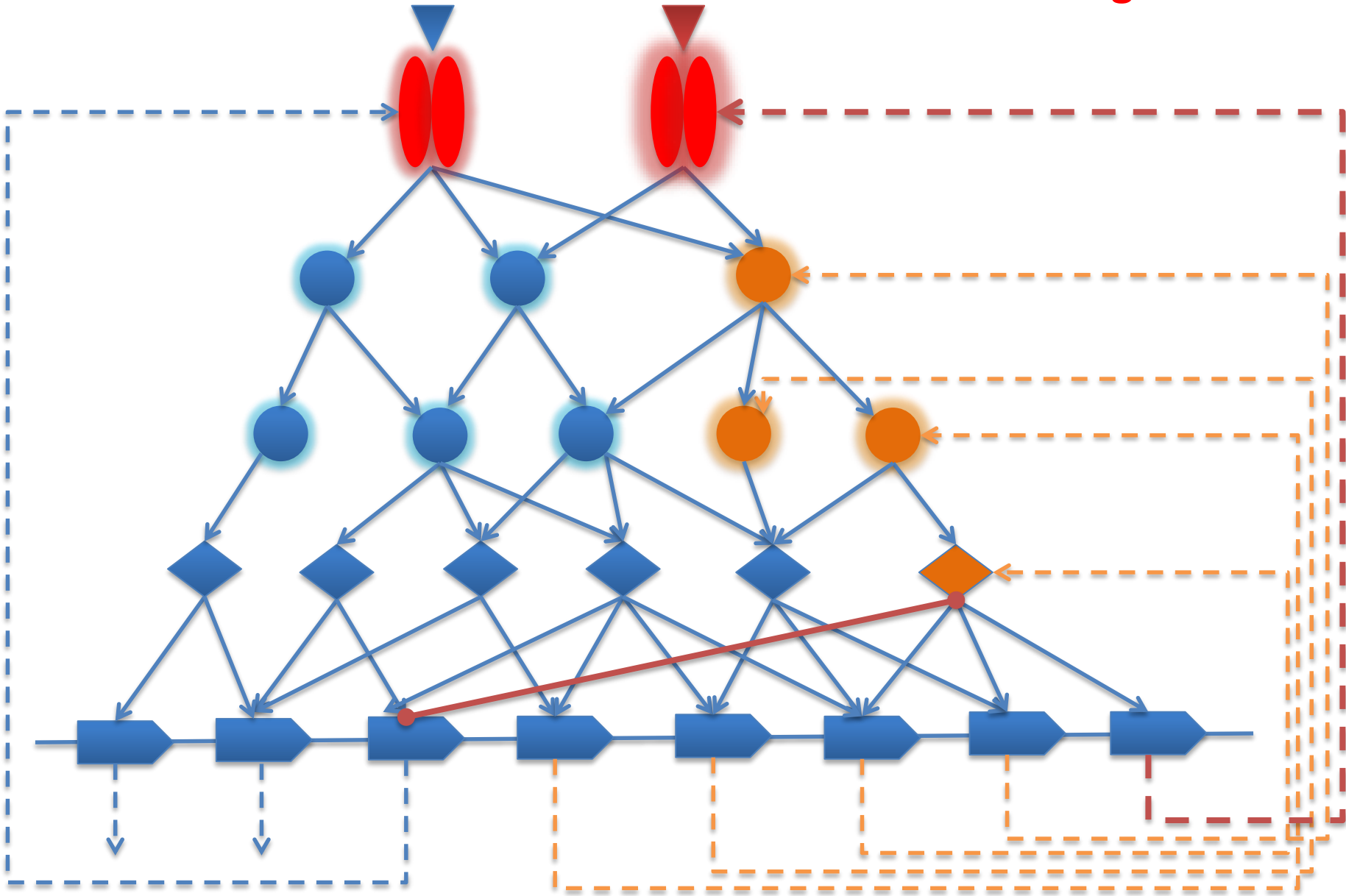


Master regulator ?

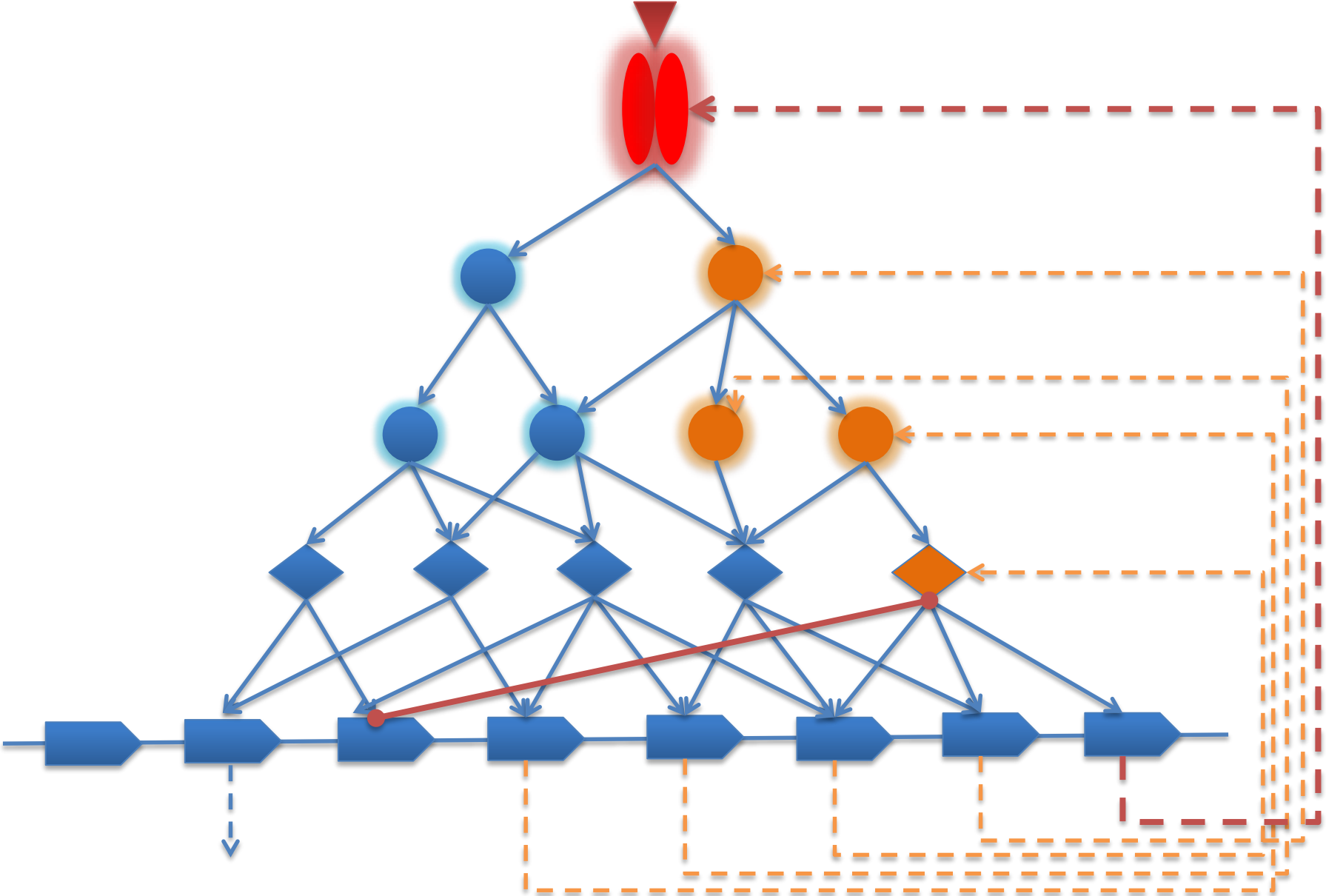


Master-regulator

New master-regulator



New master-regulator

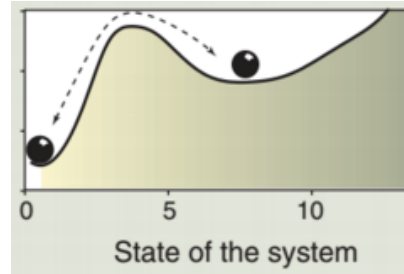
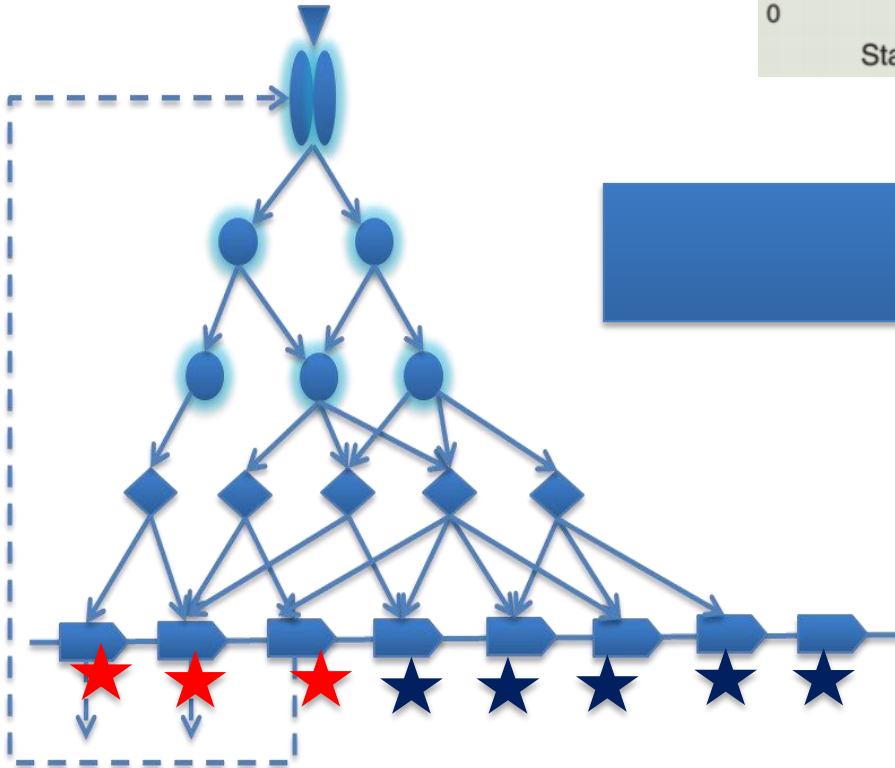


Pathway corruption –

In cancer new rewired networks appear with multiple feedback loops

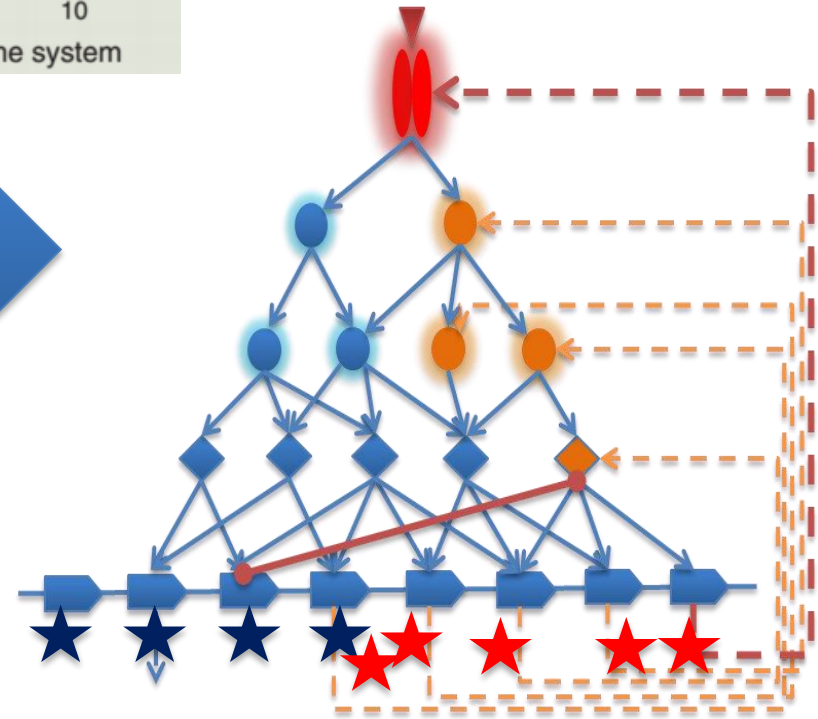
Healthy

Canonical pathways

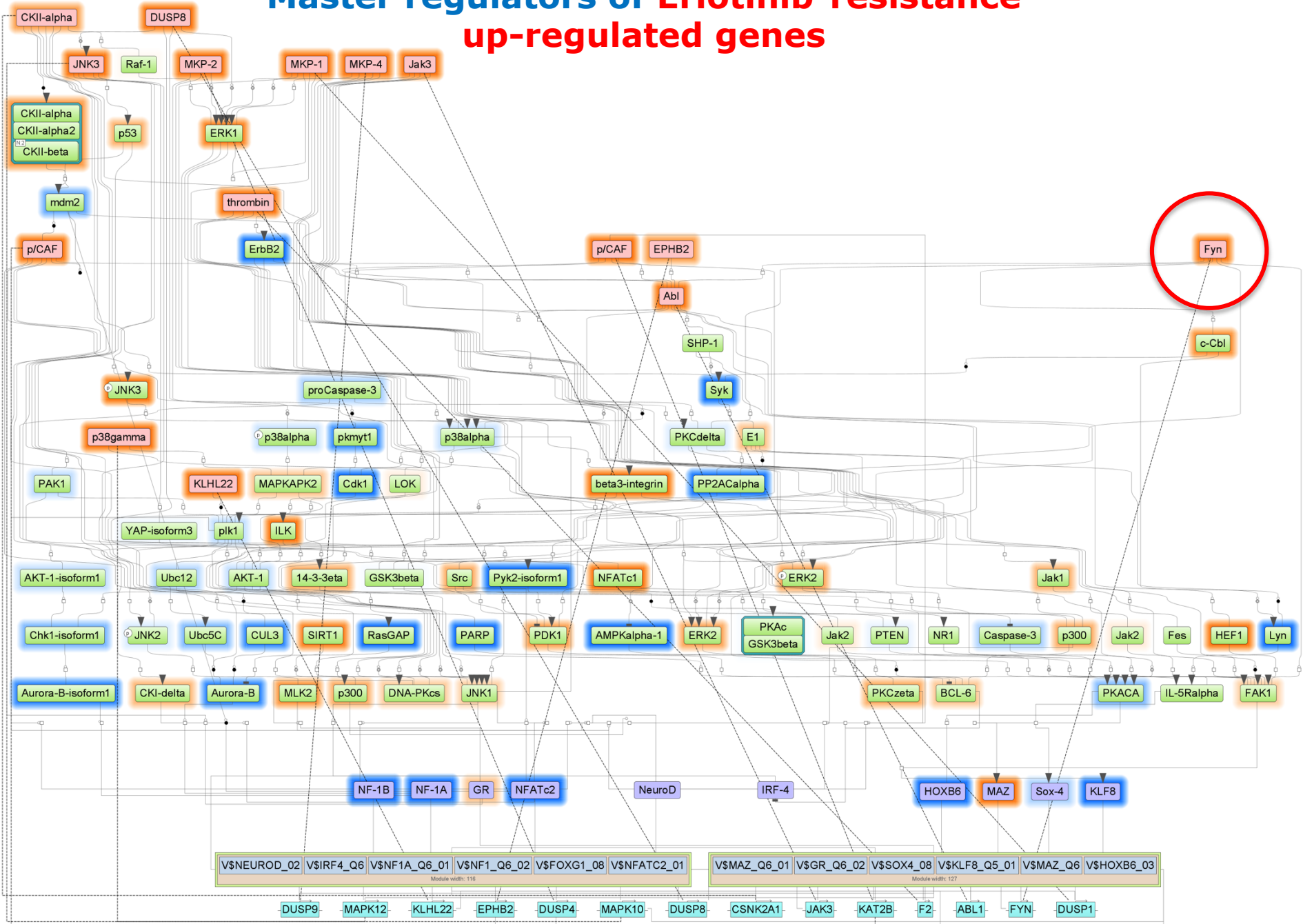


Cancer

Canonical pathways



Master regulators of Erlotinib-resistance up-regulated genes



Drugs approved in clinical trials



Table 12. FDA approved drugs or drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

[See full table →](#)

Name	Target names	Drug rank	Disease activity score	Phase 4	Status (provided by Drugbank)
Dasatinib	SRC, ABL1, PDGFRB, FYN	21	6	Leukemia, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Precursor Cell Lymphoblastic Leukemia-Lymphoma	small molecule, approved, investigational
Darbepoetin alfa	EPOR	35	10	Anemia, Cardiomyopathies, Colorectal Neoplasms, Hyperparathyroidism, Secondary, Kidney Diseases, Kidney Failure, Chronic...	biotech, approved, investigational
Epoetin alfa	EPOR	35	10	Anemia, Cardiomyopathies, Colorectal Neoplasms, Delayed Graft Function, HIV Infections, Hemorrhage, Hyperparathyroidism...	biotech, approved
Ruxolitinib	JAK2, JAK1	37	7	Splenomegaly	small molecule, approved
Imatinib	ABL1, PDGFRB	40	5	Breast Neoplasms, Gastrointestinal Stromal Tumors, Leukemia, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Mastocytosis...	small molecule, approved

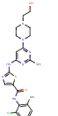
Dasatinib

Targets (23)

Enzymes (6)

Transporters (2)

IDENTIFICATION

Name	Dasatinib	Accession Number	DB01254
Description	Dasatinib is an oral dual BCR/ABL and Src family tyrosine kinase inhibitor approved for use in patients with chronic myelogenous leukemia (CML). The main targets of Dasatinib, are BCRABL, SRC, Ephrins and GFR.		
Type	Small Molecule	Groups	Approved, Investigational
Structure			Weight Average: 488.006 Monoisotopic: 487.155721508
	Chemical Formula		C ₂₂ H ₂₆ ClN ₇ O ₂ S

3D Download Similar Structures

Repurposing drugs/compounds



Table 14. Prospective drugs, predicted by PASS software to be active against the identified drug targets with predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

[See full table →](#)

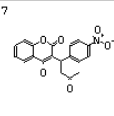
Name	Target names	Drug rank	Target activity score
K101	PTPRR, PTPRJ, PTPN23, PTPRA, PTPRE, DUSP4, DUSP18...	12	1.8

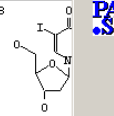


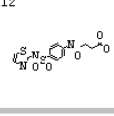
Table 15. Prospective drugs, predicted by PASS software to be active against the identified drug targets, though without cheminformatically predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

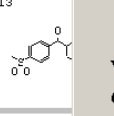
[See full table →](#)

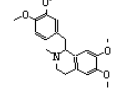
Name	Target names	Drug rank	Target activity score
3-[1-(3-AMINOPROPYL)-1H-INDOL-3-YL]-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE	MAPK12, MAP3K10, PRKAA2, PRKG1, SIRT1, PRKCE, PRKCA...	11	2.2
Rbt205 Inhibitor	PTK2, MAP3K10, PRKAA2, SIRT1, PRKCE, PRKCA, MAP2K4...	14	1.8
3-[1-(3-Aminopropyl)-1h-Indol-3-Yl]-4-(1-Methyl-1h-Indol-3-Yl)-1h-Pyrrole-2,5-Dione	MAP3K10, PRKAA2, SIRT1, PRKCE, PRKCA, PKN1, CDK7...	16	1.56
2,5,7-Trihydroxynaphthoquinone	MAPK10, MAPK8, MAPK1, DUSP22, DUSP16, DUSP4, DUSP5...	27	1.23
Busulfan	PTPRR, PTPRJ, PTPN23, PTPRA, PTPRE, DUSP4, DUSP18...	39	2.8

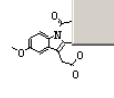
7


8


12


13


17


18


PASS

Prediction of Activity Spectra for Substances

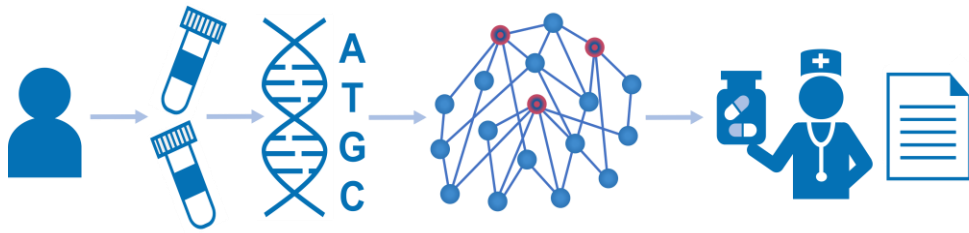
Version 9.1 *Professional*

Copyright © 2009

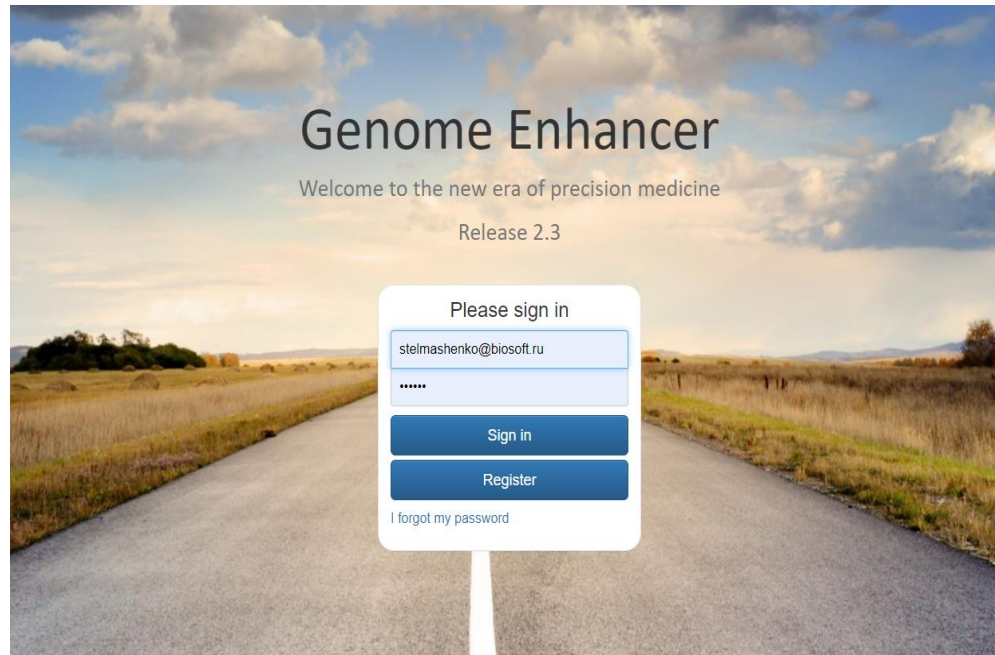
V. Poroikov, D. Filimonov & Associates

<http://www.ibmc.msk.ru/PASS/>

48 Substructure
There are 6 kno
Drood likeness:



**Genome
Enhancer**



<https://ge.genexplain.com>

Колоректальный рак

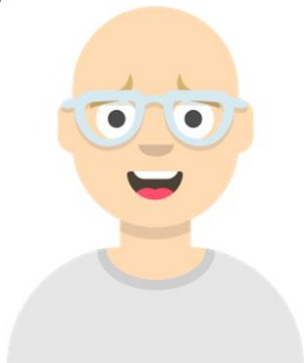
RNA-seq опухолевой и нормальной тканей



САНКТ-ПЕТЕРБУРГСКОЕ ГОСУДАРСТВЕННОЕ БЮДЖЕТНОЕ УЧРЕЖДЕНИЕ ЗДРАВООХРАНЕНИЯ

ГОРОДСКАЯ БОЛЬНИЦА №40
КУРОРТНОГО РАЙОНА

3



Химиотерапия

Ремиссия

Мастер-регуляторов с
обратными связями - 39

4 мишени

12



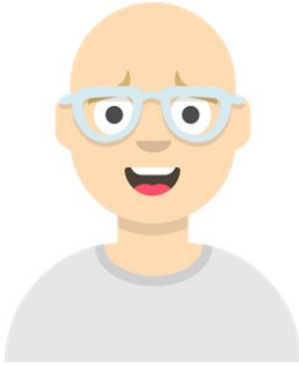
Химиотерапия + Бевацизумаб

Частичный регресс
Метастазы – легкие, печень

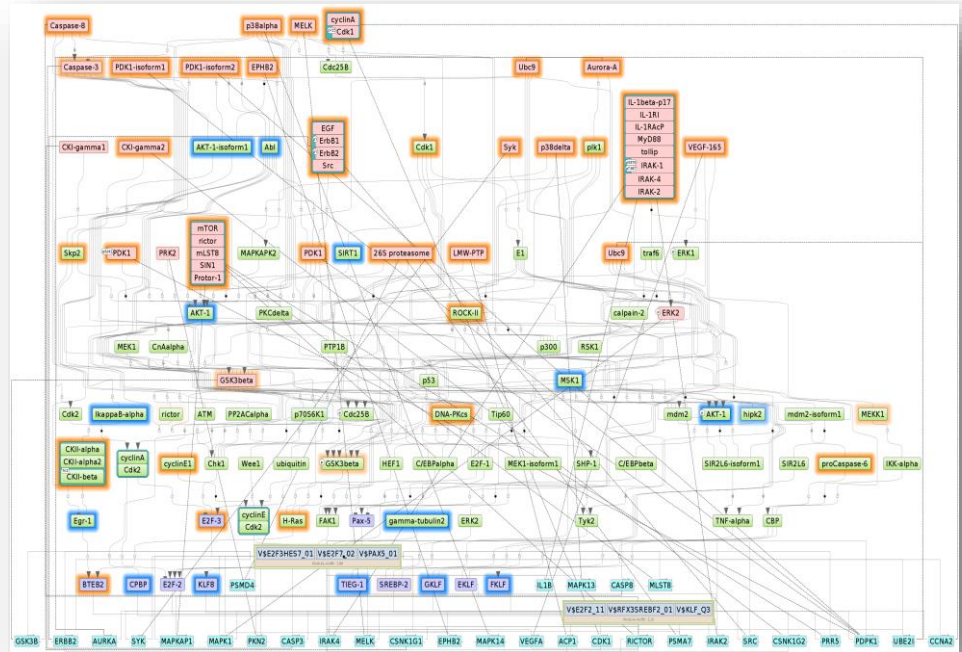
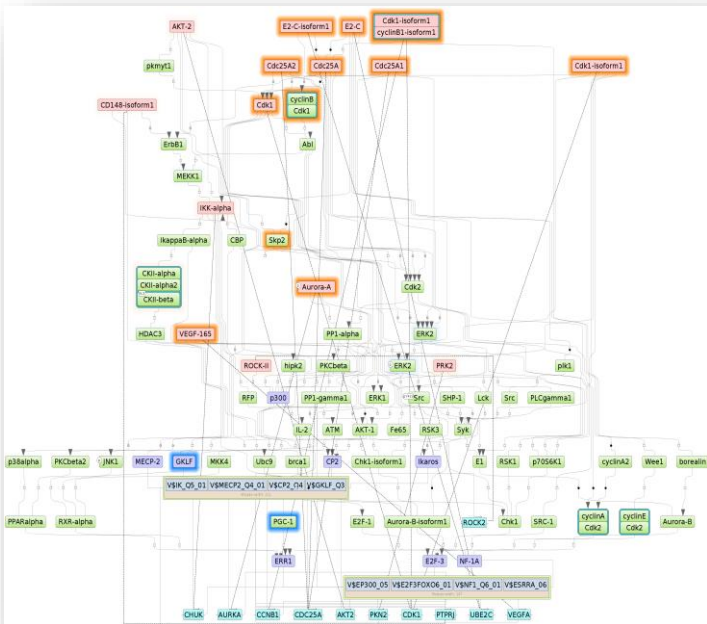
Мастер-регуляторов с
обратными связями - 110

12 мишеней

3



12



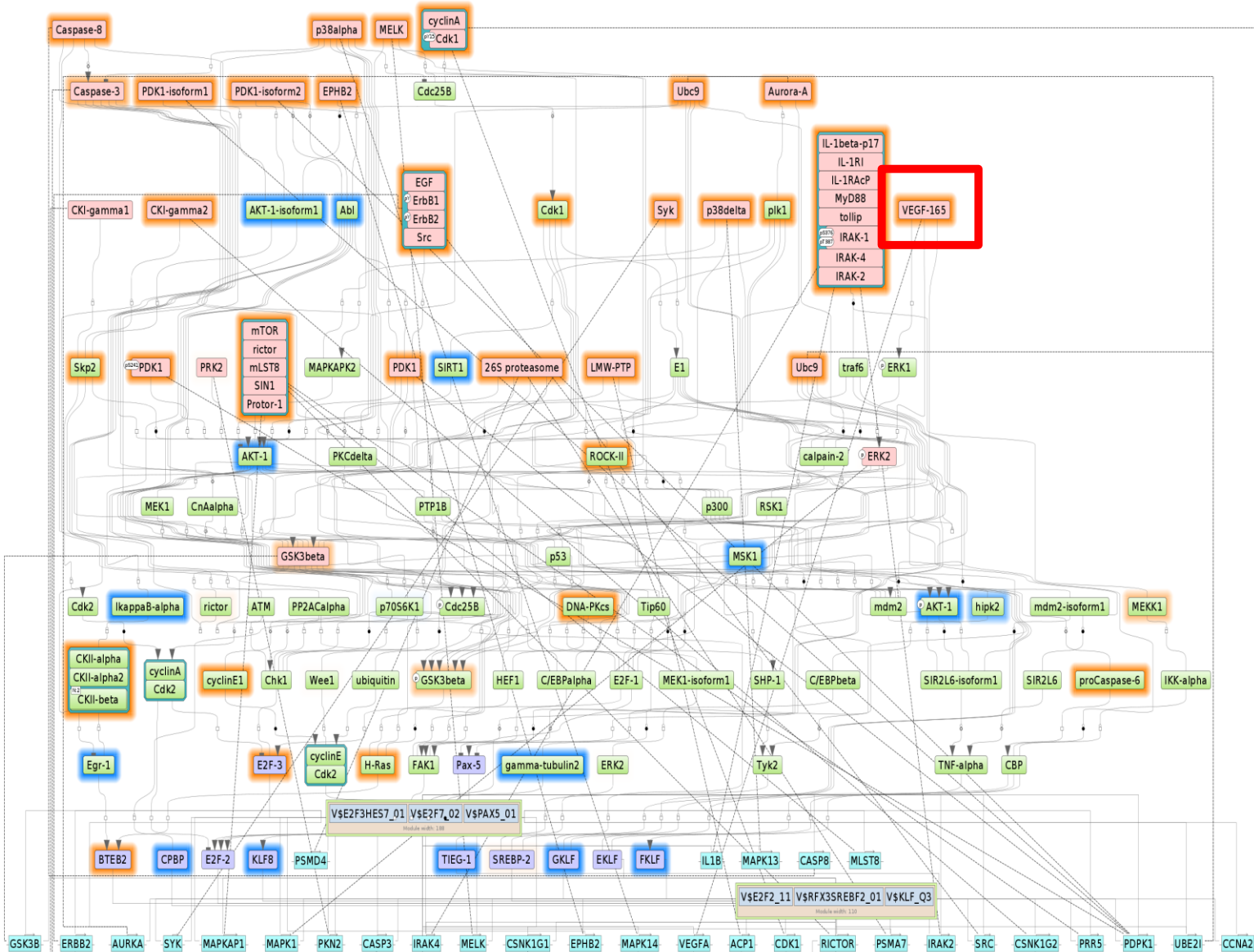
Мастер-регуляторы пациента 12



VEGF-165



**Бевацизумаб +
НО
+ другие
препараты**



Терапевтические мишени пациента 12

ID	Druggability score	Gene description	Gene symbol	HumanPSD title line	Name	Structures	LogFC_TvN	Total rank
ENSG00000101182	3	proteasome 20S subunit alpha 7	PSMA7	Proteasome subunit alpha type 7, a peptidase that is involved in endosomal transport, inhibits cell proliferation, upregulated in colorectal cancer; mRNA is downregulated in prostate cancer	PSMA7	Bortezomib, 2-ACETYLAMINO-4-METHYL-PENTANOIC ACID [1-(1-FORMYL-PENTYL-CARBAHOYL)-3-METHYL-BUTYL]... (more)	1.62966	75
ENSG00000117650	1	NIMA related kinase 2	NEK2	NIMA related kinase 2, a protein phosphatase inhibitor that induces chromosome segregation and spindle assembly checkpoint in mitosis, protein is upregulated in non-small cell lung cancer; mRNA is upregulated in breast, ovarian, and pancreatic cancer	NEK2	5-[(Z)-(5-CHLORO-2-OXO-1,2-DIHYDRO-3H-INDOL-3-YLIDENE)METHYL]-N-(DIETHYLAMINO)ETHYL]-2,4-DIMETHYL... (more)	2.77086	185
ENSG00000165025	6	spleen associated tyrosine kinase	SYK	Spleen tyrosine kinase, a signal transducer that acts in Fc-receptor mediated signaling, B cell differentiation, platelet activation, phagocytosis, and immunity, aberrantly expressed in breast cancer, lymphocytic leukemia, and systemic lupus erythematosus	SYK	Staurosporine, N-(2-hydroxy-1,1-dimethylethyl)-1-methyl-3-[(1H-pyrrolo[2,3-b]pyridin-2-yl)]... (more)	1.94292	186
ENSG00000198001	1	interleukin 1 receptor associated kinase 4	IRAK4	Interleukin-1 receptor-associated kinase 4, mediates the activation of NF-kappaB in TLR mediated innate immunity, acts in TNF production and LDL-mediated signaling; gene mutations correlate with invasive pneumococcal disease and prostate cancer	IRAK4	1-(3-HYDROXYPROPYL)-2-[[3-NITROBENZYL)AMINO]-1H-BENZIMIDAZOL-5-YL]PIVALATE	2.29815	246
ENSG00000164305	11	caspase 3	CASP3	Caspase 3 apoptosis-related cysteine peptidase, induces apoptosis, acts in GPCR signaling and long term depression, upregulated in Alzheimer disease, diabetes, arteriosclerosis, dermatitis, and several cancers; knockout of the mouse Casp3 causes cataract	CASP3	Minocycline, 5-[4-(1-Carboxymethyl-2-Oxo-Propylcarbamoyl)-Benzylsulfamoyl]-2-Hydroxy-Benzic Acid... (more)	0.70169	247
ENSG00000178999	3	aurora kinase B	AURKB	Aurora kinase B, acts in megakaryocyte differentiation, spermatogenesis, chromosome segregation, and meiotic spindle stabilization, regulates apoptosis, G2-M transition in mitosis, and cytokinesis, upregulated in prostate and several other neoplasms	AURKB	HESPERIDIN, AT9283, N-6-cyclohexyl-N-2-((4-morpholin-4-yl)phenyl)-9H-purine-2,6-diamine	1.6847	258
ENSG00000145386	33	cyclin A2	CCNA2	Cyclin A2, a cyclin-dependent protein kinase regulator that regulates cell cycle, cell proliferation, protein localization, and nuclear envelope breakdown, upregulated in Barrett esophagus, liver cirrhosis, germinoma, and breast and vulval neoplasms	CCNA2	4-(2,4-Dimethyl-Thiazol-5-Yl)-Pyrimidin-2-Ylamine, 6-O-Cyclohexylmethyl Guanine, [4-(2-Amino-4-... (more)	2.80857	261
ENSG00000134318	2	Rho associated coiled-coil containing protein kinase 2	ROCK2	Rho-associated coiled-coil containing protein kinase 2, mediates smooth muscle contraction, stress fiber formation, and focal adhesion assembly, upregulated in testicular cancer; gene polymorphism correlates with increased blood pressure and breast cancer	ROCK2	5-(1,4-DIAZEPAN-1-SULFONYL)ISOQUINOLINE, (R)-TRANS-4-(1-AMINOETHYL)-N-(4-PYRIDYL) ... (more)	1.5829	262
ENSG00000133275	3	casein kinase 1 gamma 2	CSNK1G2	Casein kinase 1 gamma 2, a protein kinase that acts in estrogen receptor signaling pathway, inhibits transcription; gene polymorphisms are associated with febrile seizures, mRNA expression is increased in osteosarcoma	CSNK1G2	IC261, N-(2-Aminoethyl)-5-Chlorosulfonamide-8-Sulfonamide, 5-iodotubercidin	0.95595	263
ENSG00000134058	2	cyclin dependent kinase 7	CDK7	Cyclin-dependent kinase 7, regulates cell cycle and DNA repair, acts in transcription initiation and protein catabolic process, increased expression correlates with Alzheimer disease; mRNA expression is downregulated in ovarian cancer	CDK7	Phosphothreonine, Flavopiridol	1.56184	263
ENSG00000170312	7	cyclin dependent kinase 1	CDK1	Cyclin-dependent kinase 1, acts in DNA damage checkpoint, cell proliferation, apoptosis, and neuron differentiation, regulates EGFR signaling, aberrant protein expression correlates with Alzheimer disease, HIV infection, and colonic and several neoplasms	CDK1	Indirubin-3'-Monoxide, Olomoucine, Hymenialdisine, SU9516, Flavopiridol, Alsterpaullone, AT7519	2.80857	274
ENSG00000140992	13	3-phosphoinositide dependent protein kinase 1	PDPK1	3-phosphoinositide-dependent protein kinase-1, acts in GPCR pathway, cell cycle regulation, cell migration, and ovarian follicle development, upregulated in breast cancer; knockout of the mouse Pdpk1 causes premature ovarian failure	PDPK1	Celecoxib, Inositol 1,3,4,5-Tetrakisphosphate, 7-Hydroxystaurosporine, 3-[1-(3-Aminopropyl)-... (more)	1.52583	278
ENSG00000133216	1	EPH receptor B2	EPHB2	EPH receptor-B2, a tyrosine kinase that acts in Ras signaling, axonal fasciculation, vasculogenesis, nervous system development, and memory, regulates apoptosis, cell adhesion, and synaptic plasticity, upregulated in brain, prostate, and several neoplasms	EPHB2	Phosphoaminophosphonic Acid-Adenylic Ester	2.21598	284



Бевацизумаб + доп.
(нужна была комбинация)

ENSG00000143727	2							
ENSG00000116478	5							
ENSG00000166851	5	polo like kinase 1	PLK1	Polo-like kinase 1, a serine-threonine kinase that acts in Golgi organization, mitotic cell cycle G2-M transition DNA damage checkpoint, spindle assembly, cytoskeleton organization, and apoptosis, upregulated in thyroid and various other neoplasms	PLK1	3-[3-chloro-5-[[5-((1S)-1-phenylethyl)amino]isoxazolol[5,4-c]pyridin-3-yl]phenyl]propan-1-ol, 3-[3-... (more)	2.11909	343
ENSG000000087586	13	aurora kinase A	AURKA	Aurora kinase A, acts in centrosome separation, cell cycle, cell proliferation, and in-utero embryonic development, upregulated in fibrocystic breast disease, medulloblastoma, Barrett esophagus, and several other cancers	AURKA	Phosphothreonine, AT9283, CYC116, MLN8237, 4-(4-METHYLPYPERAZIN-1-YL)-N-[5-(2-THIENYLACETYL)-... (more)	2.41513	348
ENSG00000070770	1	casein kinase 2 alpha 2	CSNK2A2	Casein kinase 2 alpha prime polypeptide, a protein tyrosine kinase and transcription regulator that acts in mitotic spindle checkpoint, cell proliferation, and spermatogenesis, upregulated in villous adenoma	CSNK2A2	[1-(6-(6-((1-methylethyl)amino)-1H-indazol-1-yl)pyrazin-2-yl)-1H-pyrrol-3-yl]acetic acid	1.16968	351
ENSG00000254087	4	LYN proto-oncogene, Src family tyrosine kinase	LYN	Homolog of v-yes-1 Yamaguchi sarcoma viral related oncogene, a protein tyrosine kinase that acts in apoptosis, cytokine-mediated signaling pathway, leukocyte chemotaxis, and phagocytosis, upregulated in squamous cell carcinoma and several other neoplasms	LYN	1-Tert-Butyl-3-(4-Chloro-Phenyl)-1H-Pyrazol[3,4-D]Pyrimidin-4-Ylamine, Bosutinib, Ponatinib, ... (more)	1.47931	351
ENSG00000141736	7	erb-b2 receptor tyrosine kinase 2	ERBB2	V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, activates MAPK activity and positively regulates cell proliferation, inhibits apoptosis, acts in angiogenesis and organ development, upregulated in breast, prostate, and several other cancers	ERBB2	Trastuzumab, Lapatinib, IGN311, XL647, ado-trastuzumab emtansine, Pertuzumab, Afatinib	1.36958	353
ENSG00000205629	1	leucine carboxyl methyltransferase 1	LCMT1	Leucine carboxyl methyltransferase 1, a protein phosphatase type 2A activator that plays a role in spindle checkpoint, apoptotic nuclear fragmentation, and regulation of cell proliferation, downregulated in heart failure	LCMT1	L-Leucine	1.09522	381
ENSG00000174775	5	HRas proto-oncogene, GTPase	HRAS	Homolog of v-Ha-ras Harvey rat sarcoma viral oncogene, a signal transducer that mediates aging, upregulated in cervical and several neoplasms; gene polymorphism is associated with arteriosclerosis, autistic disorder, psoriasis, and tobacco use disorder	HRAS	Hexane-1,6-Diol, Trifluoroethanol, Guanosine-5'-Triphosphate, Guanosine-5'-Diphosphate, N,N'-... (more)	1.08844	388
ENSG00000112742	1	TTK protein kinase	TTK	TTK protein kinase, a dual specificity protein kinase that induces mitosis transition, inhibits apoptosis and protein ubiquitination, upregulated in stomach and breast neoplasms; gene mutation correlates with colorectal cancer	TTK	2,6-Dihydroanthra[1,9-Cd]Pyrazol-6-One	2.71685	393
ENSG00000112715	12	vascular endothelial growth factor A	VEGFA	Vascular endothelial growth factor A, acts in angiogenesis, heart development, and cell migration, regulates cell proliferation and cytokine secretion, upregulated in breast neoplasm, hepatocellular carcinoma, rheumatoid arthritis, and Alzheimer disease	VEGFA	Bevacizumab, Minocycline, Glucizide, Carvedilol, Ranibizumab, Pyroglutamic Acid, Tris, ... (more)	1.27704	397
ENSG00000112062	53	mitogen-activated protein kinase 14	MAPK14	Mitogen activated protein kinase 14, a signal transducer that is involved in cell proliferation and differentiation, apoptosis, cell cycle, muscle development, and prostaglandin biosynthesis, upregulated in psoriasis and lung and brain diseases	MAPK14	4-[5-[2-(1-Phenyl-Ethylamino)-Pyrimidin-4-Yl]-1-Methyl-4-(3-Trifluoromethylphenyl)-1H-Imidazol-2-... (more)	1.13976	399
ENSG00000166483	6	WEE1 G2 checkpoint kinase	WEE1	WEE1 homolog, a protein tyrosine kinase that regulates G2-M transition of cell cycle and circadian rhythm, upregulated in liver cirrhosis; mRNA is downregulated in azoospermia and HIV infections, map position correlates with Beckwith-Wiedemann syndrome	WEE1	9-HYDROXY-4-PHENYL-6H-PYRROLO[3,4-C]CARBAZOLE-1,3-DIONE, 9-HYDROXY-6-(3-HYDROXYPROPYL)-4-(2-... (more)	0.0199	406
ENSG00000100030	14	mitogen-activated protein kinase 1	MAPK1	Mitogen-activated protein kinase 1, a signal transducer that acts in chemotaxis and antiapoptosis, regulates phosphorylation, neurogenesis, ossification, and transcription, aberrant expression correlates with depression, breast and various other neoplasms	MAPK1	Isoprenaline, Arsenic trioxide, Olomoucine, Phosphothreonine, Purvalanol, SB220025, N,... (more)	1.93006	427
				Interleukin 1 beta, a signal transducer that acts in cell migration, upregulated in AIDS, anemia, brain diseases, diabetes,		Minocycline, AV411, VP025, 681323, Gallium nitrate,		

Предсказанные лекарства для пациента 12



Table 12. FDA approved drugs or drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

[See full table →](#)

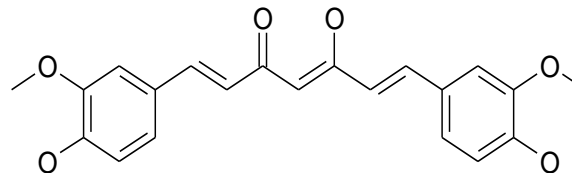
Name	Target names	Drug rank	Disease activity score	Phase 4	Status (provided by Drugbank)
Minocycline	VEGFA, IL1B, CASP3	30	2	Acne Vulgaris, Affect, Alopecia, Autistic Disorder, Bacterial Infections, Bipolar Disorder, Chronic Periodontitis...	small molecule,approved,investigational
Celecoxib	PDPK1	77	11	Colorectal Neoplasms, Adenoma, Adenomatous Polyposis Coli, Adenomatous Polyps, Ankle Injuries, Arteriosclerosis, Arthritis...	small molecule,approved,investigational
Pertuzumab	ERBB2	103	3	Breast Neoplasms, Neoplasms	biotech,approved
Afatinib	ERBB2	114	4	Carcinoma, Non-Small-Cell Lung, Noma	small molecule,approved
Aflibercept	VEGFA	115	7	Central Serous Chorioretinopathy, Choroidal Neovascularization, Cysts, Diabetic Retinopathy, Edema, Macular Degeneration, Macular Edema...	biotech,approved



12



Pharmacological Potential of Curcumin



332 *Current Drug Targets*, 2011, 12, 332-347

The Targets of Curcumin

Hongyu Zhou¹, Christopher S. Beavers¹ and Shile Huang^{*1,2}

¹Department of Biochemistry and Molecular Biology and ²Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA

Abstract: Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of the plant *Curcuma longa*. For centuries, curcumin has been used in some medicinal preparation or used as a food-coloring agent. In recent years, extensive *in vitro* and *in vivo* studies suggested curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties. The underlying mechanisms of these effects are diverse and appear to involve the regulation of various molecular targets, including transcription factors (such as nuclear factor- κ B), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, curcumin has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease, and other inflammatory illnesses. This review summarizes various *in vitro* and *in vivo* pharmacological aspects of curcumin as well as the underlying action mechanisms. The recently identified molecular targets and signaling pathways modulated by curcumin are also discussed here.

Keywords: Curcumin, molecular targets, transcription factors, growth factors, inflammatory cytokines, protein kinases, enzymes.

Mol. Nutr. Food Res. 2008, 52, 000-000 DOI 10.1002/mnfr.200700354

Review

Multi-targeted therapy by curcumin: how spicy is it?

Ajay Goel¹, Sonia Jhurani² and Bharat B. Aggarwal²

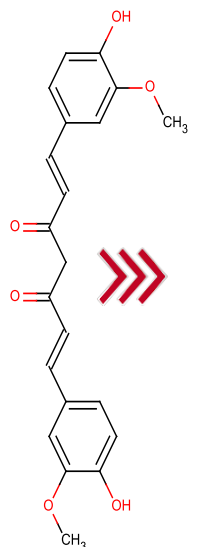
¹ Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA
² Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteasome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

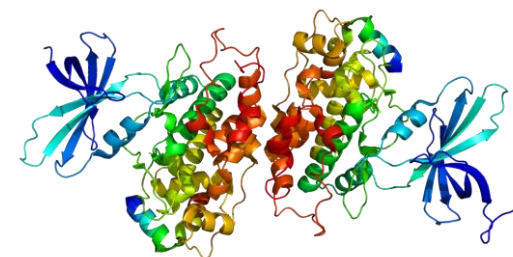
Key words: Cancer / Curcumin / Cyclooxygenases / Multi-targeted therapy / Tumor necrosis factor
 Received: September 7, 2007; revised: October 12, 2007; accepted: October 21, 2007

Targets predicted for curcumin by PASS 2021 Advanced ChEMBL-27

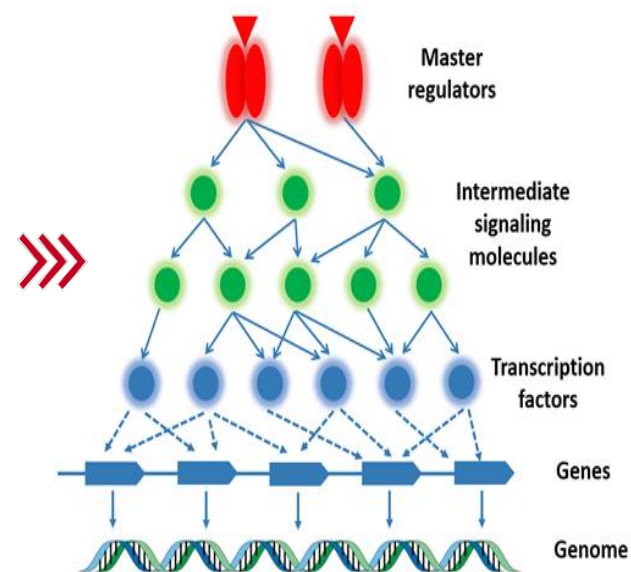
Gene Symbol	Unspecified ID	Pa	Pi	action
GSK3B	Glycogen synthase kinase-3 beta	0.846	0.039	inhibitor
AOX1	Aldehyde oxidase	0.789	0.058	inhibitor
PIK3R1	PI3-kinase p85-alpha subunit	0.767	0.009	inhibitor
TOP2A	DNA topoisomerase II alpha	0.716	0.001	inhibitor
BRCA1	Breast cancer type 1 susceptibility protein	0.697	0.004	inhibitor
ALOX12	Arachidonate 12-lipoxygenase	0.653	0.062	inhibitor
LIG1	DNA ligase I	0.651	0.076	inhibitor
TDP1	Tyrosyl-DNA phosphodiesterase I	0.638	0.039	inhibitor
AKR1A1	Aldehyde reductase	0.621	0.026	inhibitor
CA3	Carbonic anhydrase III	0.62	0.004	inhibitor
CRYZ	Quinone oxidoreductase	0.601	0.005	activator
GLA	Alpha-galactosidase A	0.585	0.095	inhibitor
CELA1	Elastase I	0.527	0.057	inhibitor
UGT1A1	UDP-glucuronosyltransferase 1-1	0.505	0.024	inhibitor
HSD17B10	Endoplasmic reticulum-associated amyloid beta	0.502	0.091	inhibitor
MPG	DNA-3-methyladenine glycosylase	0.485	0.034	inhibitor
LPL	Lipoprotein lipase	0.48	0.104	inhibitor
ALPI	Intestinal alkaline phosphatase	0.471	0.039	inhibitor
CBS	Cystathionine beta-synthase	0.465	0.003	inhibitor
PLCG1	Phospholipase C-gamma-1	0.46	0.019	inhibitor
CA6	Carbonic anhydrase VI	0.457	0.004	inhibitor
BLM	Bloom syndrome protein	0.457	0.092	inhibitor
CAMK2B	CaMK kinase II beta	0.452	0.285	inhibitor
RECQL	ATP-dependent DNA helicase Q1	0.451	0.231	inhibitor
CYP1A2	Cytochrome P450 1A2	0.45	0.013	inhibitor
MAOA	Monoamine oxidase A	0.448	0.007	inhibitor
ALOX15	Arachidonate 15-lipoxygenase	0.438	0.106	inhibitor
ATG4B	Cysteine protease ATG4B	0.434	0.072	inhibitor
CA13	Carbonic anhydrase XIII	0.427	0.006	inhibitor
DHODH	Dihydroorotate dehydrogenase	0.425	0.062	inhibitor
DYRK1A	Dual-specificity tyrosine-phosphorylation regulator	0.419	0.007	inhibitor
PTPRCAP	Protein tyrosine phosphatase receptor type C-as	0.418	0.007	inhibitor
CYP2C9	Cytochrome P450 2C9	0.398	0.044	inhibitor
LYPLA1	Acyl-protein thioesterase I	0.388	0.03	inhibitor
POLK	DNA polymerase kappa	0.387	0.115	inhibitor
HNMT	Histamine N-methyltransferase	0.38	0.157	inhibitor
CHRM1	Muscarinic acetylcholine receptor M1	0.376	0.072	antagonist
ALPG	Alkaline phosphatase placental-like	0.367	0.007	inhibitor
ABAT	Gamma-amino-N-butyrate transaminase	0.362	0.021	inhibitor
CHRM5	Muscarinic acetylcholine receptor M5	0.358	0.077	antagonist



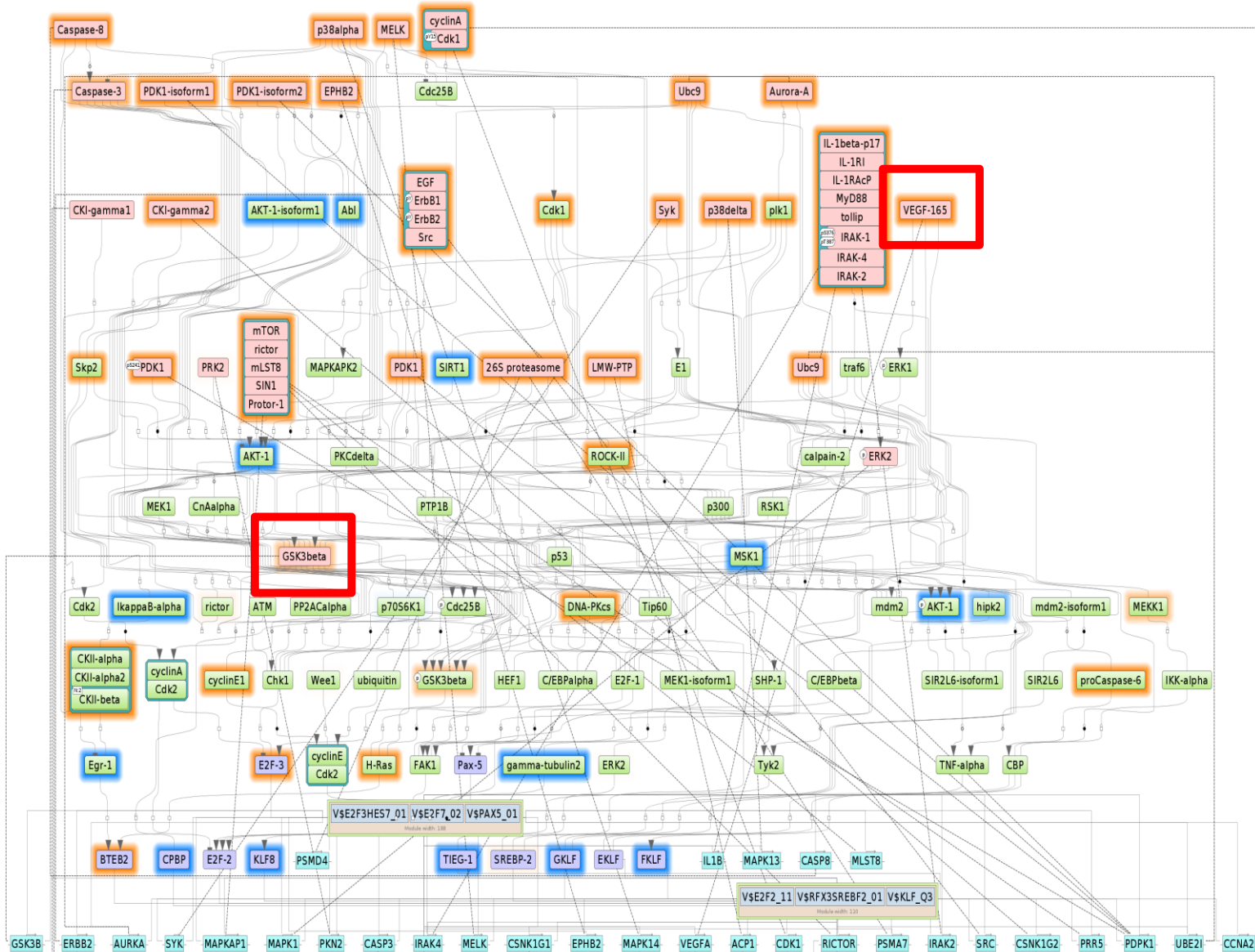
Curcumin



GSK3-beta



Мастер-регуляторы пациента 12



VEGF-165



**Бевацизумаб
+
Curcumin?**

GSK3beta

Биомаркеры негативно ассоциированные с CRC

CRC negative biomarkers from case 12

12

First Previous Page 1 of 1 Next Last Showing 1 to 7 of 7 entries Show 50 entries

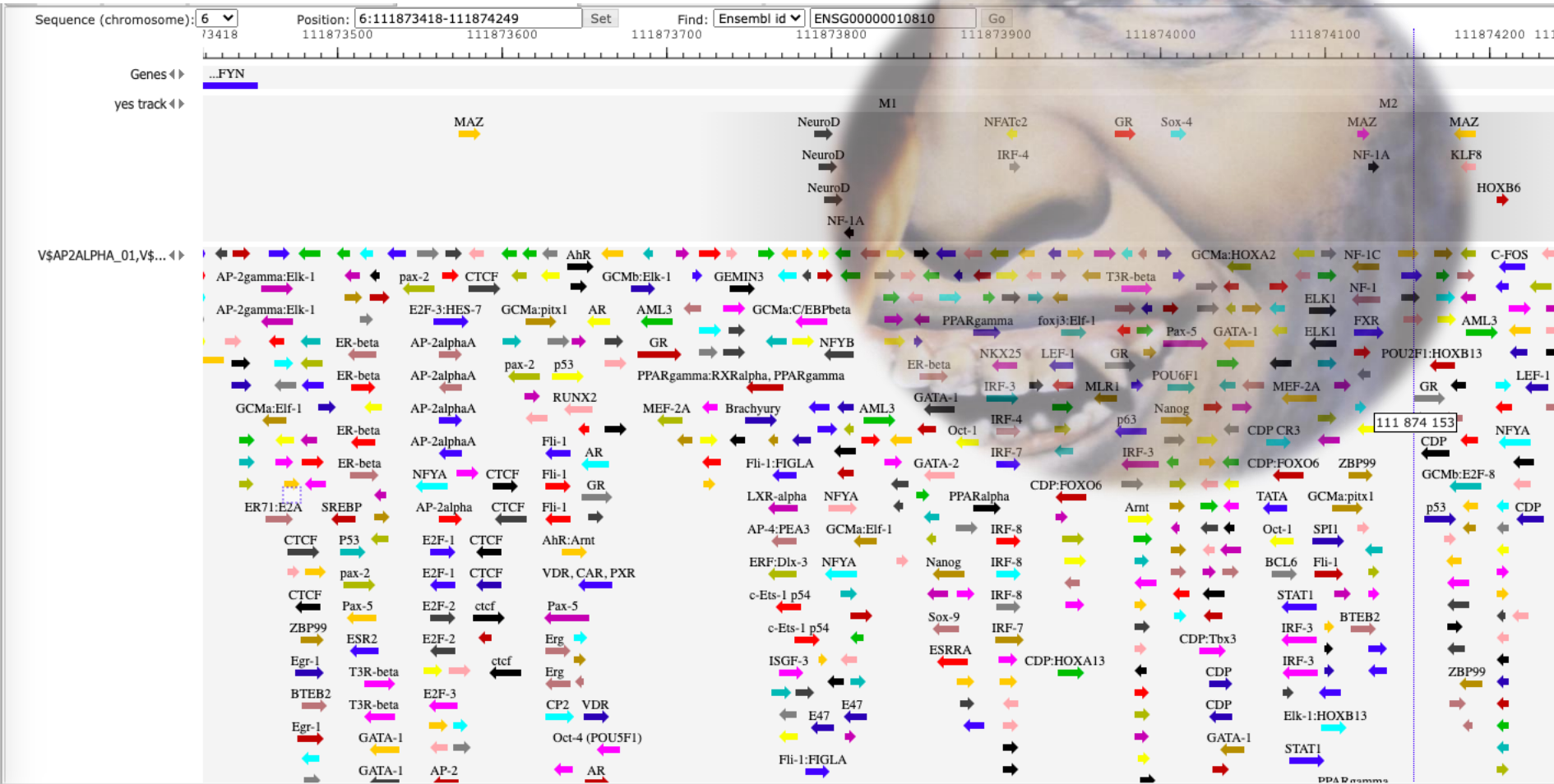
ID	LogFC_TvN	Gene description	Gene symbol	Ensembl ID
ENSG00000133216	2.21598	EPH receptor B2	EPHB2	ENSG00000133216
ENSG00000183765	1.83091	checkpoint kinase 2	CHEK2	ENSG00000183765
ENSG00000146648	1.36958	epidermal growth factor receptor	EGFR	ENSG00000146648
ENSG00000197122	1.36958	SRC proto-oncogene, non-receptor tyrosine kinase	SRC	ENSG00000197122
ENSG00000064012	1.22894	caspase 8	CASP8	ENSG00000064012
ENSG00000133703	1.08844	KRAS proto-oncogene, GTPase	KRAS	ENSG00000133703
ENSG00000082701	0.53519	glycogen synthase kinase 3 beta	GSK3B	ENSG00000082701



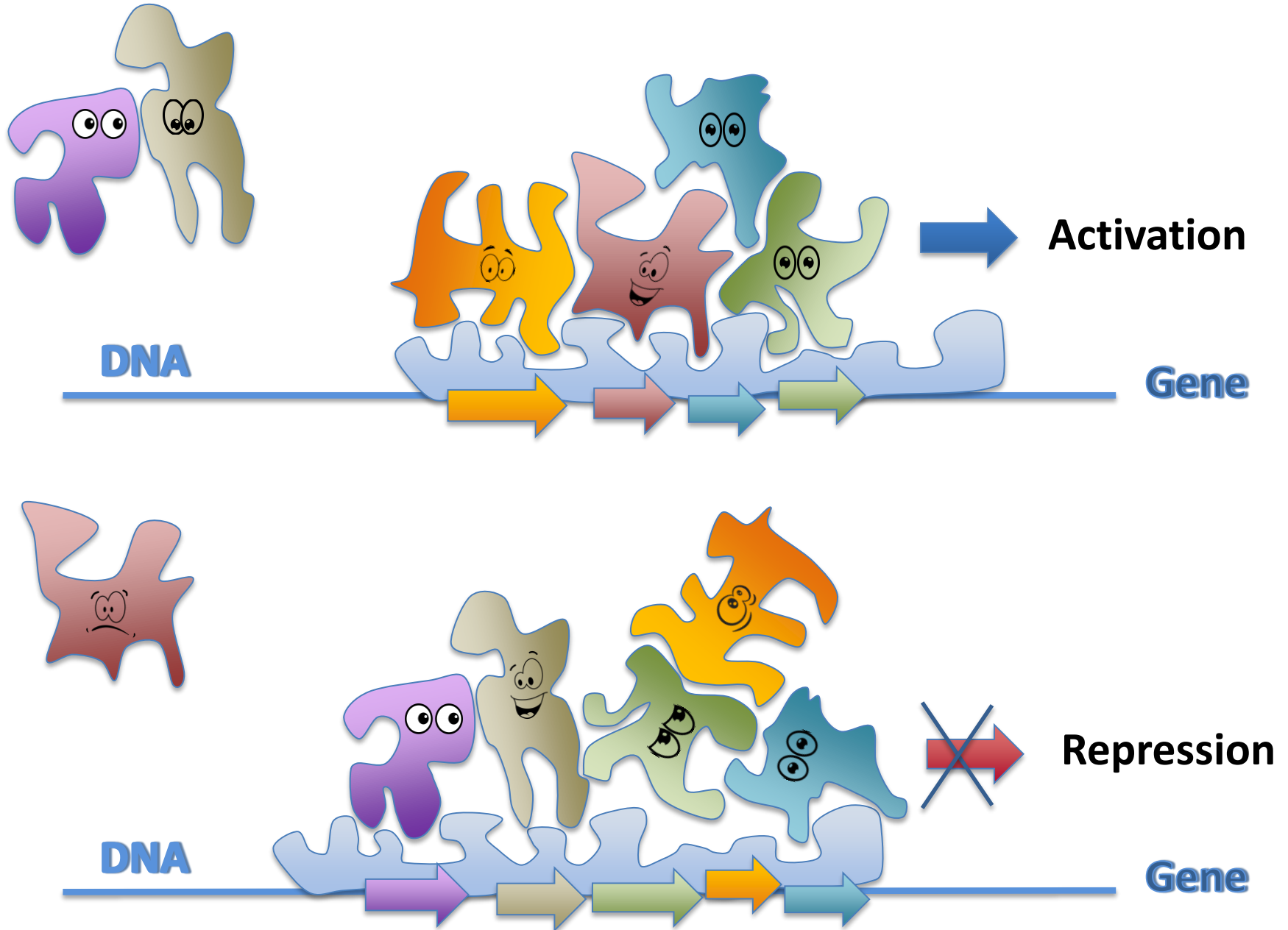
HumanPSD™

- Increased activity of GSK3B associated with Alzheimer disease
- GSK3B gene does not correlate with colorectal neoplasms
- Increased dephosphorylation of GSK3B may cause increased response to drug associated with lung neoplasms
- expression of EPHB2 protein does not correlate with colorectal neoplasms
- increased expression of EPHB2 mRNA correlates with bone neoplasms associated with lung neoplasms

TF clusters in the promoter of **FYN** gene



It's a fuzzy puzzle!



A Phase Separation Model for Transcriptional Control

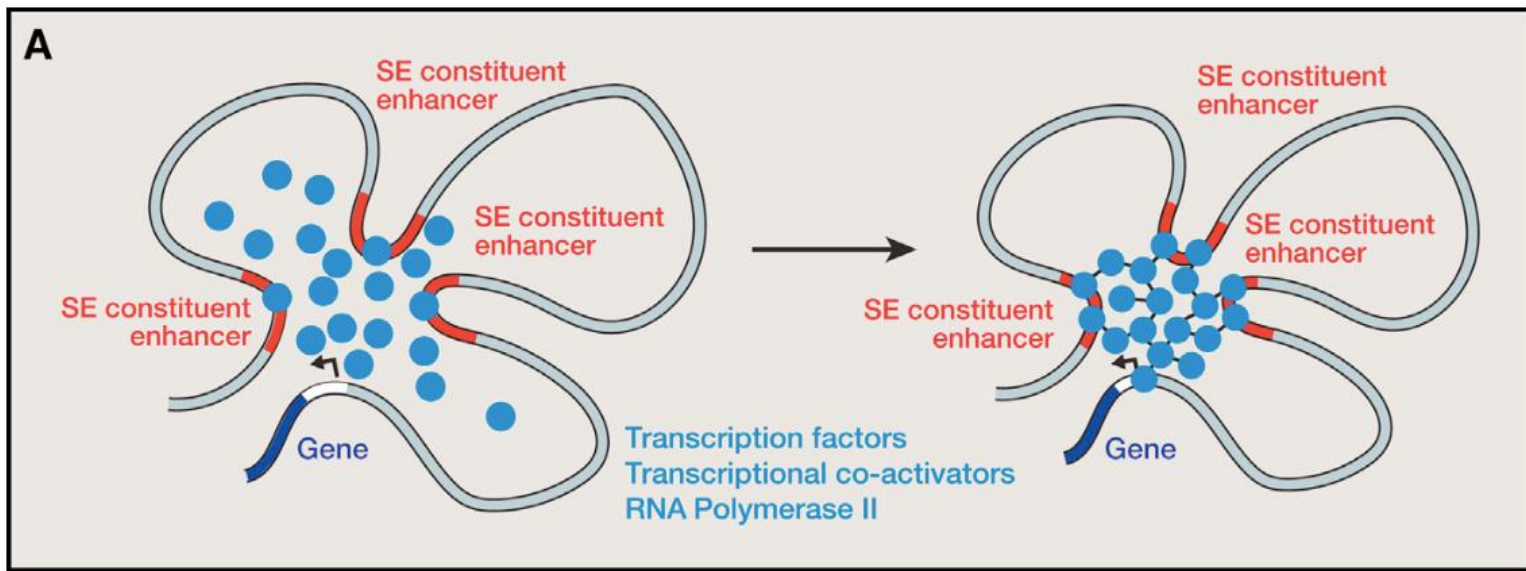
Denes Hnisz,^{1,10} Krishna Shrinivas,^{2,7,8,10} Richard A. Young,^{1,3,*} Arup K. Chakraborty,^{2,4,5,6,7,8,*} and Phillip A. Sharp^{3,9,*}

¹Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA

²Department of Chemical Engineering

³Department of Biology

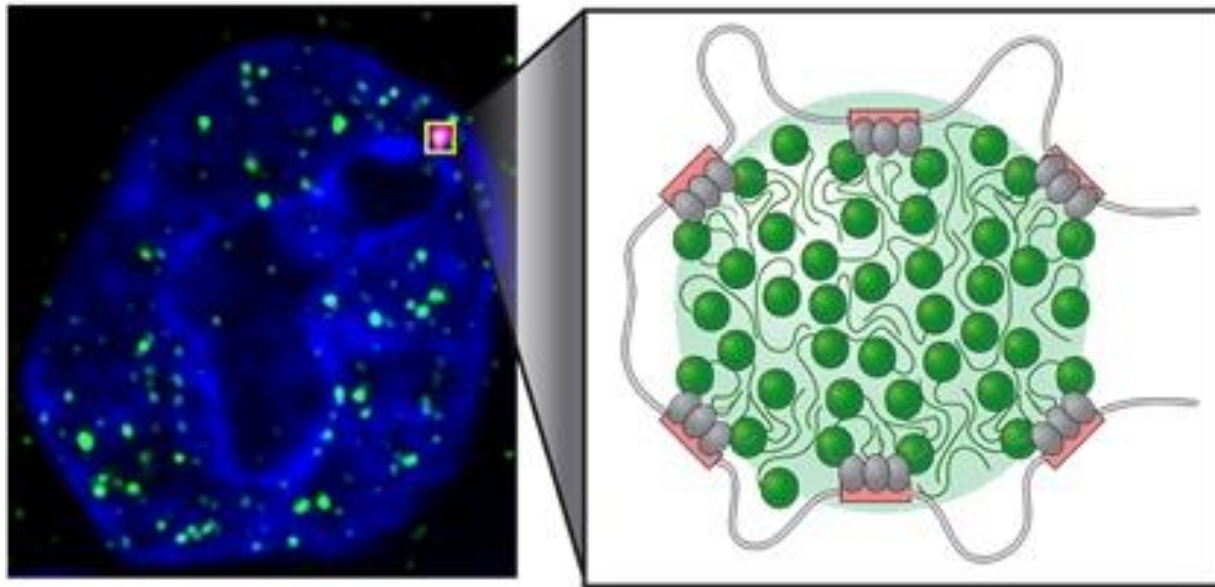
⁴Department of Physics





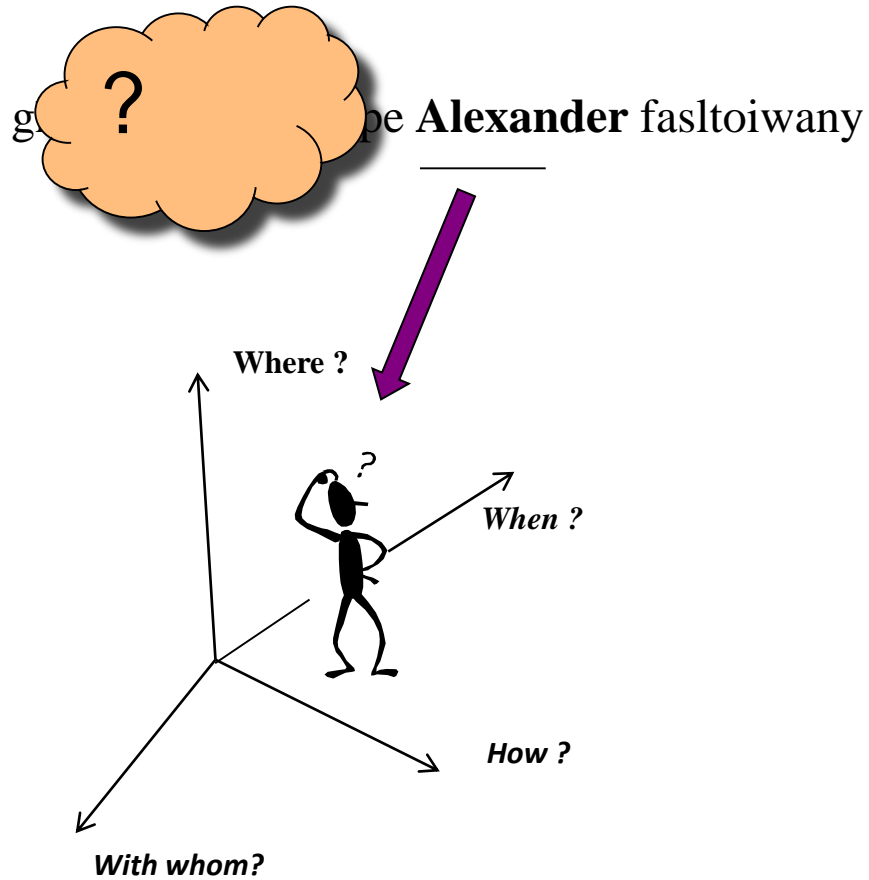
Phase-separated condensates

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



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

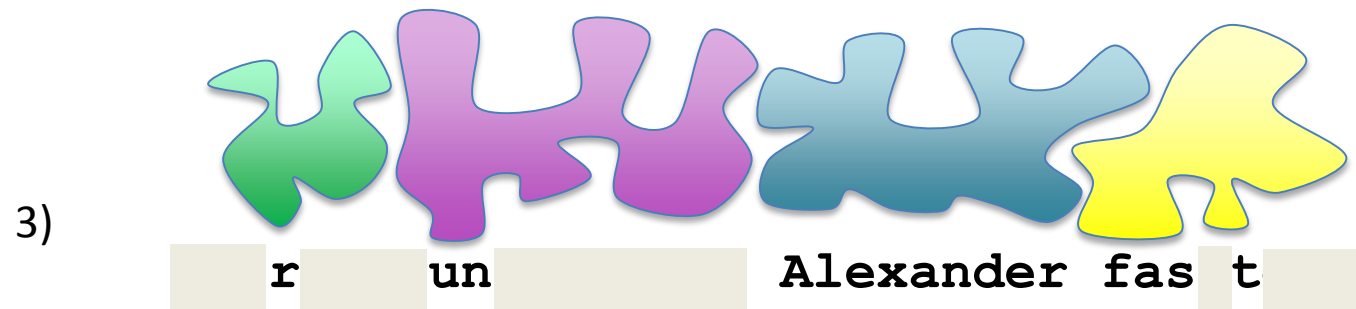
“Regulatory code”



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

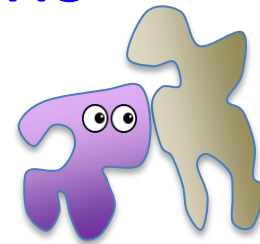
gherllojunomd-bype Alexander fasltoiwany



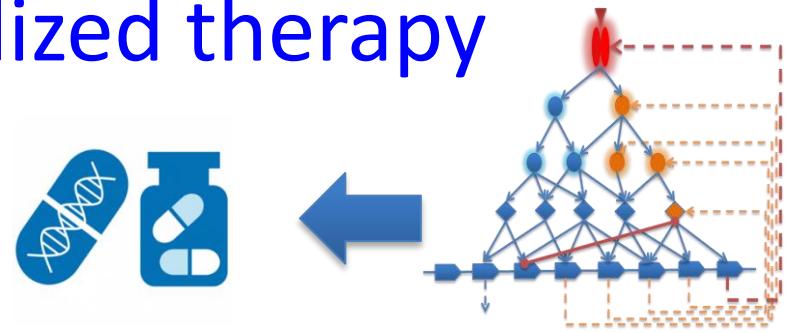
- Sites are short but genome is big- sites are everywhere!



- Fuzzy puzzle of site combinations



- Corrupted pathways. Master-regulators drug targets, personalized therapy



Thank you!

E-REDALERT

FindingMS

PD-MitoQUANT

COLOSSUS

OxidoCurin

GlioTrain

miRCol

Optogenerapy

miRNA DisEASY

MyPathSem



ERA PerMed



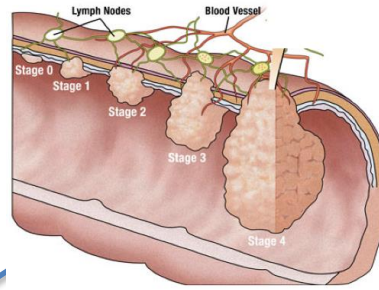
www.genexplain.com

Thank you!



Colorectal cancer (CRC):

EU Project SysCol
300 patients:



RESEARCH

Open Access

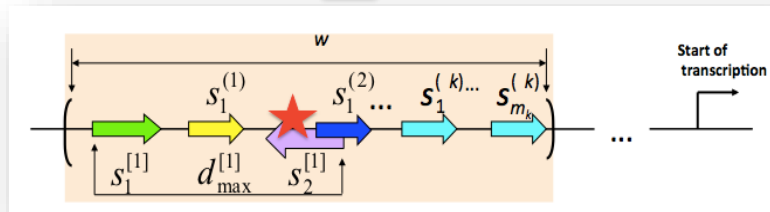
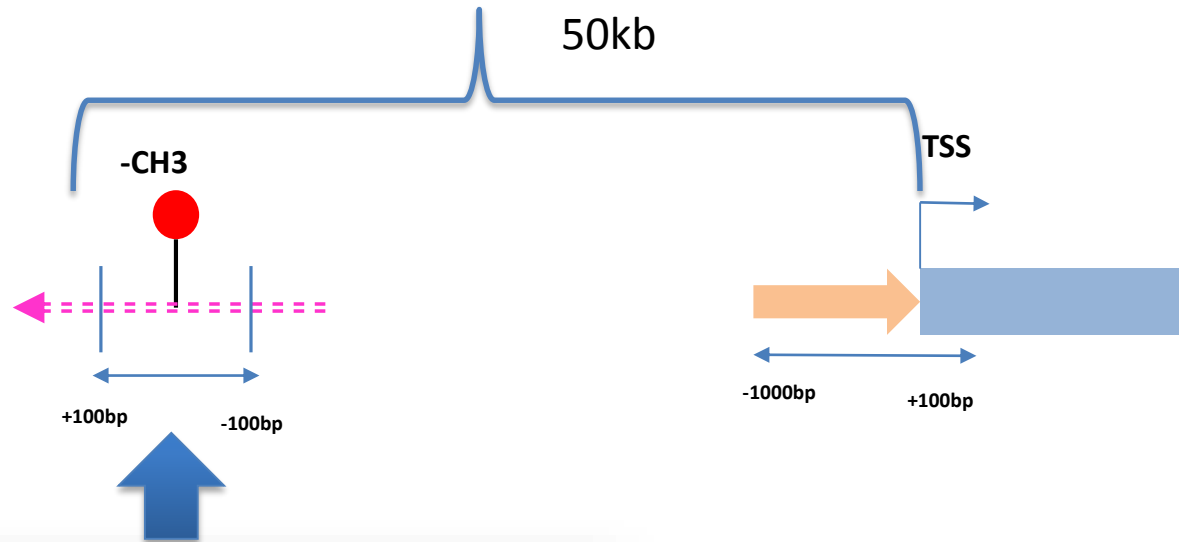
Walking pathways with positive feedback loops reveal DNA methylation biomarkers of colorectal cancer



CpG methylation profiles

Correlation

Gene expression profiles

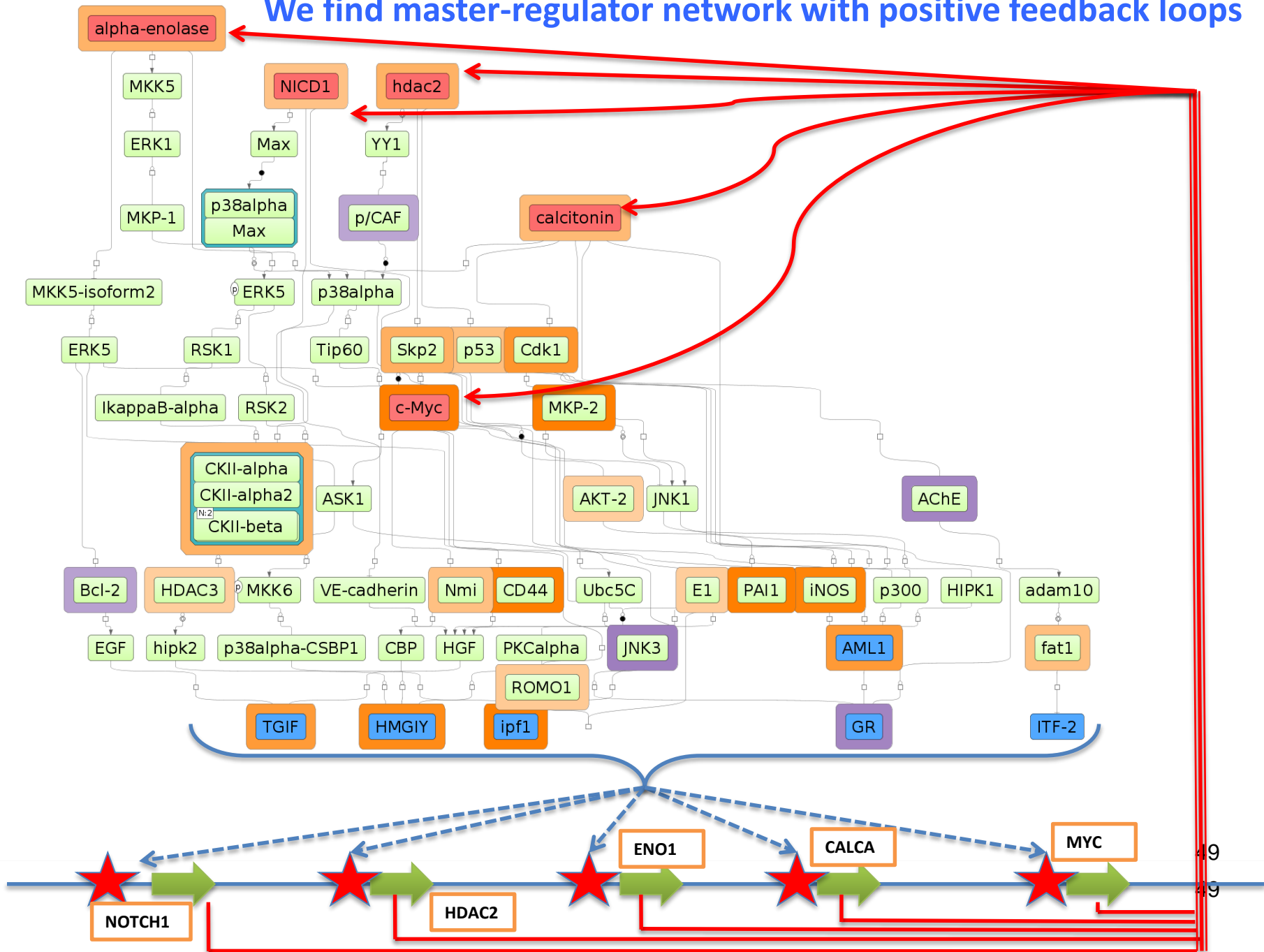


SYSCOL
SYSTEMS BIOLOGY OF COLORECTAL CANCER

Systems Biology of Colorectal Cancer



We find master-regulator network with positive feedback loops



We identified 6 CpG methylation biomarkers for early detection of CRC

Probe ID	Chromosome	Gene Symbol	Gene Name
cg01421342	11	CALCA	calcitonin-related polypeptide alpha
cg06972019 (CpG No 3)	1	ENO1	enolase 1, (alpha)
cg00163372	8	MYC	v-myc avian myelocytomatosis viral oncogene homolog
cg02991571	13	PDX1	pancreatic and duodenal homeobox 1
cg24093411	5	TCF7	transcription factor 7 (T-cell specific, HMG-box)
cg02612618	19	ZNF43	zinc finger protein 43

?

93% success rate on independent cohort (from Siberia)

In liquid biopsy