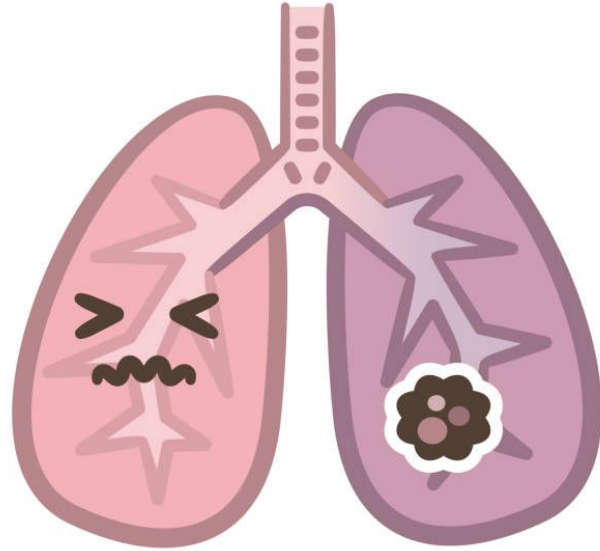

Exploration of Prognostic Markers and Therapeutic Targets in Lung Cancer

— Nathan Wong, Tyler Kwok, Julian Han —

Why Lung Cancer?

- Lung cancer is one of the deadliest diseases in the world
- Multiple subtypes
 - NSCLC and SCLC, specifically lung adenocarcinoma (LUAD)
- Critical challenge in therapy - LUAD remains asymptomatic in early stages, leading to late diagnoses



Project Questions

- Is there an overlap between gene expression profiles of patients with early-stage LUAD versus invasive LUAD, can it reveal markers of LUAD progression?
- What can we gather from genes unique to invasive LUAD?

Method - Find Overlapping Genes

- GSE10799
- 16 lung adenocarcinoma samples
- GSE118370
- 6 invasive lung adenocarcinoma samples

> [Clin Cancer Res.](#) 2009 Mar 1;15(5):1566-74. doi: 10.1158/1078-0432.CCR-08-2188.
Epub 2009 Feb 10.

Genomic profiles associated with early micrometastasis in lung cancer: relevance of 4q deletion

Michaela Wrage ¹, Salla Ruosaari, Paul P Eijk, Jussuf T Kaifi, Jaakko Hollmén, Emre F Yekebas, Jakob R Izbicki, Ruud H Brakenhoff, Thomas Streichert, Sabine Riethdorf, Markus Glatzel, Bauke Ylstra, Klaus Pantel, Harriet Wikman

> [BMB Rep.](#) 2018 Dec;51(12):648-653. doi: 10.5483/BMBRep.2018.51.12.205.

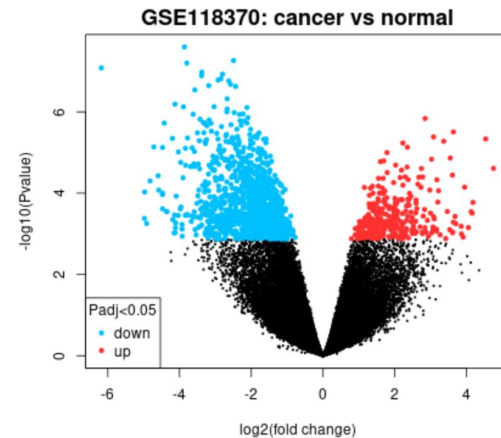
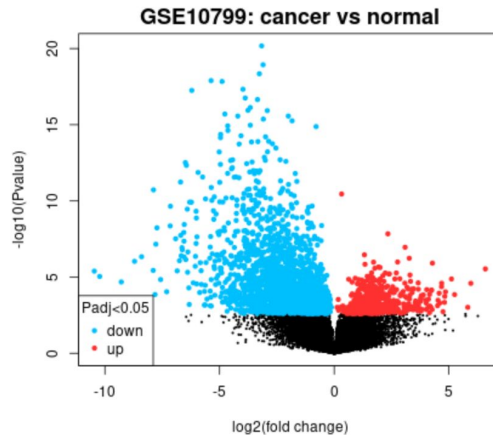
SPINK1 promotes cell growth and metastasis of lung adenocarcinoma and acts as a novel prognostic biomarker

Liyun Xu ¹, Changchang Lu ¹, Yanyan Huang ¹, Jihang Zhou ¹, Xincheng Wang ¹, Chaowu Liu ², Jun Chen ², Hanbo Le ²

Method - Find Overlapping Genes

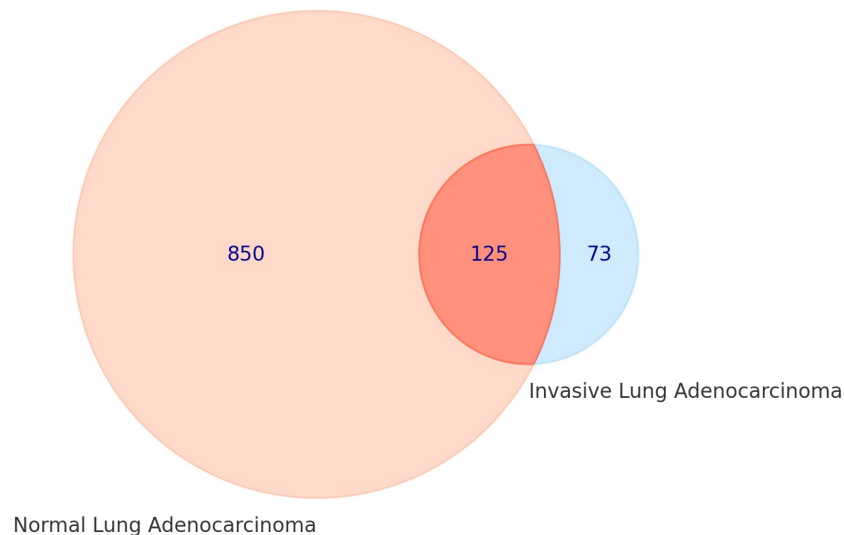
Ran differential expression against normal samples using GEO2R (DESeq2)

Filtered genes based on $\log_2FC > 1$ and $p_{adj} < 0.01$, then found overlapping genes



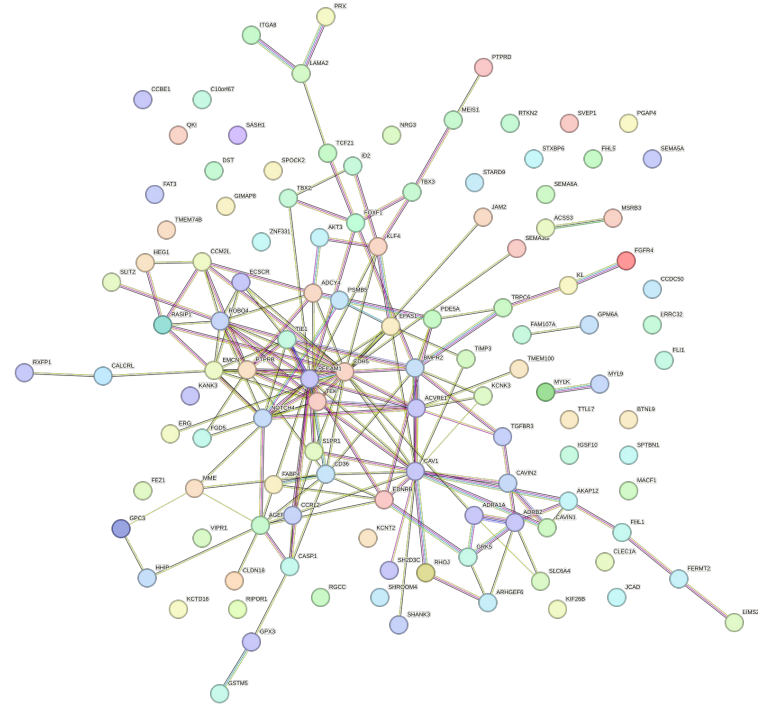
Method - Find Overlapping Genes

- 975 filtered genes in early lung cancer dataset
- 198 filtered genes in invasive lung cancer dataset
- Found **125** overlapping genes, and 73 genes unique to metastatic lung cancer



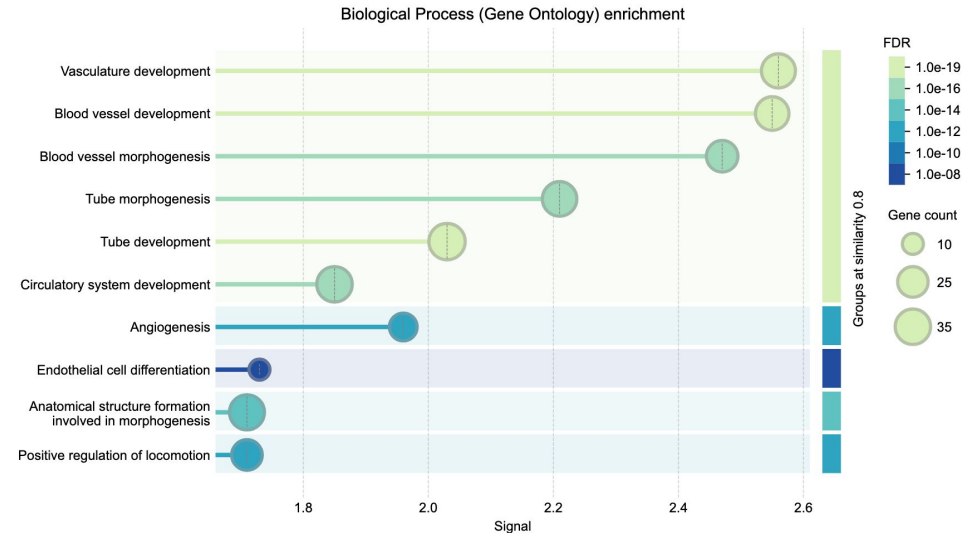
Analysis 1 - Step 1: Functional Enrichment - STRING

- PPI enrichment value: $<1e-16$
- Biological Processes:
 - Vasculature development, blood vessel development, blood vessel morphogenesis
- Molecular function:
 - Protein binding
- Cellular Component:
 - Intrinsic component of plasma membrane, plasma membrane, cell periphery
- KEGG Pathways:
 - cGMP-PKG signalling, regulation of lipolysis in adipocytes



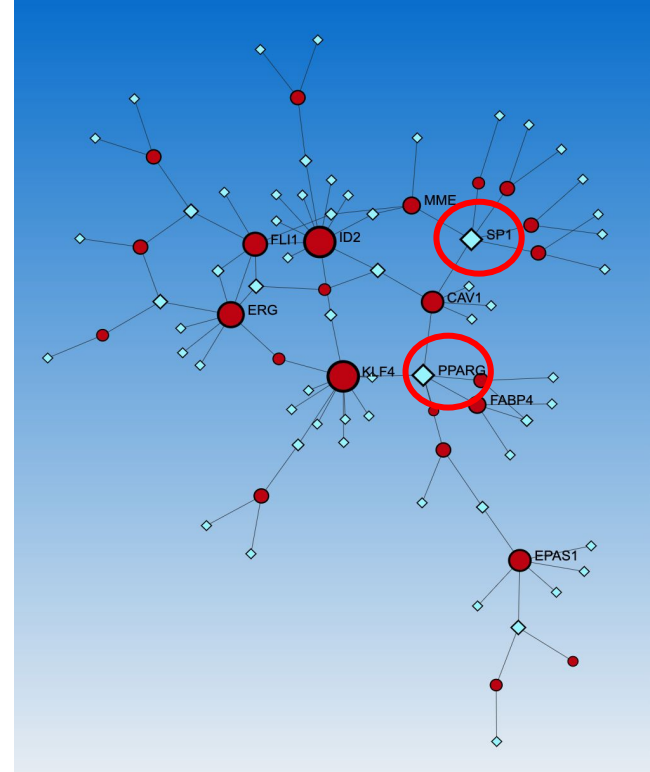
Analysis 1 - Step 1: Functional Enrichment - STRING

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- Molecular function:
 - Protein binding
- Cellular Component:
 - Intrinsic component of plasma membrane, plasma membrane, cell periphery
- KEGG Pathways:
 - cGMP-PKG signalling, regulation of lipolysis in adipocytes



Analysis 1 - Step 2: Regulatory Network Analysis

- Using NetworkAnalyst
 - Find transcription factors that regulate the overlapping genes based on the TRRUST database
- Found 2 specific transcription factors of interest
 - **PPAR gamma** - 6 genes
 - **SP1** - 6 genes



Analysis 1 - Step 2: Regulatory Network Analysis

- Traceback to DE results, all genes regulated by PPAR gamma are downregulated
- Most likely inactivation of PPAR gamma in both early and late stage LUAD
- In this analysis, evidence for SP1 activation/inactivation is lacking

PPAR γ Modulators in Lung Cancer: Molecular Mechanisms, Clinical Prospects, and Challenges

by Jiyun Zhang ^{1,2,3} ✉, Miru Tang ^{2,*} ✉ and Jinsai Shang ^{1,2,*} ✉ 

¹ School of Basic Medical Sciences, Guangzhou Laboratory, Guangzhou Medical University, Guangzhou 511436, China

² Guangzhou National Laboratory, Guangzhou 510005, China

³ School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

* Authors to whom correspondence should be addressed.

Biomolecules **2024**, *14*(2), 190; <https://doi.org/10.3390/biom14020190>

Analysis 2 - Drug Interaction Analysis

List of Approved Drugs with Duplicates

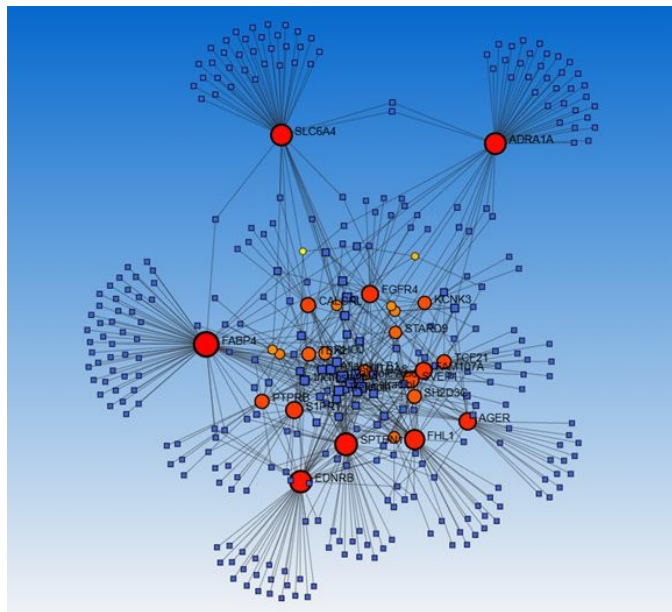
Total number of drugs in dataset: 728

Number of approved drugs: 365

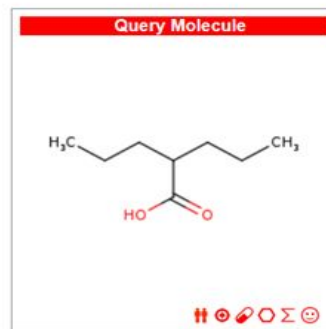
Number of approved drugs with duplicates: 68

- DISULFIRAM: 3 occurrences - used to treat chronic alcoholism
- PSEUDOEPHEDRINE: 3 occurrences - used to treat nasal and sinus congestion from common cold and allergies.
- All others: 2 occurrences each

Analysis 2 - Chemical-Gene Interaction Analysis



Valproic Acid - 16 genes



Export results:

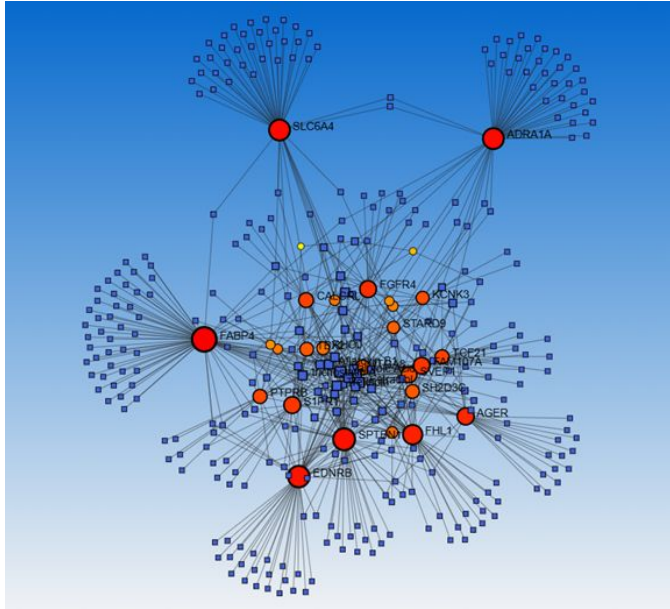
Show 15 entries

Search: fabp4

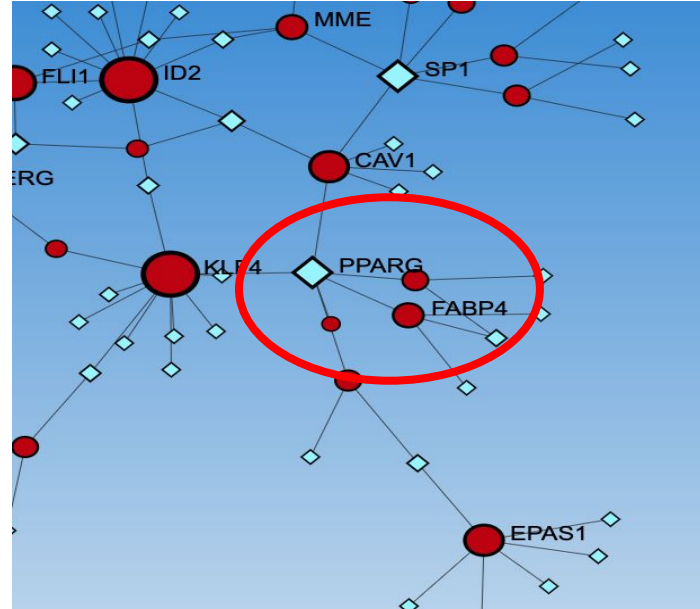
Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Fatty acid binding protein adipocyte	FABP4	P15090	CHEMBL2083	Fatty acid binding protein family	<div><div></div></div>	2 / 4

SMILES: CCCC(CCC)C(=O)O

Analysis 2 - Chemical-Gene Interaction Analysis



Valproic Acid - 16 genes



Analysis 2 - FABP4 expression in LUAD

Therapeutic Implications of FABP4 in Cancer: An Emerging Target to Tackle Cancer



Naihui Sun¹



Xing Zhao^{2*}

¹ Department of Anesthesiology, The First Affiliated Hospital of China Medical University, Shenyang, China

² Department of Pediatrics, The First Affiliated Hospital of China Medical University, Shenyang, China

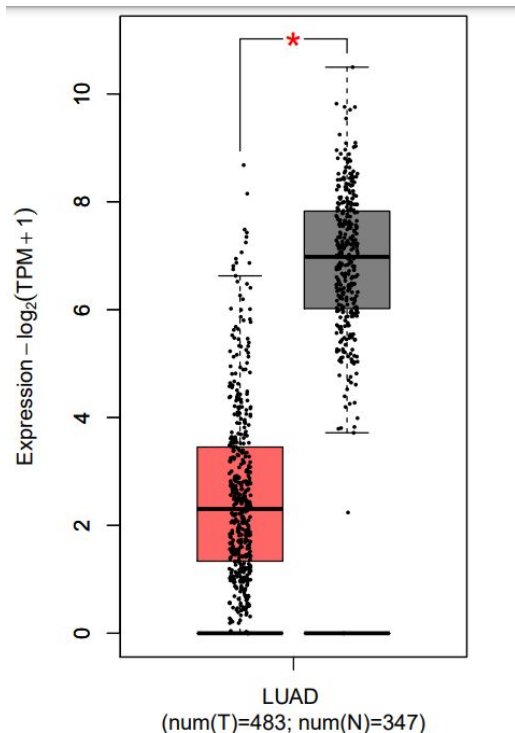
Elevated expression of FABP3 and FABP4 cooperatively correlates with poor prognosis in non-small cell lung cancer (NSCLC)

Zhiyuan Tang ¹, Qin Shen ¹, Hao Xie ², Xiaoyu Zhou ¹, Jun Li ¹, Jian Feng ¹, Hua Liu ¹, Wei Wang ³, Shu Zhang ³, Songshi Ni ¹



Affiliations + expand

PMID: 27323829 PMCID: [PMC5216795](#) DOI: [10.18632/oncotarget.10086](#)

Interesting findings



Inhibition of oncogenic Src induces FABP4-mediated lipolysis *via* PPAR γ activation exerting cancer growth suppression

Tuyen N.M. Hua^{a c d}, Min-Kyu Kim^{a c d}, Vu T.A. Vo^{a c d}, Jong-Whan Choi^a, Jang Hyun Choi^h, Hyun-Won Kim^a, Seung-Kuy Cha^{b c d e f g}, Kyu-Sang Park^{b c d e f}, Yangsik Jeong^{a c d e f g}  

Novel FABP4⁺C1q⁺ macrophages enhance antitumor immunity and associated with response to neoadjuvant pembrolizumab and chemotherapy in NSCLC via AMPK/JAK/STAT axis

Dong Zhang, Min Wang, Gen Liu, Xin Li, Wenwen Yu, Zhenzhen Hui, Xiubao Ren  & Qian Sun 

Cell Death & Disease 15, Article number: 717 (2024) | [Cite this article](#)

1275 Accesses | 9 Altmetric | [Metrics](#)

Diagnostic, Prognostic, and Immunological Roles of FABP4 in Pancancer: A Bioinformatics Analysis

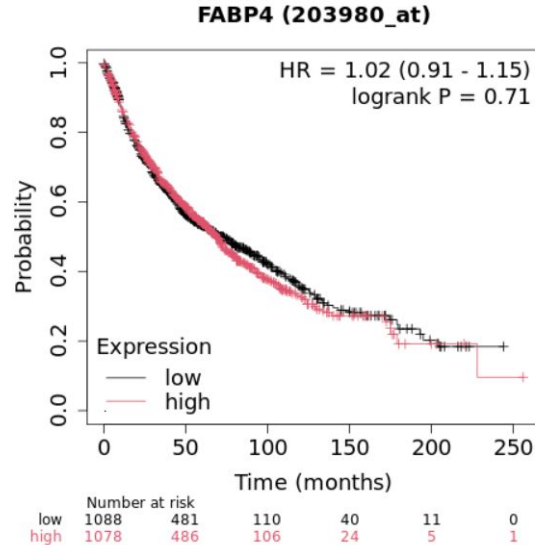
Jing Yang, Xiaojing Liu, Yueqin Shao, Hong Zhou, Lijun Pang  Wei Zhu 

First published: 08 December 2022 | <https://doi.org/10.1155/2022/3764914> | Citations: 2

Academic Editor: Chung-Min Liao

Interesting findings

P value: 0.7063



Kaplan-Meier(KM) plotter

Inhibition of oncogenic Src induces FABP4-mediated lipolysis *via* PPAR γ activation exerting cancer growth suppression

Tuyen N.M. Hua^{a c d}, Min-Kyu Kim^{a c d}, Vu T.A. Vo^{a c d}, Jong-Wan Choi^a, Jang Hyun Choi^h, Hyun-Won Kim^a, Seung-Kuy Cha^{b c d e f g}, Kyu-Sang Park^{b c d e f}, Yangsik Jeong^{a c d e f g}

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First published: 08 December 2022 | <https://doi.org/10.1155/2022/3764914> | Citations: 2

Academic Editor: Chung-Min Liao



Further Analysis



Hidden pharmacological activities of valproic acid: A new insight

Dhirendra Singh^a, Sumeet Gupta^a  , Inderjeet Verma^a, Mohamed A. Morsy^{b c}, Anroop B. Nair^b, Al-Shaimaa F. Ahmed^d

Anti-tumor effects of valproate zinc complexes on a lung cancer cell line

Emanuelle Fraga da Silva^a, Paulo Roberto dos Santos^b, Krist Helen Antunes^a, Caroline Marinho Franceschina^a, Deise Nascimento de Freitas^a, Priscila Konrad^a, Rafael Fernandes Zanin^c, Pablo Machado^d, Sidnei Moura^b, Ana Paula Duarte de Souza^a  

[Show more](#)

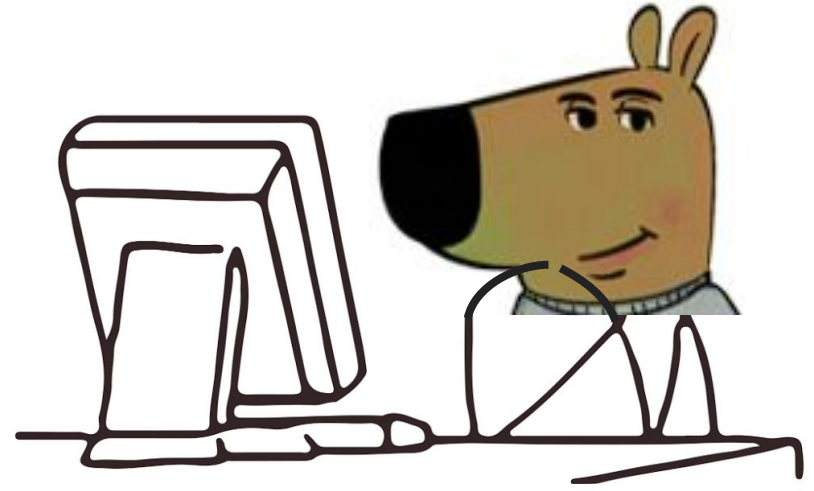
Question:

Does valproic acid also affect FABP4 expression by inhibiting Histone deacetylases (HDACs)?

Analysis 3 – Digging into non-overlapping genes

Why Different?

What is the reason of
invasive behavior?



Analysis 3 – Functional Enrichment

Functional Enrichment(GSEA)



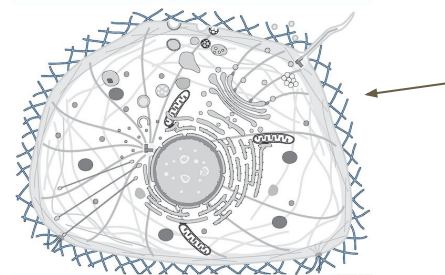
LAMA3, LAMA4, TNXB...



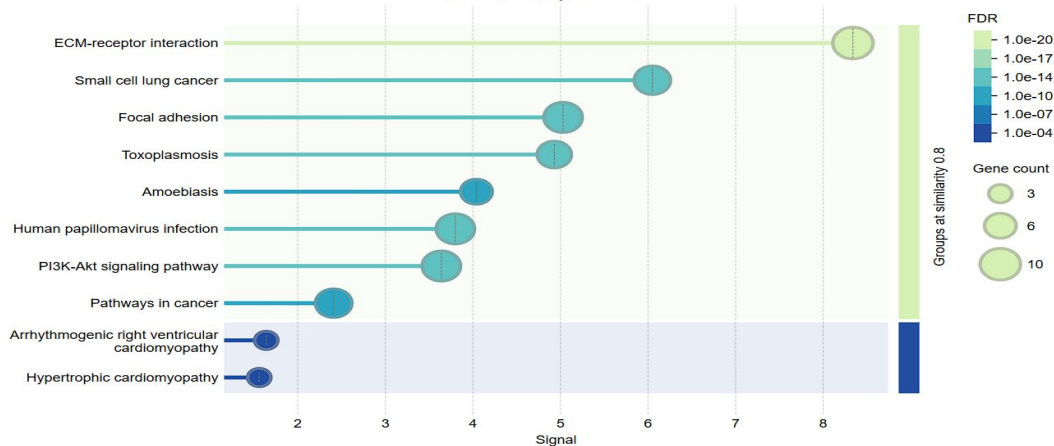
ECM-receptor interaction

Extracellular Matrix(ECM)

ECM is a network of proteins and carbohydrates that provides structural support and regulates cell behavior in tissues. It plays key roles in cell adhesion, migration, and signaling, essential for development, repair, and homeostasis.



KEGG Pathways enrichment



LAMA3, LAMA4 encodes the laminin family of secreted molecules

TNXB encodes a member of the tenascin family of extracellular matrix glycoproteins.





They are Up-Regulated!

Analysis 3 – Digging into non-overlapping genes

Some Evidences...

Review

Extracellular matrix functions in lung cancer

Martin Götte^a  , Ilona Kovalszky^b  

[Show more](#) ▼

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<https://doi.org/10.1016/j.matbio.2018.02.018> ↗

[Get rights and content](#) ↗

Expression of Invasion-Related Extracellular Matrix Molecules in Human Glioblastoma Versus Intracerebral Lung Adenocarcinoma Metastasis

I. Varga¹, G. Hutóczki², M. Petrás³, B. Scholtz⁴, E. Mikó⁴, A. Kenyeres⁵, J. Tóth⁶, G. Zahuczky⁴, L. Bognár², Z. Hanzély⁷, A. Klekner²

¹Kenezy Hospital, Debrecen, Department of Pulmonology, Debrecen, Hungary

²University of Debrecen, Department of Neurosurgery, Debrecen, Hungary

³Medical and Health Science Center, University of Debrecen, Biophysics and Cell Biology, Debrecen, Hungary

⁴University of Debrecen, Department of Biochemistry and Molecular Biology, Debrecen, Hungary

⁵University of Debrecen, Department of Anatomy, Histology and Embryology, Debrecen, Hungary

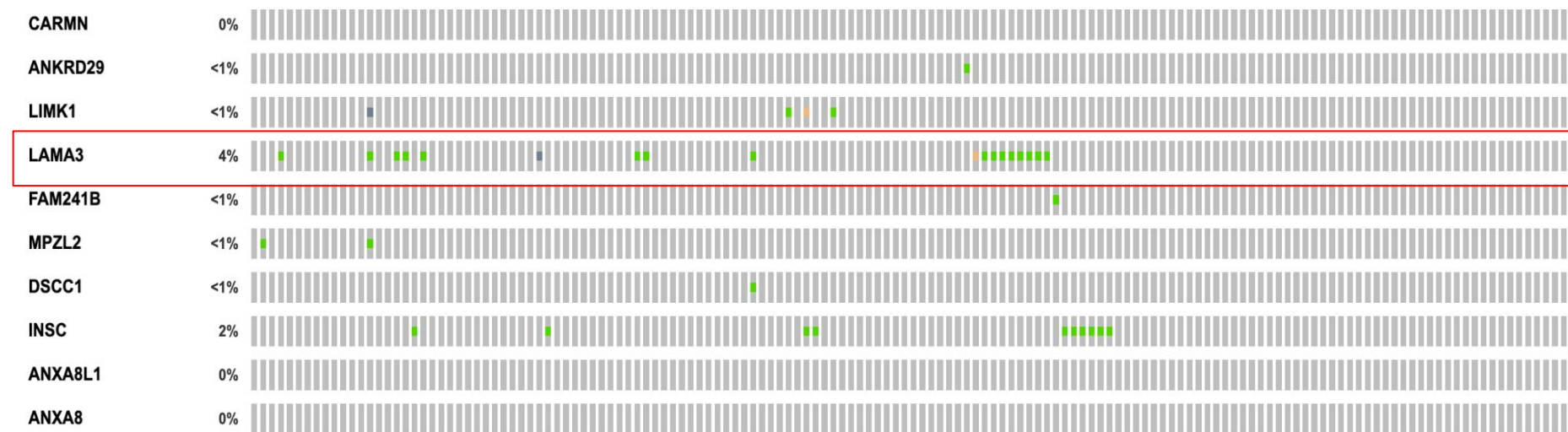
⁶University of Debrecen, Department of Oncology, Debrecen, Hungary

⁷National Institute of Neurosurgery, Department of Pathology, Budapest, Hungary

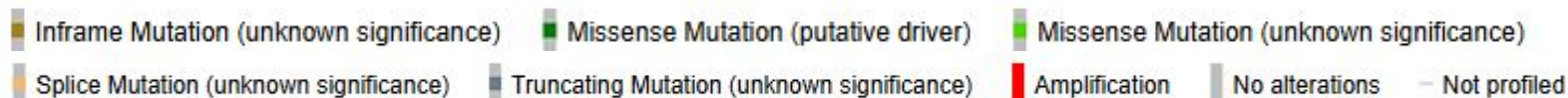
- **Laminin is a key Glycoprotein in the basement membrane of the ECM.**
- **Functions:** Laminin is thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components
- **In an invasive behavior:** Laminin interacts with **integrins**, which send signals that help cancer cells detach from the ECM, move through tissues (invasion), and become more aggressive.

Analysis 3 – Pan-Cancer Analysis

Combined Study (747 samples)



Genetic Alteration



Analysis 3 - Conclusion

- Genes like LAMA3 and LAMA4 ,which encoding Laminin family, are enriched in ECM-related pathway.
- Laminins interact with integrins to facilitate cell detachment and migration, contributing to the invasive behavior of metastatic LUAD.
- The identified gene signature, especially LAMA3, is not limited to LUAD but is also significant in other metastatic cancers, highlighting its potential as a pan-cancer biomarker.

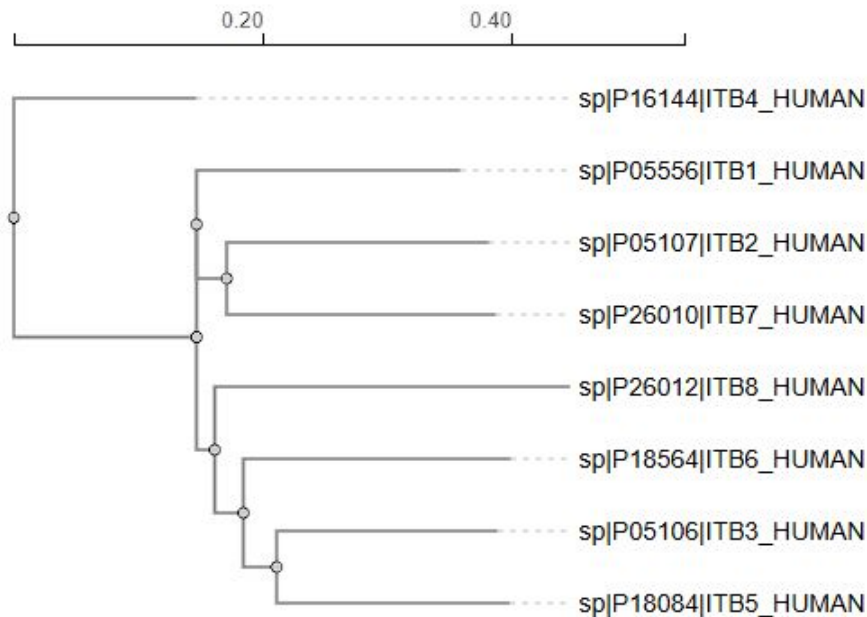
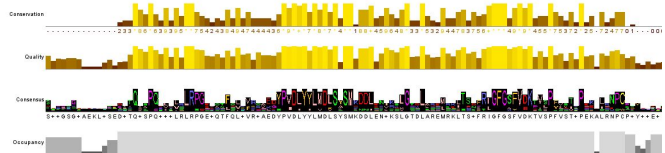
Thank You!

Analysis 3 - MSA

```

140 150 160 170 180 190 200 210 220 230 240 250
ITB4_HUMAN>182 DTT.....LRSDSPQDLRVLPPEEKHFLEVFLSPDVLVLMDFSNMSDDLNLKHWONLÄRVGLTSDYTIISFVYVDVSVPTDMPEK.LPEWPK.....
ITB6_HUMAN>708 .....NEINTQTPREVIGLPPRAEAKMLVPLVLPDVLVYVGVSAAMNNIKLKSNGVNDLRMAFTSDFRLGTSVGVSTQVPSISIPER.LHDCSEY.....NL
ITB2_HUMAN>708 .....LBNH.....GGDLSPGVLTLPAPDAAGPNTFPRADVPLDLYLMDLSTYMLDNLKRVGLDGLKALNEITEDSRIGFSGVDTLVPVSTQPSK.LHWPKA...SEK
ITB7_HUMAN>708 SGRARSS.....GATGLAPGVRLTPRSPDGLVRLRAEDVPDVLVYLMDSVSMDDLFRVGLSHALLVGLDSTVSRVIGFSGVDTLVPVSTQPSK.LHWPEFT...SLK
ITB3_HUMAN>708 TMSVTAELKRLTGIDIGDGLVLRSESPPTFLVLPRAEDVPDVLVYLMDSVSMDDLFRVGLDGLKALNEITEDSRIGFSGVDTLVPVSTQPSK.LHWPKA...SEK
ITB4_HUMAN>708 SVSRGKN.....SSDIVGIPAGDLILKLRPSAOTLVGVKRTEDVPDVLVYLMDSVSMDDLTLTIELGRSLRSEMHLTNSFRIGFSGVDEKVPVPTTFEE.LANPSS...IPV
ITB2_HUMAN>708 SSKSSSS.....SSGVTSVDFPRLALPPSSDNTFIDVGRDVPDVLVYLMDSVSMDDLGLDGLKALNEITEDSRIGFSGVDTLVPVSTQPSK.LHWPKA...SEK
ITB6_HUMAN>708 SSKSSSS.....AWGVQMTPEIAVNLPRDQKTTGOLGVQVEDVPDVLVYLMDSVSMDDLTLTIELGRSLRSEMHLTNSFRIGFSGVDEKVPVPTTFEE.LANPSS...IPV

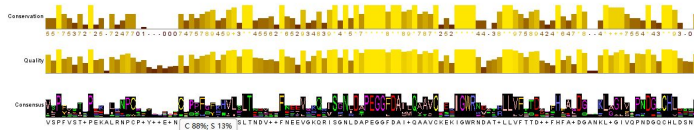
```



```

230 240 250 260 270 280 290 300 310 320 330 340
ITB4_HUMAN>182 SVPTDMPEK.LPEWPK.....SDPPFSKNNVILTDVGVDFRNKLDENISNLDAPEDFDALGLTAVCTRIQWPFDSHLLVSTESAFHYEADGANLQIIMSRDGRCHLDTT
ITB6_HUMAN>708 VSPYISIPER.LHDCSEY.....NLCMPFHYVHVLSTENITFESAVNRDKISNIDTFEEDFAMLGAAVCEHIOWRKEAKLLVMTGDTLHGLD...KLAGIVPNDGCHLKN
ITB2_HUMAN>708 VLPFVNTQPSK.LHWPKA...KEGCEPFFAFRNKLTNSNGDTEVAGDLISNLDAPESGLDAMGVKACEEIOWRNV.TLLVFTATEDSFHAFD...KLAGILTPDSRCHLKN
ITB7_HUMAN>708 VLPFVSTQPSK.LHWPKA...RLERCQPTSFHNVLLTSDAGAFEREVGSDVSGALDSEFSGDALGLAALCEDIOWRNV.SLLVFTSDDTHTAGD...KLAGIFPDSGCHLKN
ITB3_HUMAN>708 VHWYIETTPAK.LHWPKA...GNCPTFFSKNNVILTDVGVDFRNKLDENISNLDAPESGLDAMGVKACEEIOWRNV.TLLVFTSDDTHTAGD...KLAGILTPDSRCHLKN
ITB4_HUMAN>708 VSPFKVTPPE.LANPSS...IPYTCFTTFKHLPLTDAENFBEIUNHGISNIDTFEEDFAMLGAAVCEHIOWRNSLLVFTVSDASDHQMD...KLAGIVPNDGCHLKN
ITB2_HUMAN>708 VSPYVSIIPPEALRNPFP+*+E+...YDMITCLPMFQVHNVLLTSDYTFNEEVGKQVSRNRDAPEDFDALGLAACEHIOWRNSLLVFTTDAATHALD...KLAGIVPNDGCHLKN
ITB6_HUMAN>708 ISPFYSYAPRY.OTNPCIYGLFPCVPSFGRHLLPLTDVGSFNEEVKQVSRNRDAPEDFDALGLAACEHIOWRNSLLVFTTDDVPIALD...KLAGIVPNDGCHLKN

```



Analysis 3 – Protein Structure Prediction

ColabFold AlphaFold2 NoteBook

1. Input the amino acid sequence
2. Generate MSAs using tools like HMMer to identify homologous sequences and evolutionary relationships
3. Predict inter-residue distances and angles using a deep learning neural network
4. Refine these predictions iteratively to produce a final 3D protein structure with confidence scores (pLDDT) to assess reliability.
5. Download results.

- Beginner-friendly
- FAST
- Reduced Computational Requirements

ColabFold v1.5.5: AlphaFold2 using MMseqs2

Easy to use protein structure and complex prediction using [AlphaFold2](#) and [Alphafold2-multimer](#). Sequence alignments/templates are generated through [MMseqs2](#) and [HHsearch](#). For more details, see [bottom](#) of the notebook, checkout the [ColabFold GitHub](#) and [Nature Protocols](#).

Old versions: [v1.4](#), [v1.5.1](#), [v1.5.2](#), [v1.5.3-patch](#)

[Mirdita M, Schütze K, Moriwaki Y, Heo L, Ovchinnikov S, Steinegger M. ColabFold: Making protein folding accessible to all. *Nature Methods*, 2022](#)

> Input protein sequence(s), then hit `Runtime` -> `Run all`



query_sequence: "

MGTTARAALVLTYLAVASAASEGFTATGQRQLRPEHFQEVGYAAPSPPLSRSLPMDHP DSSQHGPFPFEGQSQVQPPPSQEATPLQQE

