**Table S1.** List of approved drugs targeting or having an action over target genes ALOX5 and ELOVL4 according to DrugBank database.

| Gene (entrez id) | Drug name | Drugbank Id | Action | Pharmacological action |
|---|---|---|---|---|
| ALOX5 (240) | Masoprocol | DB00179 | inhibitor | yes |
| | Aminosalicylic acid | DB00233 | inhibitor | Unknown |
| | Mesalazine | DB00244 | inhibitor | yes |
| | Montelukast | DB00471 | other/unknown | Unknown |
| | Diclofenac | DB00586 | potentiator | Unknown |
| | Diethylcarbamazine | DB00711 | inhibitor | yes |
| | Zileuton | DB00744 | inhibitor | yes |
| | Sulfasalazine | DB00795 | inhibitor | yes |
| | Meclofenamic acid | DB00939 | inhibitor | yes |
| | Balsalazide | DB01014 | inhibitor | yes |
| | Minocycline | DB01017 | inhibitor | Unknown |
| | Hyperforin | DB01892 | inhibitor | Unknown |
| | Cannabidiol | DB09061 | inhibitor | Unknown |
| | Morniflumate | DB09285 | antagonist, inhibitor | Unknown |
| | Omega-3 fatty acids | DB11133 | substrate | Unknown |
| | Diacerein | DB11994 | inhibitor | Unknown |
| | Fostamatinib | DB12010 | inhibitor | Unknown |
| | Omega-6 fatty acids | DB13168 | substrate | Unknown |
| | Rhein | DB13174 | inhibitor | Unknown |
| | Isocapent | DB00159 | substrate | Unknown |
| ELOVL4 (6785) | Vayarin | DB09328 | substrate | Unknown |
| | Omega-3-carboxylic acids | DB09568 | potentiator | yes |

**Table S2.** List of circuits affected by ALOX5 and ELOVL4 known drug targets according to the ML model of RP KEGG-based mechanistic map.

| KEGG pathway | Circuit effector | Function | ALOX5 | | ELOVL4 | |
|---|---|---|---|---|---|---|
| | | | Relevant | Value | Relevant | Value |
| MAPK signaling pathway | MAPT | Actin binding, neurogenesis | 0 | -1,99E-05 | 1 | 5,50E-05 |
| MAPK signaling pathway | STMN1 | Neurogenesis | 0 | -3,97E-06 | 1 | 3,06E-05 |
| MAPK signaling pathway | PLA2G4B | **Lipid degradation** | 0 | 1,77E-06 | 1 | 7,93E-05 |
| MAPK signaling pathway | MYC | Transcription regulation | 0 | -5,06E-06 | 1 | 4,24E-05 |
| ErbB signaling pathway | MYC | Transcription regulation | 0 | -4,21E-07 | 1 | 7,04E-06 |
| ErbB signaling pathway | ELK1 | Transcription regulation | 0 | -4,99E-07 | 1 | 3,49E-06 |
| Ras signaling pathway | PLA2G4B | **Lipid degradation** | 0 | -3,07E-06 | 1 | 1,17E-05 |
| Ras signaling pathway | ETS1 | Transcription regulation | 0 | 6,00E-06 | 1 | 1,51E-05 |
| Ras signaling pathway | FASLG | Apoptosis | 1 | 1,36E-05 | 1 | -1,04E-05 |
| Ras signaling pathway | PAK4 | Apoptosis | 0 | 3,85E-05 | 1 | 0,00016034 |
| Ras signaling pathway | RHOA | Host-virus interaction | 0 | 4,20E-05 | 1 | 0,0001648 |
| Ras signaling pathway | RAC1* | Transcription regulation | 0 | 1,50E-05 | 1 | 5,25E-05 |
| Ras signaling pathway | PLD1 | **Lipid degradation** | 0 | 1,37E-05 | 1 | 9,01E-05 |
| Ras signaling pathway | PRKCA | Apoptosis | 0 | 1,50E-05 | 1 | -0,00011985 |
| Ras signaling pathway | D-myo-Inositol 1,4,5-trisphosphate | | 0 | -2,70E-05 | 1 | -0,00026758 |
| Ras signaling pathway | ABL1 | Endocytosis | 0 | -1,19E-05 | 1 | 0,00013029 |
| Ras signaling pathway | RAB5A | Endocytosis | 0 | -1,52E-05 | 1 | 0,00018315 |
| Ras signaling pathway | RAC1** | Transcription regulation | 0 | -5,30E-06 | 1 | 0,00010014 |
| Ras signaling pathway | STK4 STK4 | Apoptosis | 1 | 7,58E-05 | 1 | 5,77E-05 |
| Ras signaling pathway | MLLT4 | Cell adhesion | 0 | -1,43E-05 | 1 | 0,00011171 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ras signaling pathway | RASSF5 | Apoptosis | 1 | 0,0003972 | 0 | 0,00021784 |
| Ras signaling pathway | TIAM1* | Axonogenesis, cell migration | 0 | 7,30E-05 | 1 | 0,00053526 |
| Ras signaling pathway | PIK3R5* | Angiogenesis | 0 | 0,0001855 | 1 | -0,00024652 |
| Ras signaling pathway | RAF1* | Apoptosis | 1 | 0,0001763 | 0 | -3,78E-05 |
| Ras signaling pathway | BRAP* | Ubl conjugation pathway | 0 | 5,02E-05 | 1 | 0,0001149 |
| Ras signaling pathway | RALGDS* | Transcription regulation | 1 | 0,0001991 | 0 | 0,00015961 |
| Ras signaling pathway | PLCE1* | **Lipid degradation** | 0 | 0,0001295 | 1 | -0,00036227 |
| Ras signaling pathway | RIN1* | Endocytosis | 0 | 8,95E-05 | 1 | 0,0004064 |
| Rap1 signaling pathway | MAPK1 | Cell cycle | 0 | -4,74E-06 | 1 | 3,25E-05 |
| Rap1 signaling pathway | PLCE1 | **Lipid degradation** | 0 | 2,34E-05 | 1 | -0,00029782 |
| cGMP-PKG signaling pathway | GTF2I | Transcription regulation | 0 | -8,80E-05 | 1 | -0,00026383 |
| cAMP signaling pathway | HHIP | Development | 0 | -8,55E-06 | 1 | -5,87E-05 |
| cAMP signaling pathway | ACOX1 | **Fatty acid metabolism** | 0 | -9,69E-06 | 1 | -3,11E-05 |
| cAMP signaling pathway | ORAI1 | Ion transport | 0 | 4,25E-06 | 1 | -5,38E-05 |
| cAMP signaling pathway | BAD | Apoptosis | 0 | -6,64E-06 | 1 | 7,68E-05 |
| cAMP signaling pathway | NFKBIA NFKB1 | Host-virus interaction | 0 | 1,36E-05 | 1 | -9,63E-05 |
| cAMP signaling pathway | PLN | Ion transport | 0 | -4,61E-05 | 1 | -0,00014106 |
| cAMP signaling pathway | RYR2 | Ion transport | 0 | 2,52E-05 | 1 | -0,00010022 |
| cAMP signaling pathway | ATP2B1 | Ion transport | 0 | -1,79E-05 | 1 | -9,22E-05 |
| cAMP signaling pathway | CACNA1C | Ion transport | 0 | 1,12E-05 | 1 | -9,66E-05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| cAMP signaling pathway | PDE3A | Angiogenesis | 0 | 5,18E-06 | 1 | -5,38E-05 |
| cAMP signaling pathway | LIPE | **Cholesterol metabolism** | 0 | -2,89E-05 | 1 | -8,53E-05 |
| cAMP signaling pathway | ATP1B4 FXYD1 | Ion transport | 0 | -3,61E-05 | 1 | -0,00011299 |
| cAMP signaling pathway | AKT3 | Glycogen biosynthesis | 0 | 3,57E-06 | 1 | -2,01E-05 |
| cAMP signaling pathway | Diacylglycerol | | 0 | 1,73E-05 | 1 | -0,00010826 |
| cAMP signaling pathway | D-myo-Inositol 1,4,5-trisphosphate | | 0 | 1,73E-05 | 1 | -0,00010826 |
| cAMP signaling pathway | AFDN | Cell adhesion | 0 | 9,68E-06 | 1 | -4,30E-05 |
| cAMP signaling pathway | MAPK8 | Biological rhythms | 0 | -2,44E-05 | 1 | -8,99E-05 |
| Chemokine signaling pathway | MAPK1 | Host-virus interaction | 1 | 2,81E-05 | 0 | 1,10E-05 |
| FoxO signaling pathway | FASLG | Apoptosis | 1 | 5,81E-17 | 0 | -4,10E-17 |
| Sphingolipid signaling pathway | MAPK1 | Apoptosis | 0 | 1,13E-05 | 1 | 2,09E-05 |
| Phospholipase D signaling pathway | MAPK1 | Host-virus interaction | 0 | 3,87E-06 | 1 | 1,14E-05 |
| PI3K-Akt signaling pathway | GYS1 | Glycogen biosynthesis | 0 | 6,70E-07 | 1 | -3,42E-06 |
| PI3K-Akt signaling pathway | G6PC | Gluconeogenesis | 0 | -9,55E-07 | 1 | -2,58E-06 |
| PI3K-Akt signaling pathway | FASLG | Apoptosis | 1 | 2,62E-06 | 1 | -2,27E-06 |
| PI3K-Akt signaling pathway | TP53 | Cell cycle | 0 | -2,00E-06 | 1 | 4,16E-06 |
| PI3K-Akt signaling pathway | MYB | Transcription regulation | 0 | 1,94E-06 | 1 | 3,40E-06 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PI3K-Akt signaling pathway | BCL2 | Apoptosis | 0 | 1,53E-06 | 1 | -4,96E-06 |
| PI3K-Akt signaling pathway | EIF4B | Initiation factor | 1 | 1,09E-05 | 0 | 6,58E-06 |
| PI3K-Akt signaling pathway | RPS6 | Cell cycle | 1 | 1,34E-05 | 0 | 1,05E-05 |
| PI3K-Akt signaling pathway | NOS3 | Translation regulation | 0 | 7,89E-06 | 1 | -1,13E-05 |
| PI3K-Akt signaling pathway | PRKCA | Apoptosis | 0 | 2,16E-05 | 1 | -4,36E-05 |
| PI3K-Akt signaling pathway | PKN3 | Transcription regulation | 1 | 3,74E-05 | 1 | -4,32E-05 |
| Longevity regulating pathway - mammal | CAT | Detoxification | 0 | -1,85E-05 | 1 | -0,0001784 |
| Longevity regulating pathway - mammal | RPS6KB1 | Translation regulation | 0 | -5,80E-06 | 1 | 0,00016615 |
| Hedgehog signaling pathway | GLI1* | Transcription regulation | 0 | 3,20E-06 | 1 | 1,23E-05 |
| Hedgehog signaling pathway | HHIP | | 0 | 5,49E-06 | 1 | -3,05E-05 |
| Axon guidance | CFL1 | Actin formation | 0 | -1,47E-05 | 1 | -4,92E-05 |
| Gap junction | GJA1 GJA1*** | Cell adhesion | 0 | -0,000188 | 1 | 0,00048918 |
| Gap junction | GJA1 GJA1 | Cell adhesion | 0 | -7,88E-10 | 1 | -1,89E-09 |
| Gap junction | GJA1 GJA1* | Cell adhesion | 0 | -7,88E-10 | 1 | -1,89E-09 |
| Gap junction | GJA1 TJP1 | Cell adhesion | 0 | -7,58E-10 | 1 | -2,02E-09 |
| Natural killer cell mediated cytotoxicity | TNF | Acute inflammatory response | 1 | 2,50E-05 | 0 | -3,86E-06 |
| Natural killer cell mediated cytotoxicity | CSF2 | Neurogenesis | 1 | 8,28E-06 | 0 | -2,41E-06 |
| Natural killer cell mediated cytotoxicity | FAS | **Fatty-acid biosynthesis** | 1 | 0,0002945 | 1 | -0,00020267 |
| Natural killer cell mediated cytotoxicity | TNFRSF10D | Apoptosis | 1 | 0,0002182 | 1 | -0,00030359 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Fc epsilon RI signaling pathway | PLA2G4B | **Lipid degradation** | 0 | 9,71E-08 | 1 | 3,71E-07 |
| Fc gamma R-mediated phagocytosis | CFL1 | Actin binding, synapse, neurogenesis | 1 | -2,96E-05 | 0 | 1,13E-05 |
| GABAergic synapse | GABRA1 GPHN | Chloride channel | 0 | -0,000311 | 1 | 0,00071121 |
| Regulation of actin cytoskeleton | ACTB ARPC5 | Actin binding | 0 | -2,31E-09 | 1 | 2,50E-08 |
| Regulation of actin cytoskeleton | CFL1 ACTB | Actin binding, synapse, neurogenesis | 0 | 4,80E-06 | 1 | -1,72E-05 |
| Regulation of actin cytoskeleton | MYL12B MYH9 ACTB | Cell shape | 0 | 4,44E-12 | 1 | -6,57E-12 |
| Regulation of actin cytoskeleton | PXN | Cell adhesion | 0 | 3,30E-06 | 1 | -1,49E-05 |
| Regulation of actin cytoskeleton | VCL* | Cell adhesion | 1 | 8,77E-11 | 1 | -1,18E-10 |
| Regulation of actin cytoskeleton | ACTN4 | Protein transport | 0 | 9,15E-11 | 1 | -1,16E-10 |
| Regulation of actin cytoskeleton | MSN | Cell shape | 1 | 1,07E-10 | 0 | -8,89E-11 |
| Insulin signaling pathway | ELK1 | Transcription regulation | 0 | -9,13E-08 | 1 | 8,13E-07 |
| Melanogenesis | TYR* | Melanin biosynthesis | 0 | -1,01E-07 | 1 | 3,08E-06 |
| Melanogenesis | TYRP1 | Melanin biosynthesis | 0 | 5,01E-07 | 1 | 3,21E-06 |
| Melanogenesis | DCT | Melanin biosynthesis | 0 | -4,80E-07 | 1 | 2,49E-06 |
| Oxytocin signaling pathway | MEF2C | Neurogenesis | 0 | 1,22E-05 | 1 | -8,31E-05 |
| Oxytocin signaling pathway | CCND1 | Cell cycle | 0 | -2,62E-05 | 1 | 0,00015234 |

* Each star refers to the number pf times the referred gene acts as an effector in that pathway.

0 means that the target is not relevant in the circuit, while 1 means that the target gene has an impact, therefore is relevant, for the prediction of the circuit activity.

**Table S3. Number of each pathway's circuits in which have an impact drug targets ALOX5 or ELOVL4**

| KEGG pathway | Number of relevant circuits | | Total number of circuits | Percentage of pathway | |
|---|---|---|---|---|---|
| | ALOX5 | ELOVL4 | | ALOX5 | ELOVL4 |
| MAPK signaling pathway | 0 | 4 | 28 | 0,00 | 14,29 |
| ErbB signaling pathway | 0 | 2 | 18 | 0,00 | 11,11 |
| Ras signaling pathway | 5 | 19 | 32 | **15,63** | **59,38** |
| Rap1 signaling pathway | 0 | 2 | 14 | 0,00 | 14,29 |
| cGMP-PKG signaling pathway | 0 | 1 | 22 | 0,00 | 4,55 |
| cAMP signaling pathway | 0 | 17 | 35 | 0,00 | **48,57** |
| Chemokine signaling pathway | 1 | 0 | 13 | 7,69 | 0,00 |
| FoxO signaling pathway | 1 | 0 | 30 | 3,33 | 0,00 |
| Sphingolipid signaling pathway | 0 | 1 | 11 | 0,00 | 9,09 |
| Phospholipase D signaling pathway | 0 | 1 | 4 | 0,00 | 25,00 |
| PI3K-Akt signaling pathway | 4 | 9 | 28 | 14,29 | **32,14** |
| Longevity regulating pathway - mammal | 0 | 2 | 13 | 0,00 | 15,38 |
| Hedgehog signaling pathway | 0 | 2 | 15 | 0,00 | 13,33 |
| Axon guidance | 0 | 1 | 31 | 0,00 | 3,23 |
| Gap junction | 0 | 4 | 5 | 0,00 | **80,00** |
| Natural killer cell mediated cytotoxicity | 4 | 2 | 11 | **36,36** | 18,18 |
| Fc epsilon RI signaling pathway | 0 | 1 | 6 | 0,00 | 16,67 |
| Fc gamma R-mediated phagocytosis | 1 | 0 | 12 | 8,33 | 0,00 |
| GABAergic synapse | 0 | 1 | 7 | 0,00 | 14,29 |
| Regulation of actin cytoskeleton | 2 | 6 | 12 | **16,67** | **50,00** |
| Insulin signaling pathway | 0 | 1 | 15 | 0,00 | 6,67 |
| Melanogenesis | 0 | 3 | 7 | 0,00 | **42,86** |
| Oxytocin signaling pathway | 0 | 2 | 22 | 0,00 | 9,09 |