

Multiscale Mapping of Transcriptomic Signatures for Cardiotoxic Drugs

Supplementary Information

Jens Hansen,^{1,2} Yuguang Xiong,^{1,2} Mustafa Siddiq,^{1,2} Priyanka Dhanan,^{1,2} Bin Hu,^{1,2} Bhavana Shewale,^{1,3} Arjun S. Yadaw,^{1,2} Gomathi Jayaraman,^{1,2} Rosa Tolentino,^{1,2} Yibang Chen,^{1,2} Pedro Martinez,^{1,2} Kristin G. Beaumont,⁴ Robert Sebra,⁴ Dusica Vidovic,⁵ Stephan C. Schürer,⁵ Joseph Goldfarb,^{1,2} James Gallo,^{2,6} Marc R. Birtwistle,^{1,7} Eric A. Sobie,^{1,2} Evren U. Azeloglu,^{1,2,8} Seth Berger,⁹ Angel Chan,^{1,10} Christoph Schaniel,^{1,11} Nicole C. Dubois,^{*,1,3} Ravi Iyengar^{*,1,2}

1 Mount Sinai Institute for Systems Biomedicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

2 Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

3 Department of Cell, Developmental and Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

4 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

5 Institute for Data Science and Computing, University of Miami, Coral Gables, FL 33146, USA

6 School of Pharmacy and Pharmaceutical Sciences, University of Buffalo SUNY System, Buffalo, NY 14260, USA

7 Chemical and Biomolecular Engineering, Clemson University, Clemson, SC, 29634, USA

8 Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

9 Center for Genetic Medicine Research, Children's National Research Institute, Washington DC USA, 20012, Washington, DC 20012, USA

10 Cardiology Division, Department of Medicine, Memorial Sloan Kettering Cancer Center New York, NY 10065, USA

11 Department of Medicine, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

*These authors jointly supervised this work.

Address correspondence to

Jens Hansen - jens.hansen@mssm.edu

or

Nicole Dubois - nicole.dubois@mssm.edu

or

Ravi Iyengar - ravi.iyengar@mssm.edu

Supplementary Note 1

Organization of Supplementary Information in two parts

The supplementary information is organized in two parts. The first part contains the supplementary notes 1 and 2, most supplementary figures and supplementary tables. The second part contains supplementary figures with very detailed information that can span multiple pages. For the first investigation of our supplementary information, we suggest to focus (and eventually print) only the first part (pages 1 - 78) that includes referenced page positions for the figures of the second part.

Part 1: Pages 1-78: Main Supplementary Information

Page 2: Supplementary Note 1

Pages 2-10: Supplementary Note 2

Pages 11-75: Most Supplementary Figures

Pages 76-78: Supplementary Tables

Part 2: Pages 79-341: Supplementary Figures with very detailed information

Pages 79-93: Supplementary Figure 11

Pages 94-97: Supplementary Figure 12

Pages 98-111: Supplementary Figure 14B

Pages 112-125: Supplementary Figure 14C

Pages 126-139: Supplementary Figure 14D

Pages 140-154: Supplementary Figure 14E

Pages 155-173: Supplementary Figure 17

Pages 174-182: Supplementary Figure 29

Supplementary Note 2

Drug-selective gene expression profiles allow for identification of SCPs which agree with prior knowledge of SCPs associated with cardiac diseases and drug effects

Up- and downregulated genes in each cell line/drug combination were subjected to enrichment analysis using the Molecular Biology of the Cell Ontology (MBCO) ²⁸ and Fisher's exact test. Predicted subcellular processes (SCPs) were ranked by decreasing significance for each list of genes and SCP level. We will refer to these ranks as enrichment ranks.

As outlined in the main text, the SVD-based identification of drug-selective gene expression profiles greatly increased the number of predicted SCPs that are up- or downregulated in at least two of three, three of four, four of five or four of six cell lines (i.e., $\geq 66\%$) by the same drugs (Supplementary Fig. 15A). The median overlap between downregulated level-1, -2, -3, -4 SCPs among the top 5, 5, 10 and 5 predicted SCPs increased from 2 to 3.5, 1 to 3, 1 to 4 and 0 to 1, respectively. The median overlap between upregulated level-1, -2, -3, -4 SCPs among the top 5, 5, 10 and 5 predicted SCPs increased from 1 to 3, 0 to 3, 1 to 4 and 0 to 1, respectively. These results depend on the complete SVD-pipeline, since removal of the first eigenarray alone improved the median number of drug-selective overlapping up- or downregulated SCPs in only one case (upregulated level-2 SCPs, from 0 to 1).

Analysis of drug-selective gene expression profiles enabled identification of enrichment patterns that were obscured within the complete gene expression profiles. For example, our decomposition pipeline allowed identification of SCPs that were selectively downregulated by the group of anthracyclines that have high rates of cardiotoxicity¹⁰⁰. These SCPs are involved in iron metabolism and single protein turn-over (Supplementary Fig. 14/B/C/D/E). They form parent-child relationships within three MBCO branches (Supplementary Fig. 15B). The observed downregulation of 'Cellular iron storage' is in agreement with the suggested interference of anthracyclines with iron metabolism¹⁰¹ and ferroptosis as a disease mechanism involved in heart failure³⁸. The clinical relevance of our unbiased findings from transcriptomic data is suggested by the use of iron chelators as supportive therapy⁴², though the protective effect of iron chelators might involve mechanisms that are not primarily targeting iron homeostasis⁴³. Identified down-regulation of SCPs involved in protein degradation might explain cardiotoxicity by interference with sarcomere turn-over³⁰, as supported by the cardiotoxic effects of proteasome inhibitors¹⁰². The almost exclusive downregulation of these SCPs by anthracyclines could not be documented using the complete gene expression profiles (Supplementary Fig. 15C).

SCPs predicted from the drug-selective gene expression profiles of other drugs often describe functions that are supported by prior knowledge as well, based on transcriptomic and orthogonal methodologies.

For example, enrichment analysis of nilotinib-selective gene expression profiles leads to a more consistent prediction of upregulated SCPs involved in centrosome and mitotic spindle dynamics as well as mitosis compared to analysis of nilotinib's complete gene expression profiles (Supplementary Fig. 14B/C/D). Similar results were obtained for the kinase inhibitors imatinib, ponatinib, sorafenib and regorafenib. In agreement, previous morphological analysis documents centrosome aberrations and mitotic spindle defects induced by treatment of primary human fibroblasts with imatinib or nilotinib¹⁰³. Centrosome defects were also observed in disease-unaffected cells from patients treated with imatinib, nilotinib, sorafenib, sunitinib, dasatinib and bosutinib¹⁰⁴.

There are two MBCO level-3 SCPs that refer to increased cholesterol synthesis activity, 'Cholesterol synthesis' and 'Cholesterol-sensitive control of SREBP activation'. Though multiple drugs upregulate these SCPs at varying ranks, analysis of lapatinib-selective gene

expression profiles predicts upregulation of both SCPs at top enrichment ranks (5x rank 1 and ranks 2, 3, 4, 5, 6, respectively) (Supplementary Fig. 14D). In agreement, mevalonate pathway activity was found to be increased in lapatinib-resistant and lapatinib + trastuzumab-resistant cells ¹⁰⁵. Resistance was reversed by statin treatment that inhibits cholesterol synthesis.

SCPs associated with cardiotoxic and non-cardiotoxic responses to TKI treatment describe cellular dysfunctions involved in drug-independent cardiomyopathy development.

In the main text, we briefly describe SCPs involved in muscle contraction and sarcomere renewal, energy metabolism and ferroptosis. Here, we discuss identified and additional pathways in more detail.

Our F1 score and AUC statistics generate lists of SCPs that are up- or downregulated by cardiotoxic or non-cardiotoxic TKIs. Within each toxicity group combined up- and downregulated SCPs were ranked by decreasing AUC. We will refer to these ranks as AUC ranks to distinguish them from the enrichment ranks that are described above.

As already indicated in the main results section, we distinguish between SCPs whose activity for an association with a cardiotoxic response reaches sufficient levels after TKI treatment or is already sufficient at baseline levels. The first set of SCPs was identified by screening for those SCPs that are up- or downregulated at higher ranks by cardiotoxic TKIs, as compared to non-cardiotoxic TKIs. Treatment with a cardiotoxic TKI might change the SCP activity beyond a threshold that separates non-association from association with a cardiotoxic response. Treatment with a non-cardiotoxic TKI might move the SCP activity across the threshold in the opposite direction, changing its status from sufficient to insufficient for association with a cardiotoxic response. Both sets of SCPs can be organized based on the SCP activity that favors a cardiotoxic response. SCPs upregulated by cardiotoxic TKIs and downregulated by non-cardiotoxic TKIs are SCPs whose higher activity could favor a cardiotoxic response ('bad SCPs'). In contrast, SCPs downregulated by cardiotoxic TKIs and upregulated by non-cardiotoxic TKIs are SCPs whose lower activity could favor a cardiotoxic response ('good SCPs'). We use this classification in comparing the inferred SCPs from this data set to previously published data, since presence or absence of sufficient SCP activity is associated with presence or absence of cardiomyopathy development. We followed this principle in our figures as well. For SCPs that are upregulated by cardiotoxic and downregulated by non-cardiotoxic TKIs we use the colors red and orange, respectively (Supplementary Figs. 17 and 18). For SCPs downregulated by cardiotoxic and upregulated by non-cardiotoxic TKIs we use the colors blue and light blue, respectively. The same color scheme was applied in our network-based visualization that integrates identified SCPs into the MBCO parent-child hierarchy and groups SCPs participating in similar functions into the same module (Fig. 2C, Supplementary Fig. 19).

For both TKI groups we focused on the top 10 level-1, 10 level-2, 25 level-3 and 10 level-4 SCPs based on increasing AUC ranks (Supplementary Fig. 18). Six level-1, two level-2, eleven level-3 and four level-4 of those SCPs were predicted to be relevant for cardiotoxicity and regulated by both TKI groups in the opposite direction. In these cases, both TKI groups link the same SCP activities (i.e., higher or lower) to be associated with a cardiotoxic response. This approach was mostly successful. We only obtained conflicting results for one level-4 SCP that was downregulated by both TKI groups.

Identified SCPs were mapped back to the TKIs that increase or decrease their activity. To document which TKIs contributed to the identification of an SCP we show which cardiotoxic (Supplementary Fig. 20) or non-cardiotoxic (Supplementary Fig. 21) TKIs up- or downregulate an identified SCP at specified enrichment ranks.

Sarcomere dynamics

SCPs involved in muscle contractility were discussed in the main section. Here we want to add some more details. Identified level-1 SCP 'Cellular contraction', its level-3 grandchild SCPs 'Thin myofilament organization', 'Myofibril formation' and the level-4 SCPs 'Actin filament depolymerization' and 'Myoglobin synthesis' (Fig. 2B, Supplementary Fig. 19), are all involved in dynamics and turnover of the sarcomere, as already described in the main results section. The identified SCPs whose lower activities favor a cardiotoxic response, belong to those SCPs that were identified with evidence for both the cardiotoxic and non-cardiotoxic group: four of five SCPs were downregulated by cardiotoxic TKIs and at the same time upregulated by non-cardiotoxic TKIs (Supplementary Fig. 18). In addition, the level-2 SCP 'Myofibril formation and organization', a child of 'Cellular contraction' is identified (Supplementary Fig. 19), because it is downregulated by the non-cardiotoxic TKIs (Supplementary Fig. 18). Overall, all cardiotoxic TKIs, except vandetinib and trastuzumab downregulate (Supplementary Fig. 20), while 13 of 17 non-cardiotoxic TKIs upregulate (Supplementary Fig. 21) at least one of the contractility-related SCPs in one to six or one to five cell lines, respectively. Four of six SCP genes of the SCP 'Thin myofilament organization' that are inhibited by cardiotoxic and induced by non-cardiotoxic TKIs are components of tropomyosin or inhibitory troponin. Both complexes interact to block the binding of the myosin head to the thin myofilament during muscle contraction. This mechanism is also targeted by the new drug mavacamten that was recently approved by the FDA to treat obstructive HCM ³³, suggesting clinical relevance of our findings.

Electrical transmission

Four cardiotoxic TKIs, trametinib, trastuzumab, lapatinib and bevacizumab upregulate 'Potassium transmembrane transport' in three of four (enrichment ranks 2, 3, 9), two of three (7, 10), two of five (7, 10) and one of four (17) cell lines (Fig. 2B, Supplementary Fig. 20), respectively. The SCP with an AUC rank of 7 (Fig. 2B, Supplementary Fig. 18) is predicted based on potassium channels, transporters and components of the sodium potassium ATPase

(Supplementary Data 11). Among the SCP genes is *SUR2A* coding for a regulatory subunit of the cardiac ATP-sensitive potassium channel involved in genetic DCM ¹⁰⁶.

The level-3 SCP 'Gap junction organization' is predicted with an AUC rank of 24 for the cardiotoxic TKIs (Fig. 2B, Supplementary Fig. 18). It is downregulated by the cardiotoxic TKI dabrafenib in one of five (enrichment rank 24), pazopanib in two of six (1, 3), ponatinib in three of six (15, 16, 17), vandetinib in one of three (9) and vevacizumab in four of four (13, 2x14, 15) treated cell lines (Supplementary Fig. 20). In agreement, multiple connexins that form the building block of gap junctions are downregulated in explanted heart from patients with idiopathic cardiomyopathy ¹⁰⁷.

Energy metabolism

We identified multiple SCPs that suggest interference with cardiac energy metabolism as a major trigger for TKI-induced cardiotoxicity.

The level-2 SCPs 'Mitochondrial energy production', 'Fatty acid metabolism', 'Carbohydrate metabolism and transport' and 'Post-translational protein modification in Mitochondria' were upregulated by cardiotoxic TKIs with the AUC ranks one to four, respectively (Supplementary Fig. 18). Their upregulated level-3 child SCPs 'Citric acid cycle' and 'Desaturation of fatty acids' were predicted with AUC ranks 1 and 11, respectively (Fig. 2B, Supplementary Figs. 18, 19). Three of these level-2 and -3 SCPs map to ventricular cardiomyocytes in the adult heart (Fig. 3A, Supplementary Fig. 23) as the cell type with the highest energy requirement. These SCPs that interact with each other to ensure energy supply were almost exclusively predicted based on their induction by pazopanib (Supplementary Fig. 20), a TKI with a high rate of cardiotoxicity (>10%) (Supplementary Data 3). Genes of these SCPs induced by pazopanib are involved in the citric acid cycle and oxidative phosphorylation, fatty acid activation, elongation and desaturation as well as glucose import, release from glycogen and degradation (Supplementary Data 11).

Many studies document an overall reduction in oxidative phosphorylation during heart failure ³⁴, in agreement with the enrichment results obtained in adult and hiPSC-derived DCM and adult HCM cardiomyocytes (Fig. 3B, Supplementary Fig. 24). Nevertheless, compensatory upregulation of oxidative phosphorylation was suggested for a large DCM subgroup that is caused by truncating titin variants ³⁵⁻³⁷. Another prominent molecular phenotype observed in these studies is a shift from fatty acid oxidation towards glycolysis. Upregulated genes mapping to carbohydrate catabolism and fatty acid anabolism might support such interpretation of our data as well, though the level-3 and -4 child SCPs that specifically describe these functions, were not among the top predictions. For the non-cardiotoxic TKIs, we predict the level-2 SCP 'Carbohydrate metabolism and transport' and its level-3 child 'Glycolysis and Gluconeogenesis' at ranks 1 and 25, respectively (Supplementary Figs. 18 and 19), based on a set of partly overlapping genes (Supplementary Data 11B and C), further supporting glucose utilization as a cellular function whose higher activity favors a cardiotoxic response to TKI-treatment.

Polyunsaturated fatty acids (PUFAs) generated by genes mapping to the upregulated SCP “Fatty acid desaturation” (Supplementary Data 11C) ^{39,40} can be deoxygenized by lipoxygenases, resulting in cardiotoxic PUVA hydroperoxides ³⁸. PUVA hydroperoxides are a main stimulator of ferroptosis, a potentially major mechanism involved in heart failure.

The involvement of ferroptosis in drug-induced cardiomyopathy was also predicted for the cardiotoxic anthracyclines based on the downregulation of ‘Cellular iron storage’ (Supplementary Figs. 14D, 15B), as discussed above. However, upregulated transporter activities involved in import of iron-containing molecules, such as transferrin or haptoglobin-hemoglobin complexes, are predicted as part of the level-3 SCP ‘Cellular iron uptake and export’ for the non-cardiotoxic TKIs with AUC rank 23 (Supplementary Fig. 18). These seemingly contradictory results could indicate that it is the balance in cellular iron content rather than an increase or decrease of iron levels that is associated with cardiotoxicity.

The level-3 SCP ‘Serine and glycine metabolism’ was identified for cardiotoxic and non-cardiotoxic TKIs as an SCP whose higher activity indicates a cardiotoxic response with the AUC ranks 19 and 5, respectively (Supplementary Fig. 18). Seven cardiotoxic (Supplementary Fig. 20) and twelve non-cardiotoxic (Supplementary Fig. 21) TKIs up- and downregulate this SCP, respectively, in one to six cell lines. Dabrafenib, a TKI with a cardiotoxicity frequency between 1 and 10%, upregulated this SCP in all five cell lines with top enrichment ranks (3x1, 2, 3), followed by pazopanib (ranks 2x2, 3, 4, 5) (Supplementary Fig. 20). Identified SCP genes are involved in serine and glycine biosynthesis (Supplementary Data 11C). Stimulation of serine biosynthesis in hiPSC-derived cardiomyocytes from patients with genetic DCM rescues contractile dysfunction in-vitro by increasing the glucose flux into the citric acid cycle and oxidative phosphorylation ¹⁰⁸. The seemingly contradictory findings could indicate a compensatory upregulation of mRNAs coding for serine and glycine metabolism proteins or suggest that levels of serine could be a driver of energy balance in cardiomyocytes. These hypotheses need to be experimentally verified.

Two level-3 SCPs involved in cholesterol synthesis and another SCP predicted based on genes involved in cholesterol export (Supplementary Data 11C) were up- and downregulated by the cardiotoxic TKIs, with the AUC ranks 15, 22 and 23, respectively (Fig. 2B, Supplementary Fig. 18). Both synthesis SCPs were also downregulated by non-cardiotoxic drugs, with the AUC ranks 3 and 24. Our results link higher intracellular cholesterol levels, either based on increased synthesis or decreased export, to a cardiotoxic response. While six cardiotoxic (Supplementary Fig. 20) and eleven non-cardiotoxic (Supplementary Fig. 21) TKIs induce the described pathway activities in opposite directions with varying enrichment ranks, it is, in particular, the cardiotoxic TKI lapatinib that upregulates both cholesterol synthesis SCPs with top enrichment ranks (5x1 and 2, 3, 4, 5, 6). Our observations agree with the results of a meta-analysis documenting a cardioprotective effect of statin treatment against chemotherapy-induced cardiomyopathy ⁴⁴, though statins might induce multiple cardioprotective mechanisms besides inhibition of HMG-CoA reductase, the rate-controlling enzyme in cholesterol synthesis ¹⁰⁹.

Since lapatinib resistance of breast cancer cells due to increased cholesterol synthesis could be reversed *in-vitro* by statin treatment¹⁰⁵, our results might suggest a potential effect of statin treatment on lapatinib's cardiotoxicity as well. Potential detrimental effects of statin treatment in heart failure¹¹⁰ and involvement of cholesterol biosynthesis intermediates in the antioxidant defense against ferroptosis³⁸ might indicate the need for correct balance of cholesterol homeostasis and TKI-selective supportive statin therapy.

Cellular antioxidant systems

The level-1 and -2 SCPs 'Cellular redox homeostasis' and 'Cellular antioxidant defense systems' in parent-child relationships (Supplementary Fig. 19) were predicted with AUC ranks 2 and 5 (Supplementary Fig. 18), respectively. Both were downregulated by vandetinib in three of three (enrichment ranks 3, 4, 5 and 3, 4, 7) and bevacizumab in two of four (6, 7 and 7, 8) treated cell lines (Supplementary Fig. 20). Multiple animal models document involvement of oxidative stress in heart failure and oxidative stress biomarkers are increasingly used in the monitoring of heart failure patients¹¹¹. Reduction of oxidative stress is a protective mechanism against ferroptosis³⁸, a cardiotoxic mechanism that is also suggested based on other identified SCPs.

Posttranslational protein modification and translational quality control

The cardiotoxic TKI dabrafenib upregulates the level-1 SCP 'Posttranslational protein modification' and its level-2 child SCP 'Posttranslational protein modification and quality control during secretory pathway' (Supplementary Fig. 19) in two of five treated cell lines (both enrichment ranks 1, 2) (Supplementary Fig. 20). Both SCPs were predicted for the cardiotoxic drugs with AUC ranks of 1 and 7, respectively (Supplementary Fig. 18). Many of the upregulated SCP genes participate in protein folding, quality control and stress response in the endoplasmic reticulum (ER) (Supplementary Data 11B). Their upregulation could be a response to protein accumulation in the ER that can be differentiated into two phases¹¹². The initial physiological ER stress response of the heart addresses the accumulation of proteins in the ER, while in case of prolonged stress a pathological response triggers autophagy and apoptosis.

Cellular signaling pathways

Among the identified signaling pathways were PDGF, Natriuretic receptor, HIF-1 alpha, Oncostatin M and Hippo signaling (Fig. 2B, Supplementary Fig. 18).

PDGF signaling was identified as an SCP that favors a non-cardiotoxic response with the AUC rank 14 (Fig. 2B, Supplementary Fig. 18) and preferentially maps to cardiac fibroblasts and smooth muscle cells in the adult human heart (Fig. 3A, Supplementary Fig. 23). It is downregulated by seven cardiotoxic TKIs in one to six cell lines (Supplementary Fig. 20). Ponatinib (cardiotoxicity 1-10%), trastuzumab (>10%) and sorafenib (1-10%) downregulated

the SCP in all treated cell lines (enrichment ranks 4, 3x6, 13; 2, 4, 5, 11 and 5, 6, 10, 15, respectively). In agreement with our results, PDGF and PDGF signaling in the heart increase during disease states and are generally considered to play an important role during cardioprotection ¹¹³, as supported by the PDGF-induced increase in cell survival and contractility of engineered cardiac tissue ^{114,115}.

The level-4 SCPs 'Atrial -', 'Brain-' and 'C-type natriuretic receptor signaling' and their level-3 parent SCP 'Natriuretic peptide receptor signaling' (Supplementary Fig. 19) were identified to favor a non-cardiotoxic response (Supplementary Fig. 18). They were upregulated by six, four, two and six overlapping non-cardiotoxic drugs in one to four cell lines, respectively (Supplementary Fig. 21). The SCP 'Atrial natriuretic peptide receptor signaling' was additionally downregulated by the three cardiotoxic TKIs lapatinib, ponatinib and vandetanib in one of their treated cell lines (enrichment ranks 4, 4 and 2, respectively). Induced genes contain the ligands *NPPA*, *NPPB* and *NPPC* as well as receptor genes (Supplementary Data 11C and D). Though our data was generated *in vitro*, the classification into cardiotoxic and non-cardiotoxic drugs is based on clinical data. A potential explanation for the identified association could be that both secreted ANP and BNP have a protective effect on cardiac preload, afterload and cardiovascular growth ¹¹⁶. The endopeptidase neprilysin degrades several endogenous vasoactive peptides including natriuretic peptides ¹¹⁷. Treatment schemes of patients with chronic heart failure that combine neprilysin and angiotensin II receptor inhibition achieve better results than treatment with an angiotensin converting enzyme (ACE) inhibitor ^{45,46}, suggesting clinical relevance of our findings ¹¹⁷.

We identified genes involved in the inhibition of HIF-1 alpha signaling (Supplementary Data 11C) as associated with a non-cardiotoxic response with the AUC rank 20 (Fig. 2B, Supplementary Fig. 18). They were downregulated by the two cardiotoxic TKIs dabrafenib and pazopanib in two (enrichment ranks 8, 8) and three (1, 6, 6) of five treated cell lines, respectively (Supplementary Fig. 20). In agreement, only short-term HIF-1 signaling in acute stress situations has a cardioprotective effect, while continuously active HIF-1 signaling might be harmful ¹¹⁸, suggesting an explanation of why its inhibition under long-term TKI treatment might improve cardiac outcomes.

A similar effect was described for Oncostatin M (OSM) receptor signaling that favors a cardiotoxic response (Supplementary Fig. 18), since it is downregulated by two non-cardiotoxic TKIs in two and four cell lines (Supplementary Fig. 21). Stimulation of OSM signaling cascades mitigates cardiac damage in acute stress conditions, while its chronic activation contributes to the development of heart failure ¹¹⁹.

The level-3 SCP 'Hippo signaling' was downregulated by cardiotoxic TKIs with an AUC rank of 13 (Fig. 2B, Supplementary Fig. 18). Pazopanib downregulates this SCP in three of five treated cell lines (enrichment ranks 1, 2x6) (Supplementary Fig. 20). It preferentially maps to cardiac fibroblasts in the adult human heart (Supplementary Fig. 23). Five of six downregulated genes inhibit the Hippo downstream transcription factor YAP1 (Supplementary Data 11C). Consistent

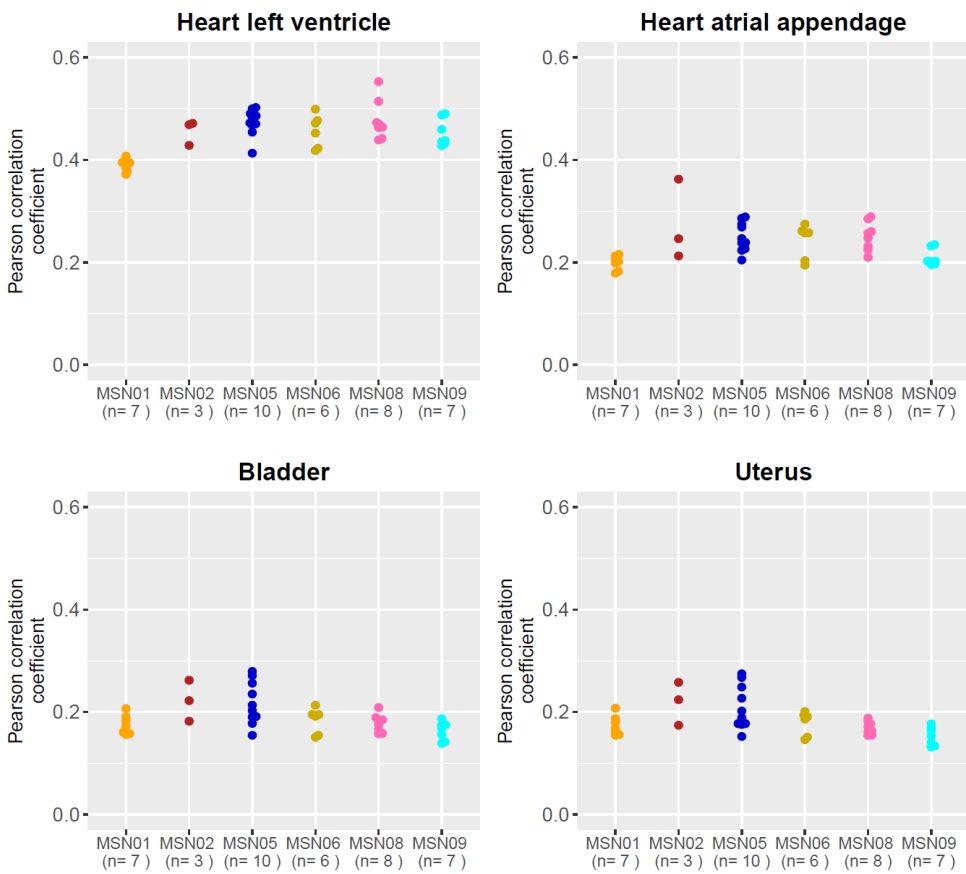
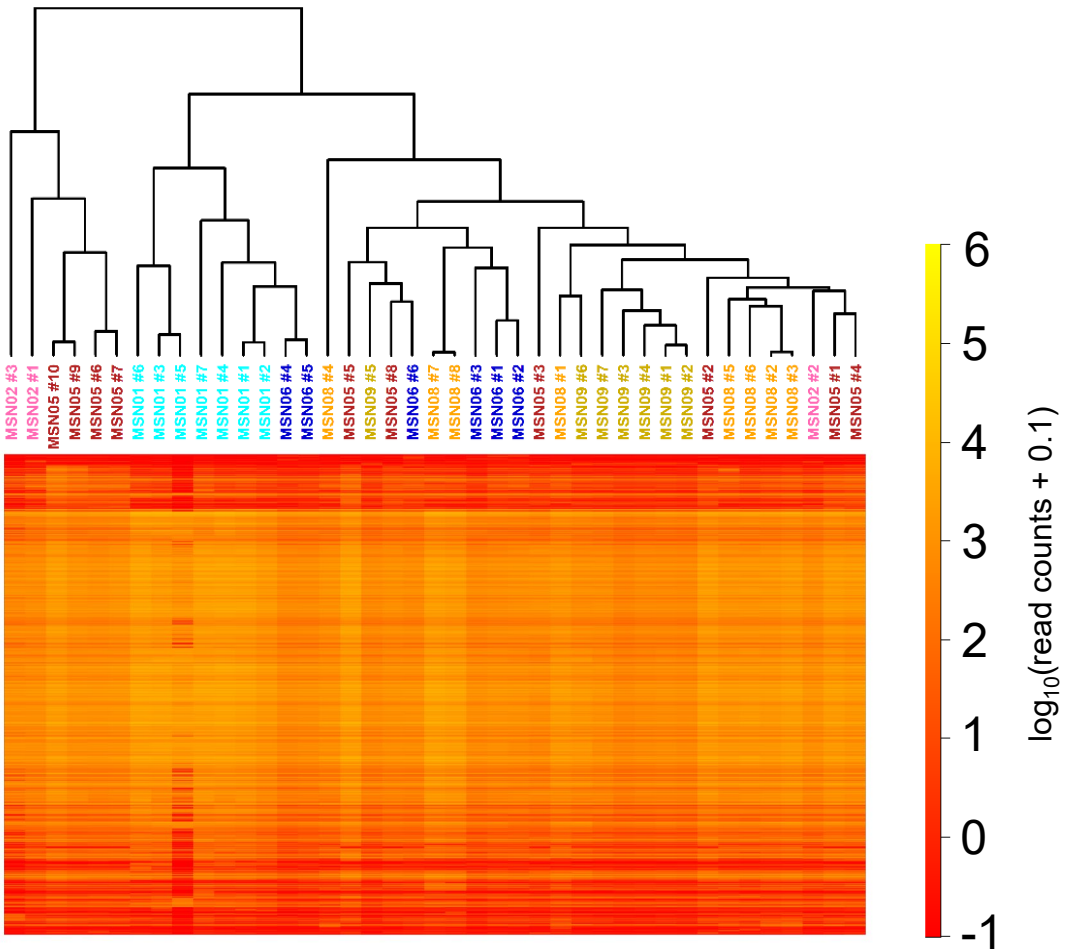
with this finding, increased YAP activity and expression of hypertrophic target genes was also observed in HCM patient tissue and a HCM murine model ¹²⁰.

Extracellular matrix organization

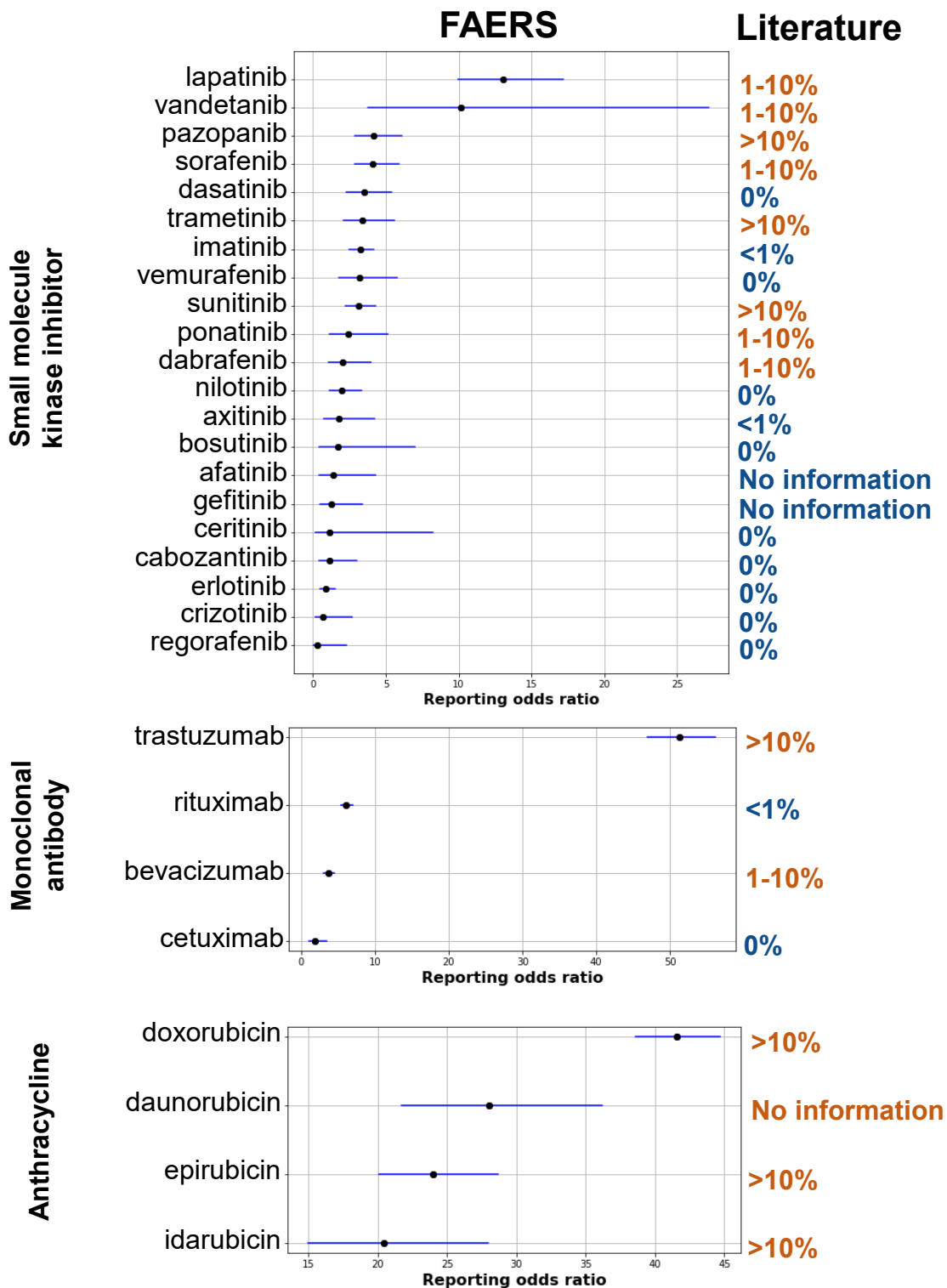
Fibrillar collagen constitutes the most abundant protein in the cardiac extracellular matrix (ECM) which provides structural organization for the correct alignment of cardiomyocytes, generates myocardial stiffness and helps in force transmission ¹²¹. Diffuse interstitial fibrosis, a histopathological feature observed in non-ischemic cardiomyopathies or hypertensive heart disease is characterized by excessive deposition of type I and III collagen, by changing ratios of type I to type III collagen and by an increase in collagen crosslinking. The degree of collagen crosslinking, but not total collagen deposition correlates with surrogate parameters (e.g., myocardial stiffness) or hospitalization in patients with hypertensive heart disease ^{47,48}. In agreement, 'Collagen fiber cross-linking' is downregulated by eleven non-cardiotoxic TKIs in one to six cell lines (Supplementary Fig. 21), identified with the AUC rank 7 and consequently categorized as an SCP that favors a cardiotoxic response (Supplementary Fig. 18). Downregulation of the SCP 'Elastin cross-linking and assembly' (AUC rank 16) is predicted based on genes shared with the collagen-cross linking SCP. The SCP 'Collagen fibril organization by fibril-associated bridges' that contains the FACIT collagens is upregulated by eleven non-cardiotoxic TKIs in one to six cell lines (Supplementary Fig. 21) and was identified with the AUC rank 17 as an SCP whose higher activity favors a non-cardiotoxic response (Supplementary Fig. 18). The reduced expression of FACIT collagen during progressive liver cirrhosis is associated with a loss of flexibility ¹²². Whether FACIT collagen can exhibit a similar effect on the cardiac wall needs to be investigated.

Water transmembrane transport

Down- and upregulation of aquaporins that are the main components of the level-3 SCP 'Water transmembrane transport' is predicted with AUC ranks of 9 and 2 for cardiotoxic and non-cardiotoxic TKIs, respectively (Fig. 2B, Supplementary Fig. 18). Three cardiotoxic drugs, dabrafenib, pazopanib and ponatinib, downregulate the SCP in two of three (enrichment ranks 6, 7), one of five (4) and two of six (6, 9) treated cell lines (Supplementary Fig. 20). The induced and repressed SCP genes, aquaporins 1, 3, 7 and 10 (Supplementary Data 11C) might be related to their function in transmembrane transport of water (AQP1, 3, 7, 10), CO₂ and NO (AQP1) or urea and the energy substrate glycerol (AQP 3, 7, 10) ¹²³.

A**B**

Supplementary Fig. 1. Basal gene expression of six hiPSC-derived cardiomyocyte cell lines map to the human heart and show cell line specificity. (A) Raw read counts of vehicle-treated replicates ¹⁶ were correlated with median gene expression levels for each tissue in the GTEx database. Pearson correlation coefficients are shown for each replicate of all cell lines and the top four tissues with the highest correlation coefficients. Numbers of replicates are provided in parentheses. **(B)** Gene expression raw counts obtained in all replicates of vehicle-treated cell lines ¹⁶ were subjected to pairwise correlation analysis, followed by hierarchical clustering. Visualized matrix shows the $\log_{10}(\text{read counts} + 0.1)$. Rows and columns were re-arranged according to clustering results. Replicates of the same cell line are colored with the same color.

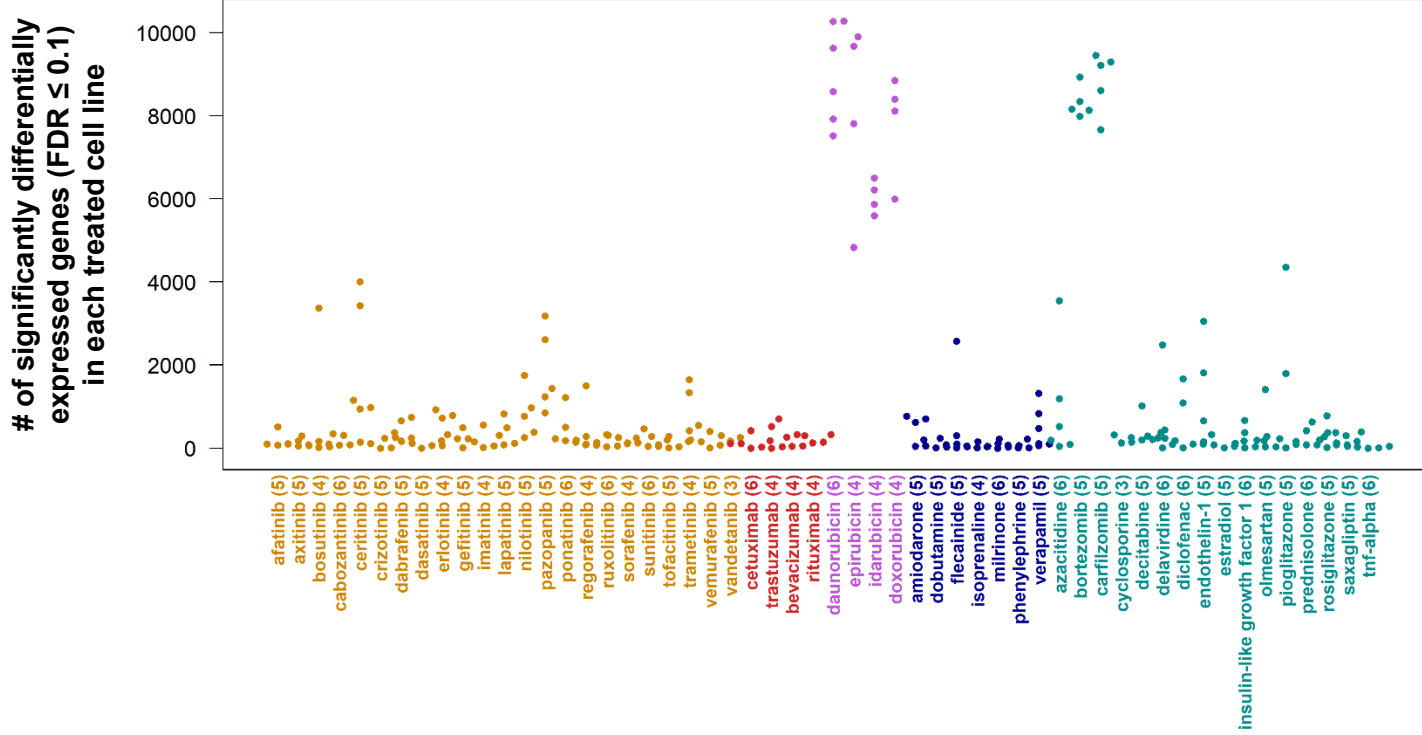


Supplementary Fig. 2

Supplementary Fig. 2. Cardiac toxicity of kinase inhibitors and monoclonal antibodies curated from the FAERS database. Risk profiles were curated from the FAERS database. Horizontal lines indicate 95% confidence intervals. Blue and orange comments describe published cardiotoxicity levels as outlined in Supplementary Data 3.

A

266 drug/cell line combinations
(54 drugs, 6 cell lines)



23 Small molecule kinase inhibitors

4 Monoclonal antibodies

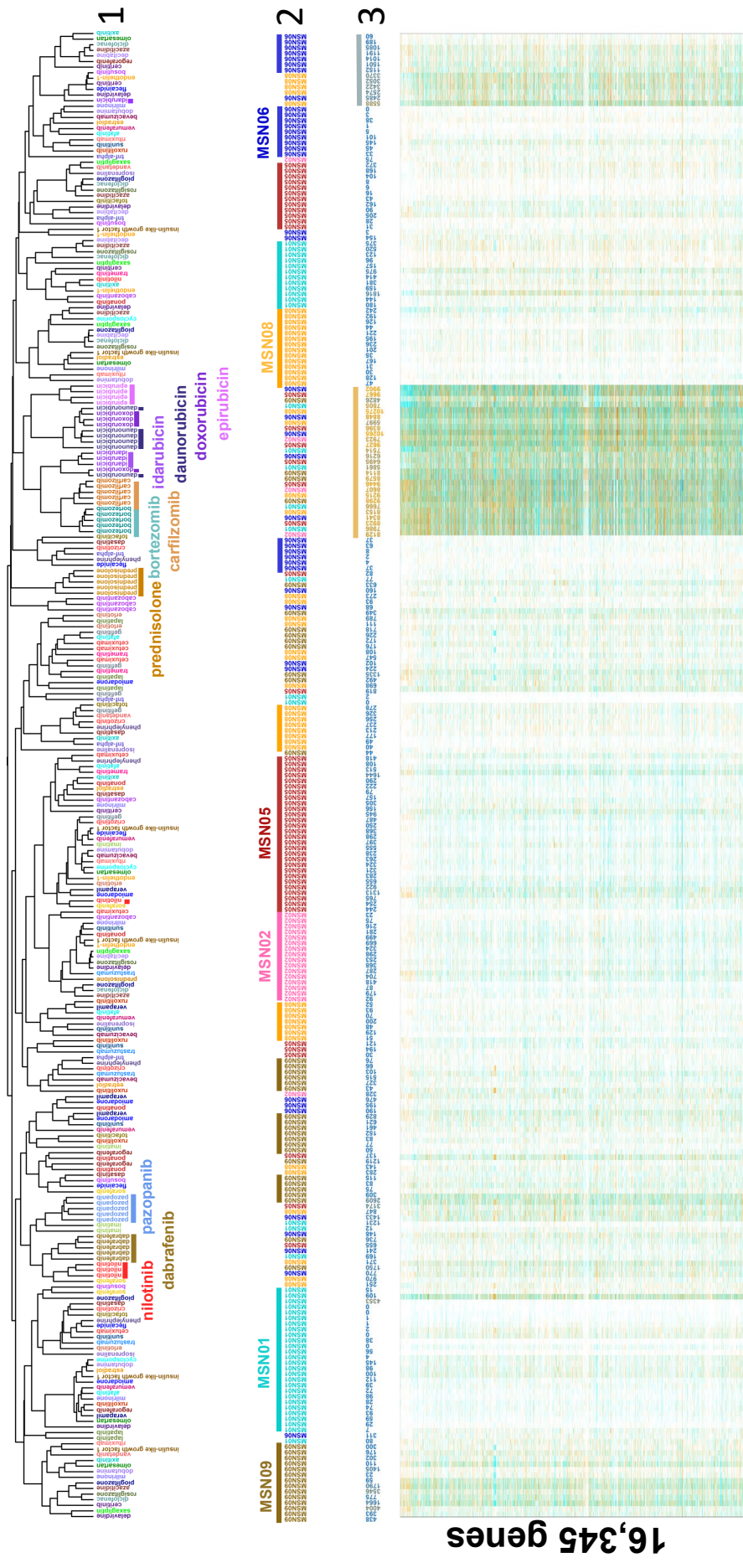
4 Anthracyclines

7 Cardiac-acting drugs

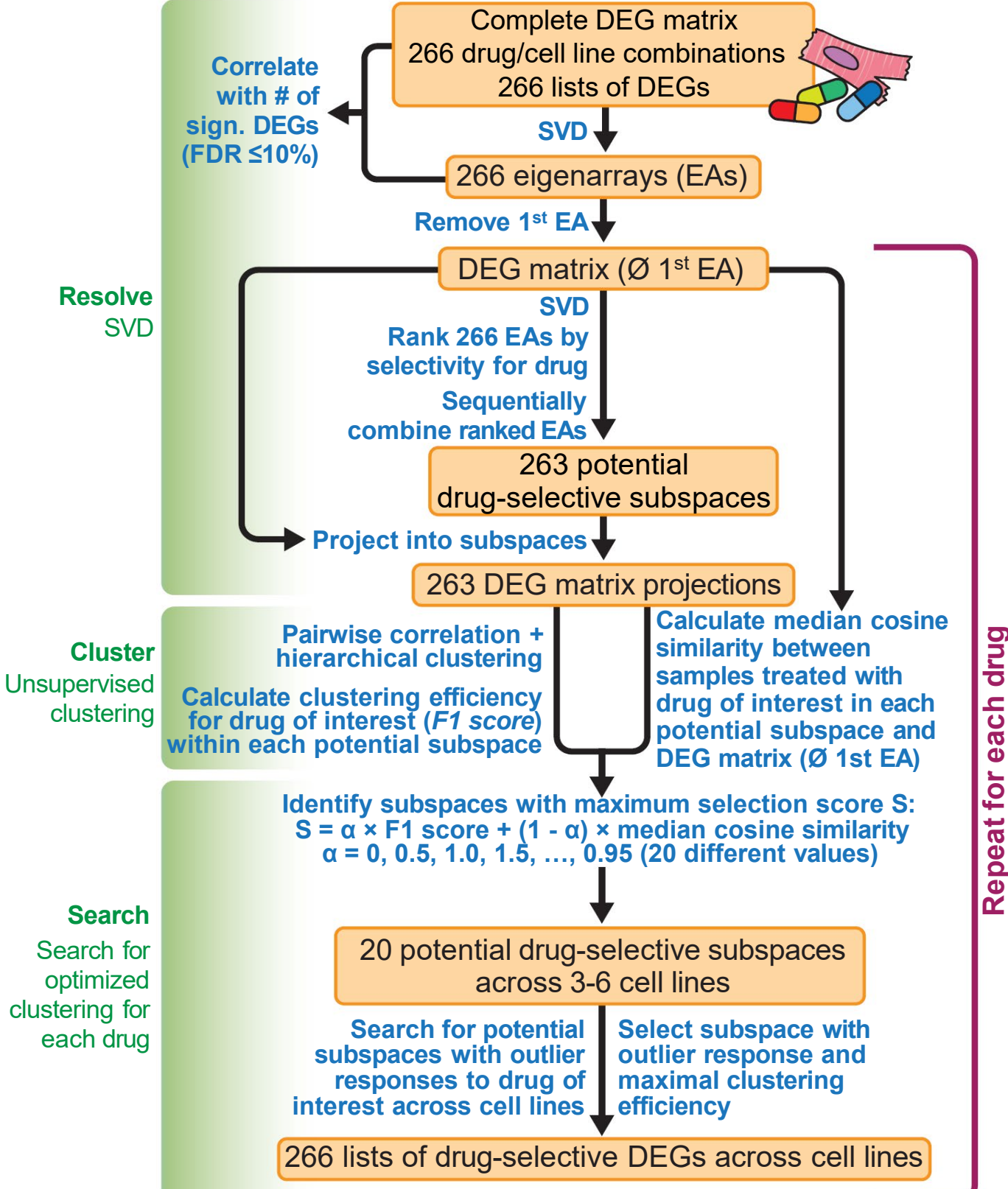
16 Non-cardiac-acting drugs

27 Tyrosine kinase inhibitors (TKIs)

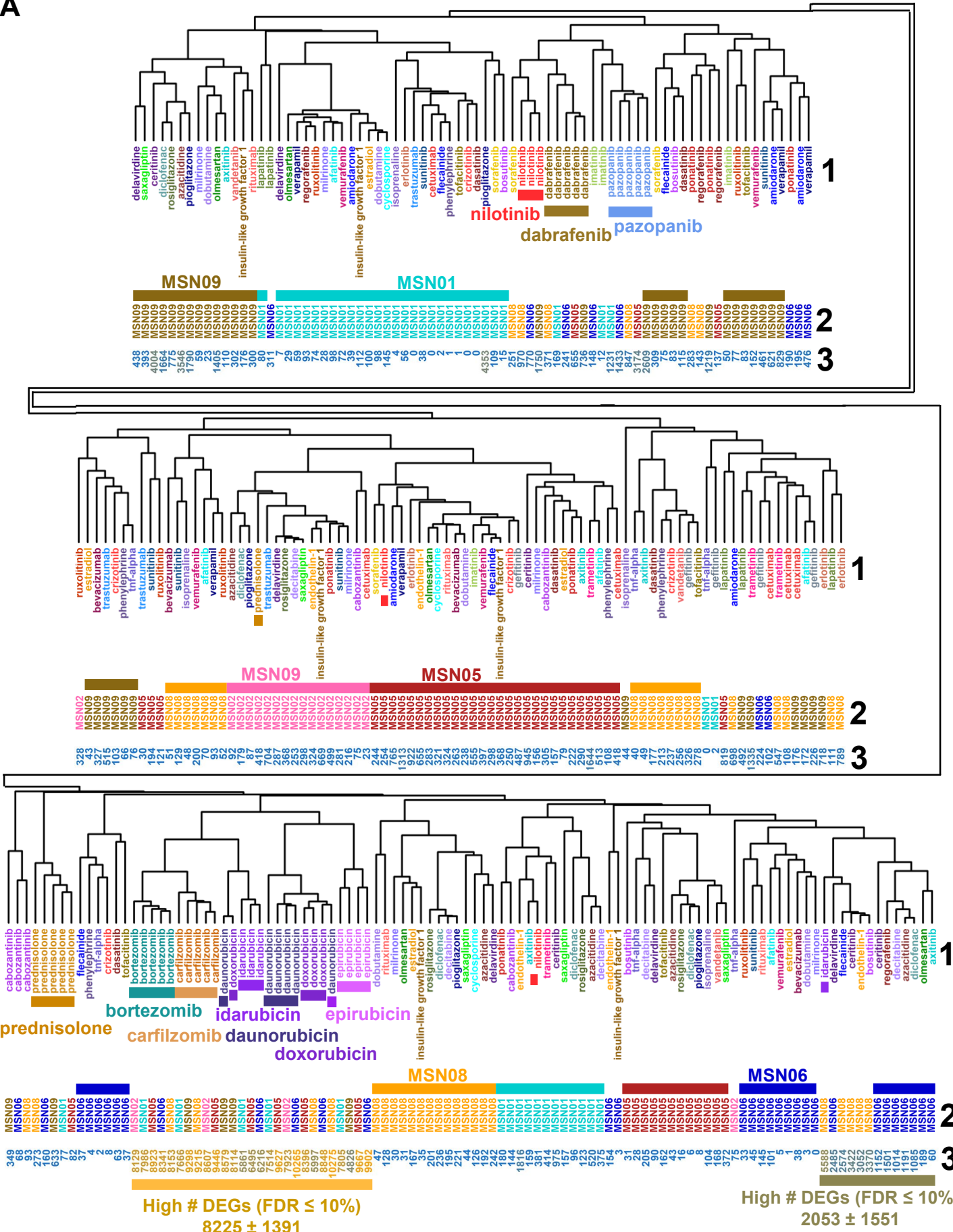
Gene expression profiles of 266 drug/cell combinations

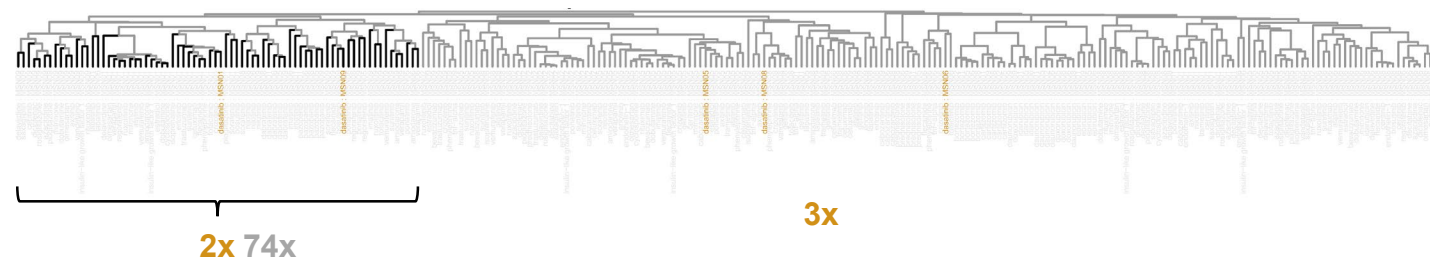


Supplementary Fig. 3. Drug-induced gene expression profiles in six hiPSC-derived cardiomyocyte cell lines. (A) Three to six hiPSC-derived cardiomyocyte cell lines were stimulated with one out of 54 drugs or vehicle for 48h, followed by bulk RNAseq and identification of 266 lists of DEGs. The number of DEGs induced by the different drugs in the different cell lines showed great variation ($FDR \leq 10\%$). Total numbers of treated cell lines for each drug are shown in parentheses next to the drug labels. (B) Significance p-values were transformed into $-\log_{10}(p\text{-values})$ and defined to be positive or negative for up- or downregulated genes, respectively. Pairwise correlation analysis followed by hierarchical clustering, documents that only a few gene expression profiles are determined by the drug used for treatment (1), while most profiles are determined by the treated cell line (2) or the number of significant DEGs (3). Fig. 1B shows the same dendrogram.



Supplementary Fig. 4. Computational pipeline for the identification of drug-selective and outlier gene expression responses. Our pipeline subjects drug-induced DEGs to Singular Value Decomposition (SVD) to identify drug-selective gene expression profiles and cell lines that respond differently to a drug of interest than the other cell lines. See methods for details. &: and; ∅: without. Flow chart is used with permission from Mount Sinai Health System, licensed under CC BY.



B**dasatinib cluster in complete gene expression profiles**

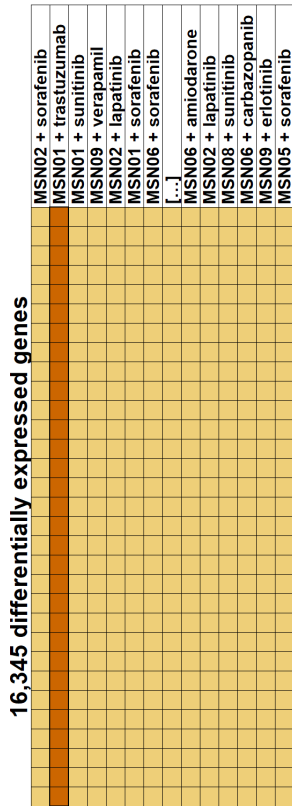
Cluster with highest F1 score
for dasatinib-treated cell lines
Precision = 2/76, Recall = 2/5, F1-score = 0.05

Supplementary Fig. 5

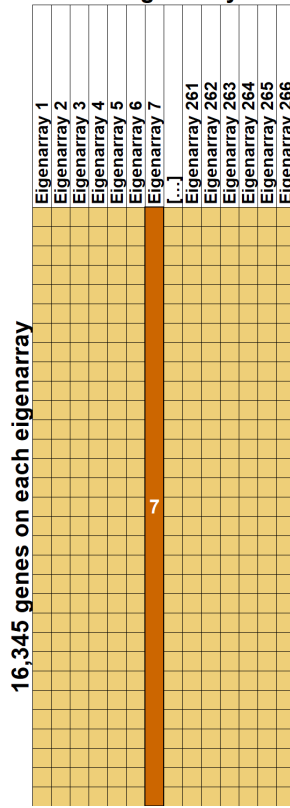
Supplementary Fig. 5. Clustering efficiency of drug-induced gene expression profiles in six hiPSC-derived cardiomyocyte cell lines. (A) To allow detailed investigation of the clustering results we visualized dendrogram and dendrogram labels of Supplementary Fig. 3B at larger sizes. Fig. 1B shows the same dendrogram with a focus on the drugs. (B) For each drug, we calculated one F1 score for each cluster that can be obtained by cutting the dendrogram at any height and contains at least two cell line/drug combinations. The F1 score is the harmonic mean of the precision (how many cell line/drug combinations within a cluster were treated with the drug) and the recall (how many cell line/drug combinations treated with the drug were in that cluster). The cluster with the highest F1 score that was selected for further analysis in this example is labeled black.

A

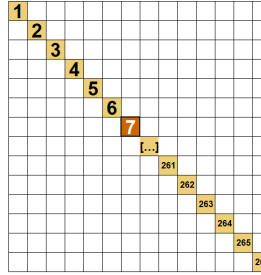
266 samples/lists of DEGs



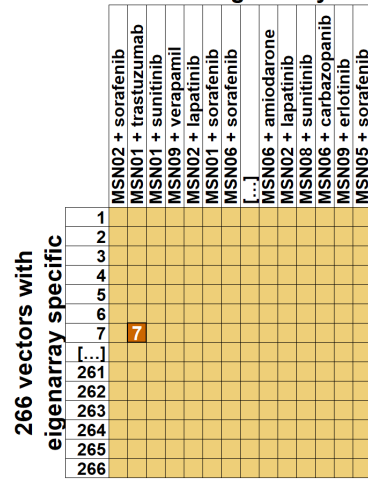
266 eigenarrays



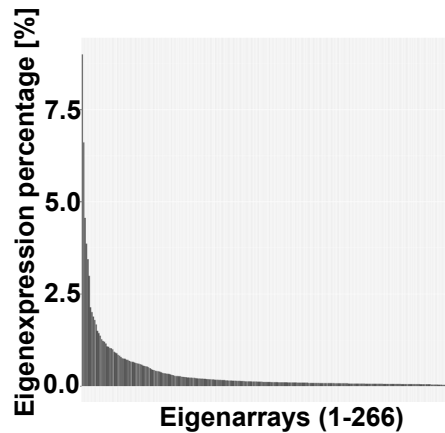
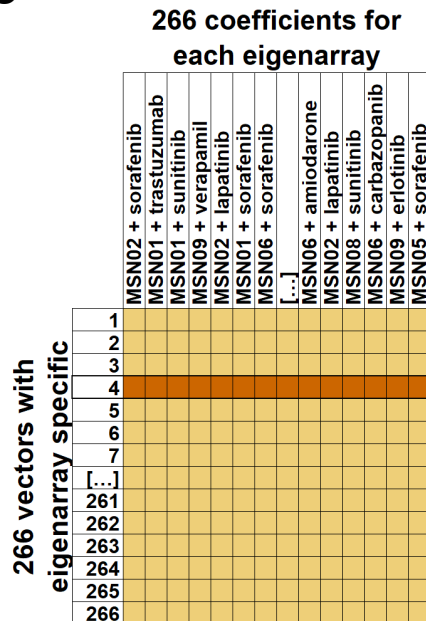
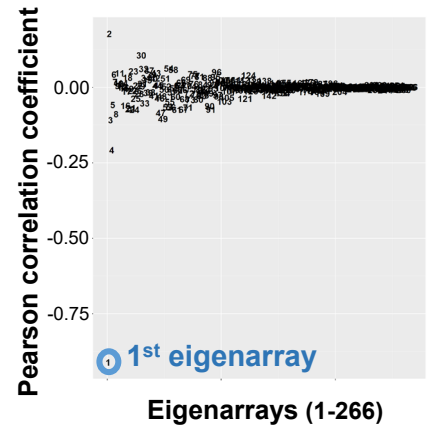
266 singular values



266 coefficients for each eigenarray



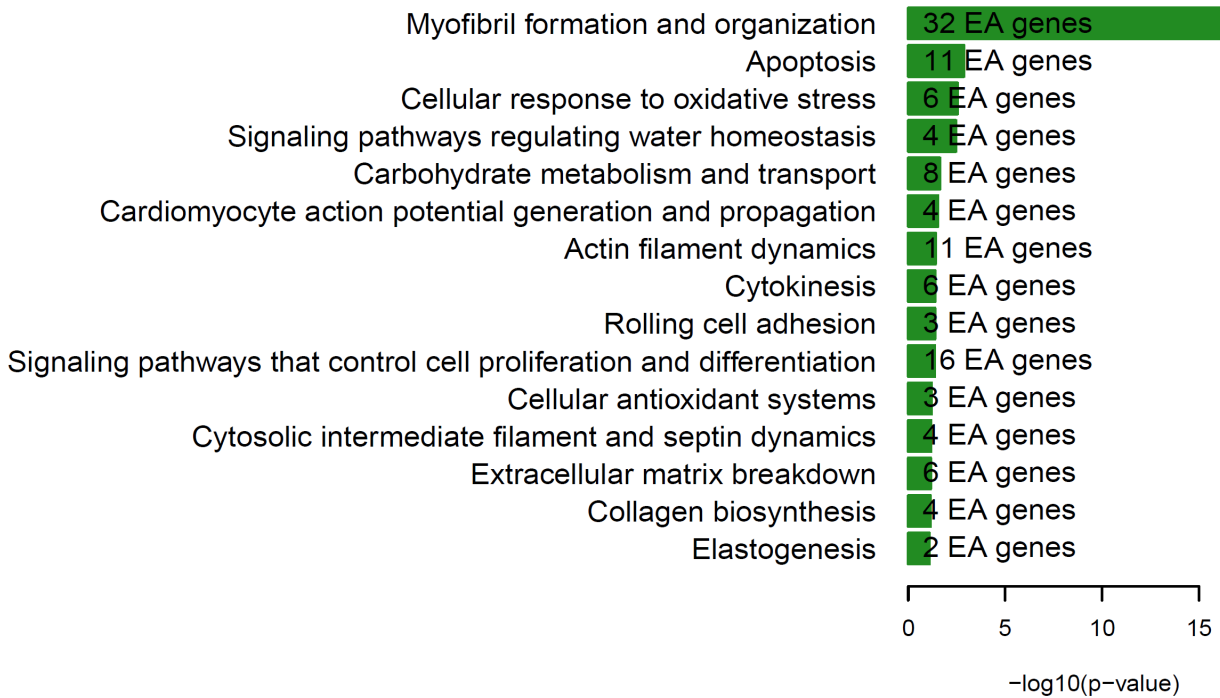
The gene expression profile of each sample is a linear combination of all eigenarrays.

B**C****D**

For each eigenarray:

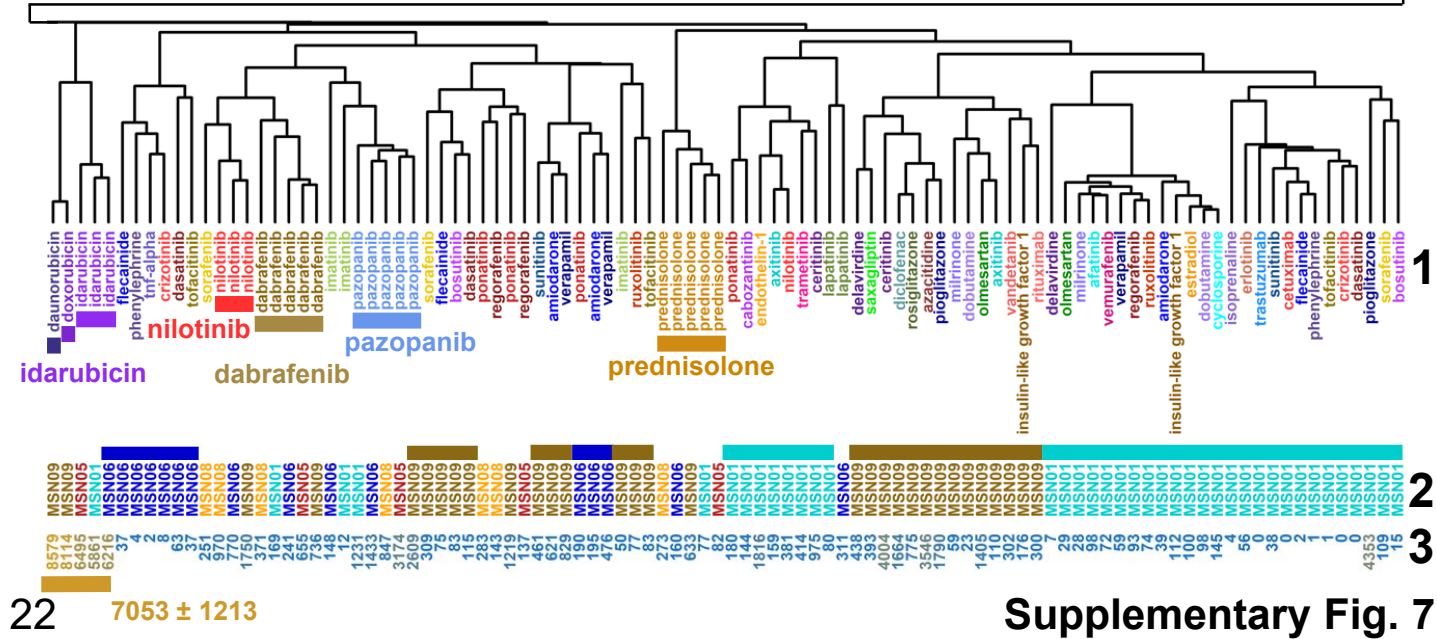
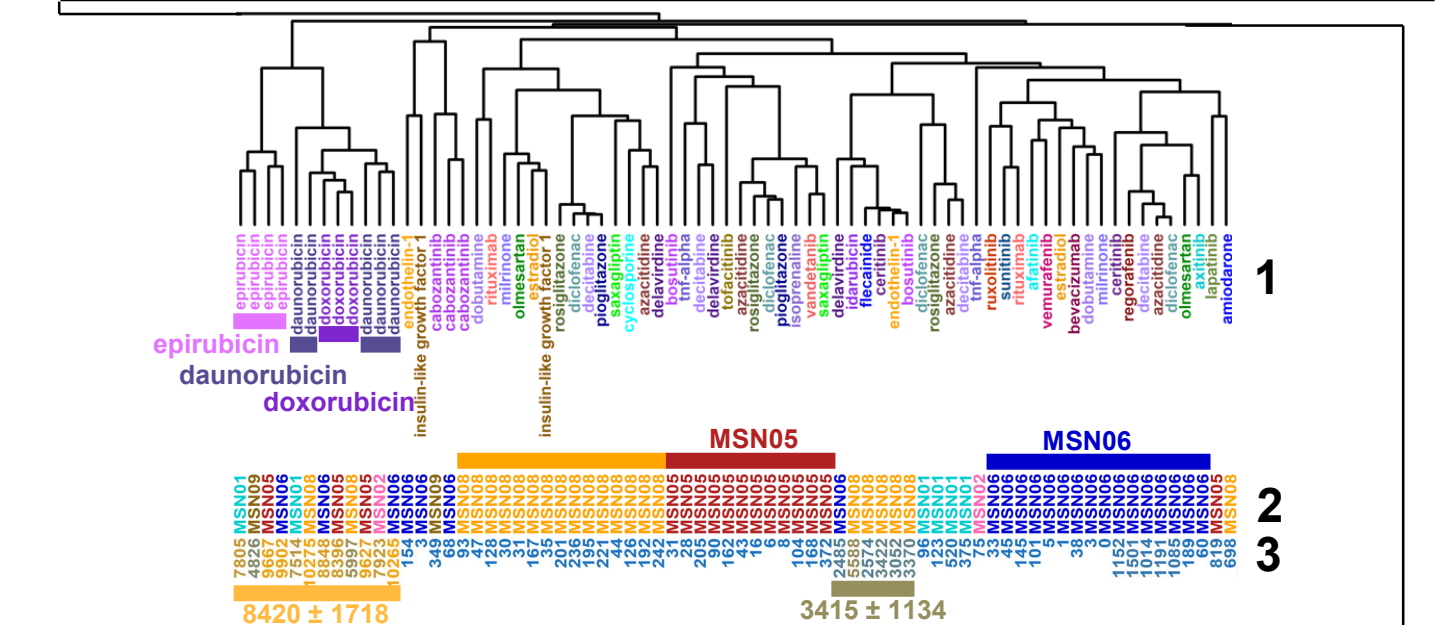
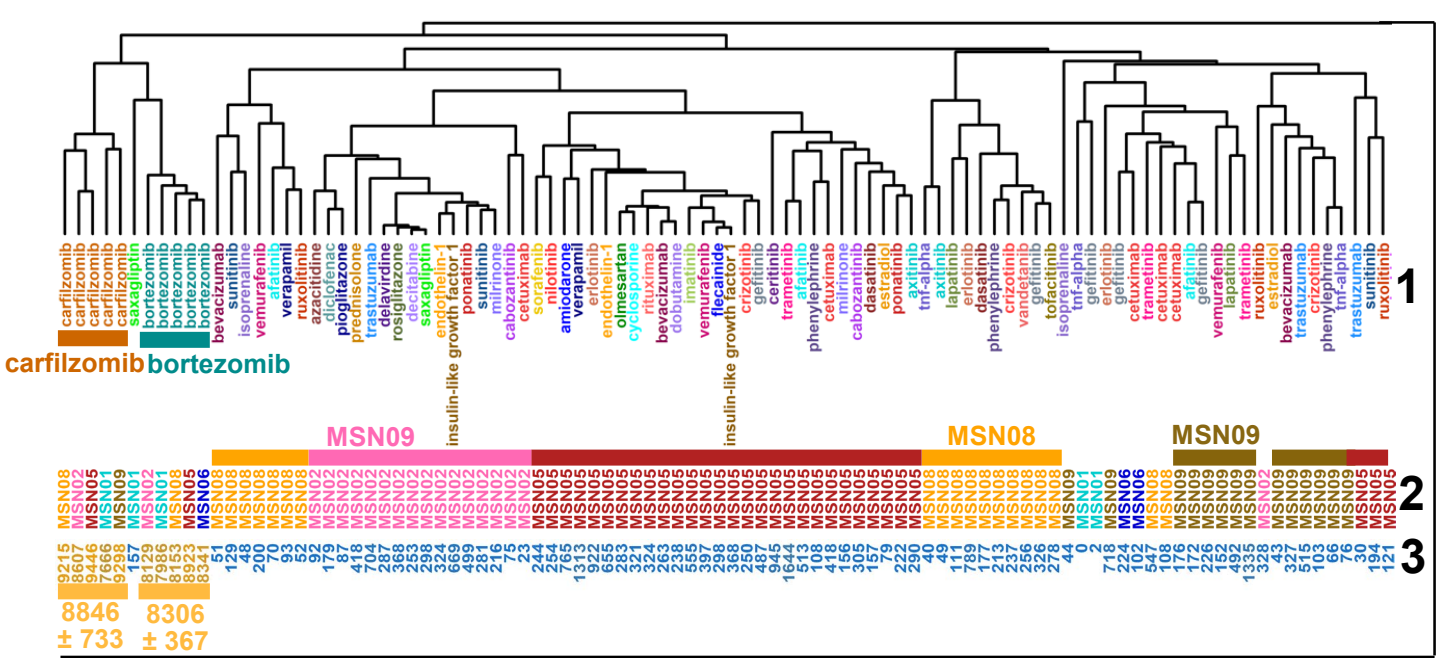
Correlate coefficients of that eigenarray with # of significantly differentially expressed genes in each sample.

E



Supplementary Fig. 6

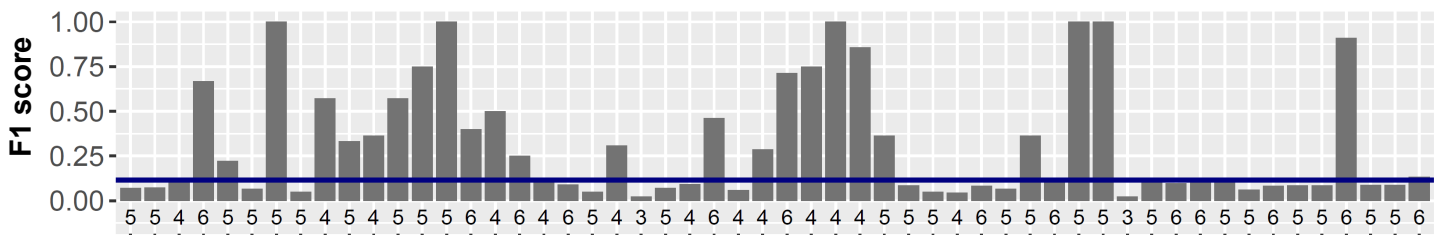
Supplementary Fig. 6. Identification of drug-selective gene expression responses using Singular Value Decomposition. (A) Singular value decomposition (SVD) decomposes the input data matrix into a matrix of left singular vectors or eigenarrays, a diagonal matrix of singular or eigenexpression values and a matrix of right singular vectors. Each cell line/drug combination gene expression vector in the full matrix is a linear combination of all eigenarrays. Cell line/drug combination specific coefficients of this linear combination are documented in the matrix of right singular vectors. The eigenexpression values in the diagonal document how much each eigenarray contributes to the complete gene expression dataset of all cell line/drug combinations and need to be considered for the linear combination as well. To calculate the contribution of the seventh eigenarray to the complete gene expression profile induced by trametinib in cell line MSN09 it must be multiplied with highlighted eigenexpression value and the highlighted coefficient, both labeled with seven. (B) SVD of the gene expression matrix identified 266 orthonormal eigenarrays that are sorted by their relative contribution to the total variance. (C) For each eigenarray, we calculated the Pearson correlation between the cell line/drug combination-specific coefficients and the number of significant DEGs in the corresponding complete gene expression profiles. (D) Our results document a high correlation with the number of significant DEGs for the first eigenarray. (E) Pathway enrichment analysis of the top 600 genes of the first eigenarray identifies muscle contraction.



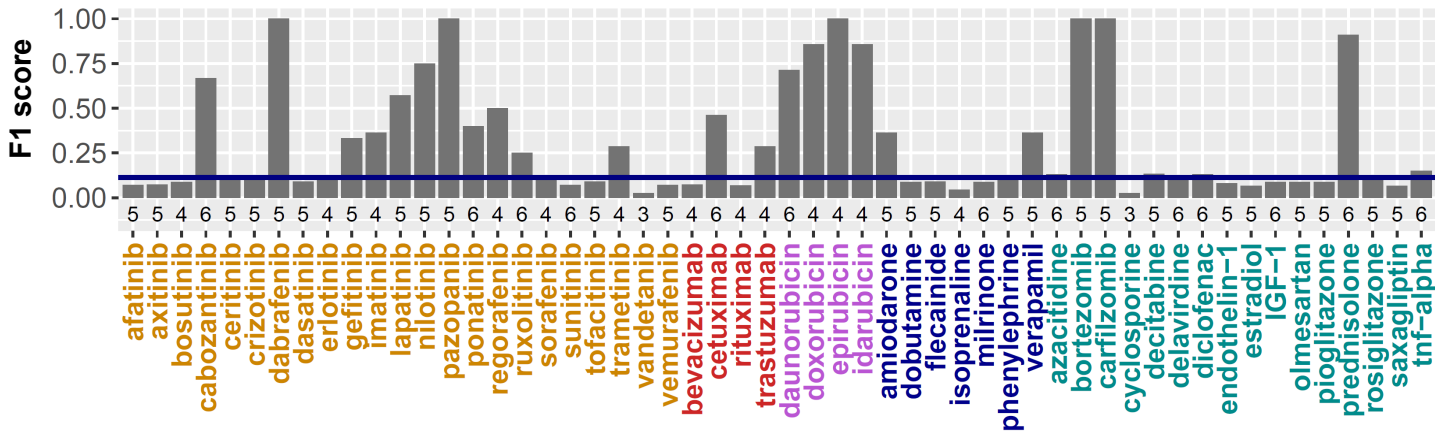
Supplementary Fig. 7

Supplementary Fig. 7. Clustering of DEGs after removal of first eigenarray. Removal of the first eigenarray from the complete DEG matrix disrupts hierarchical clustering by the number of significant DEGs (3).

Complete dataset



After removal of 1st eigenarray

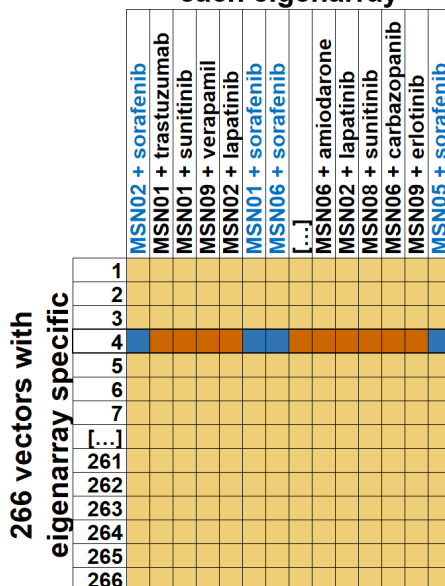


Supplementary Fig. 8

Supplementary Fig. 8. Clustering efficiency after removal of the first eigenarray. DEG matrix after removal of the first eigenarray was subjected to pairwise correlation analysis and hierarchical clustering, followed by calculation of the highest F1 scores for each drug (bottom figure). Numbers of treated cell lines are shown below the bars. To allow easier comparison, we added the F1 scores calculated for each drug using the complete DEG profiles (top figure) that is also shown in Fig. 1C.

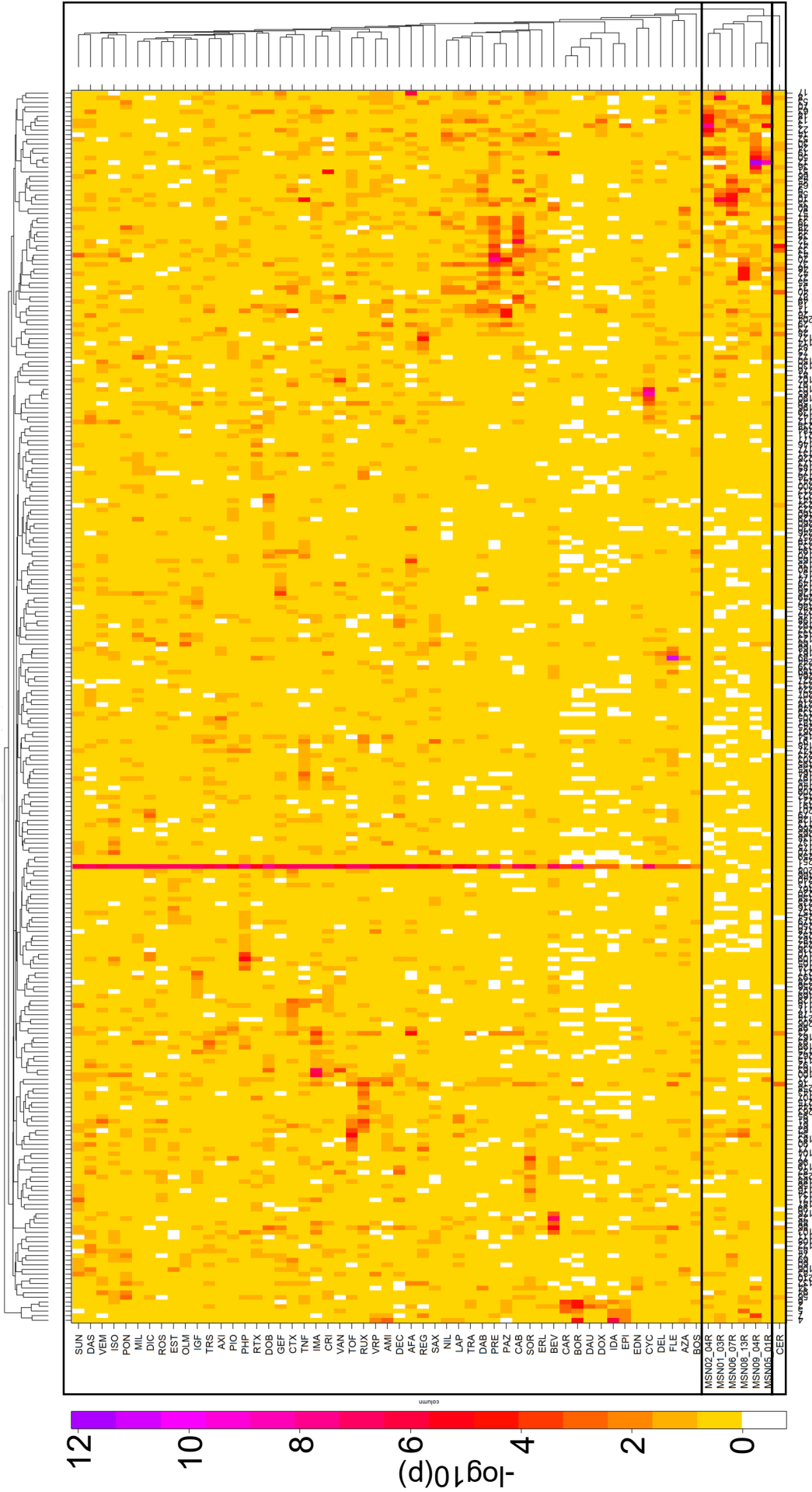
A

266 coefficients for each eigenarray



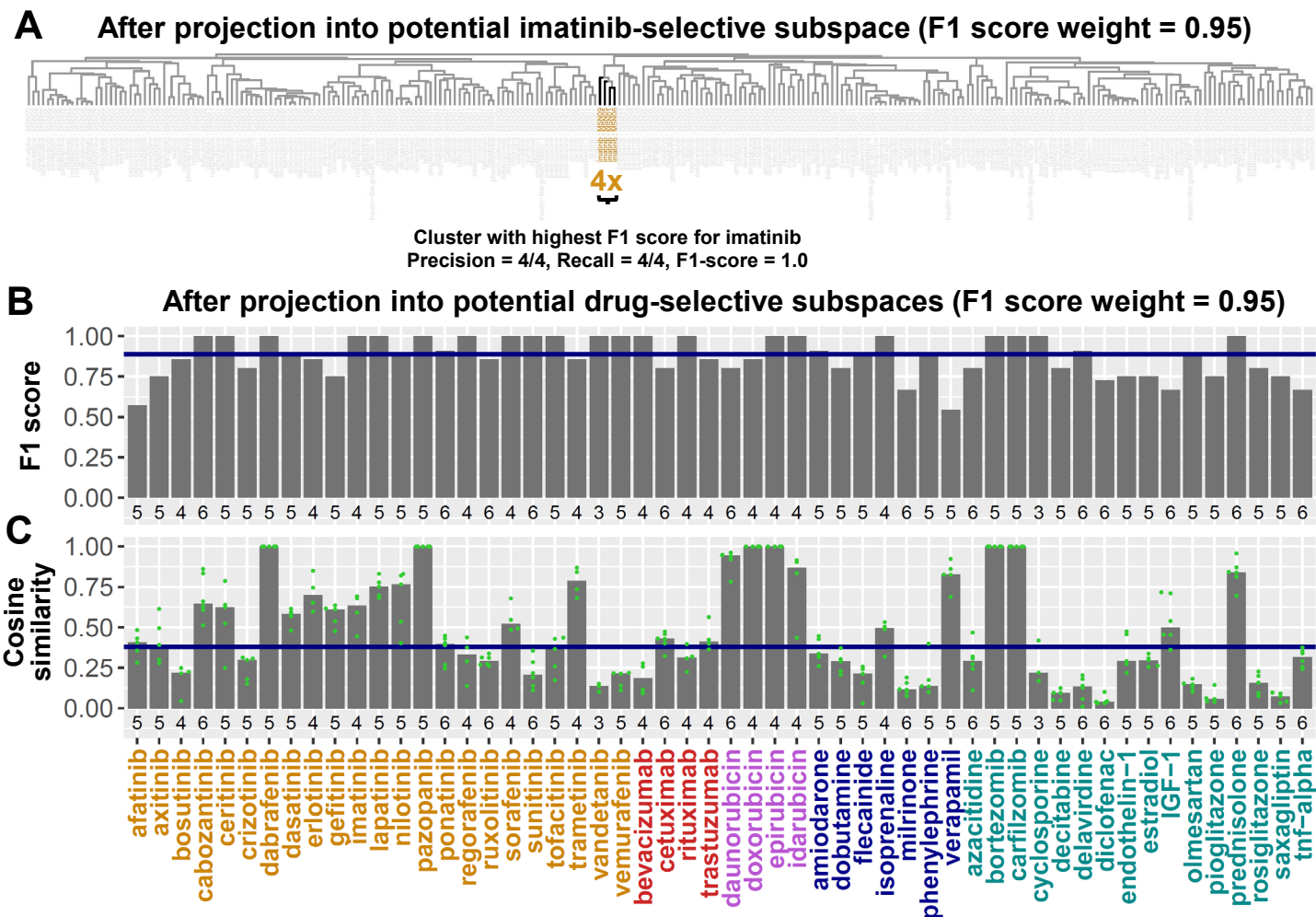
For each drug and eigenarray:

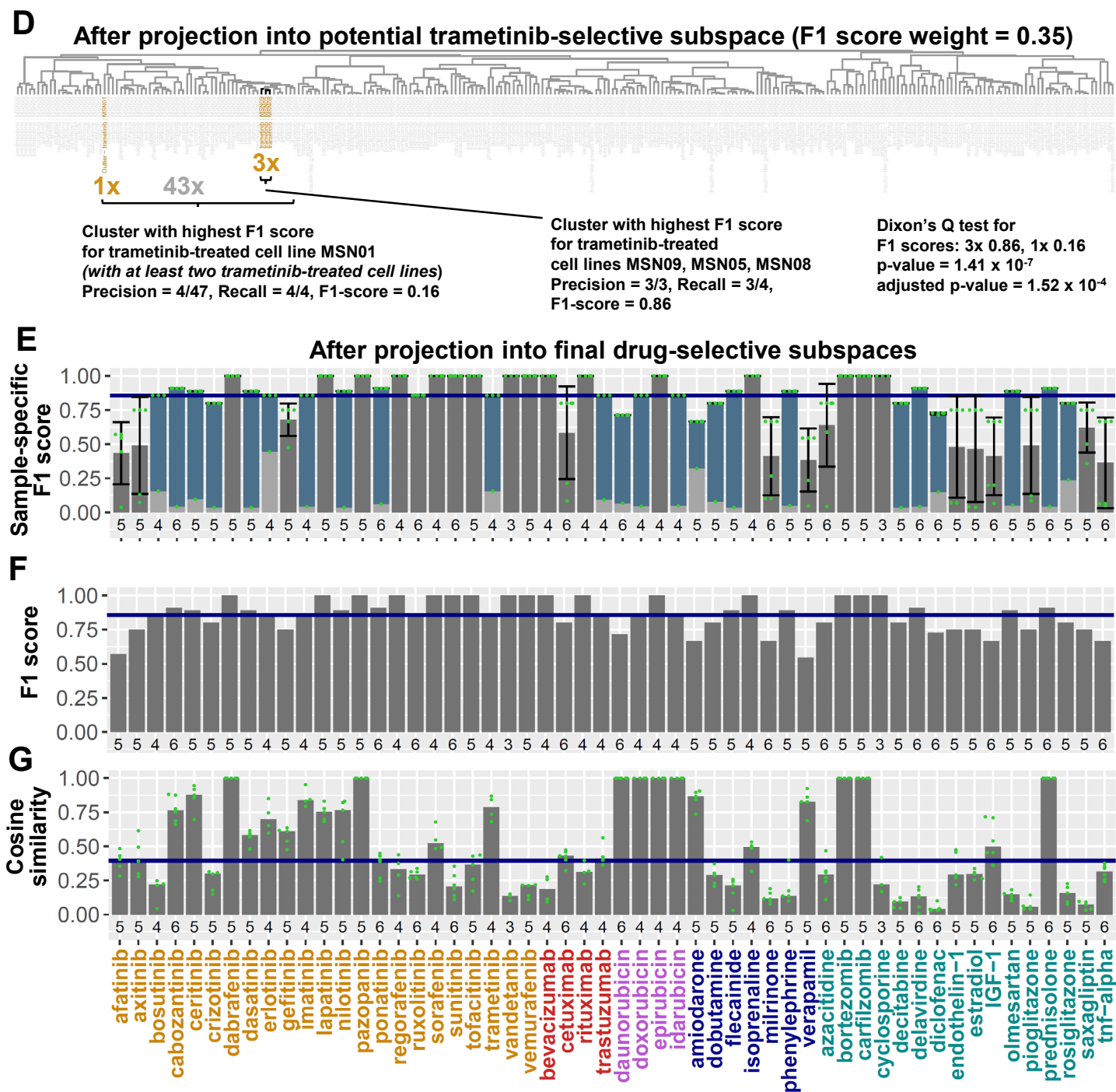
Use two-sided student's t-test to investigate if the coefficients for an eigenarray of interest significantly differ between all samples of a drug of interest and all other samples.



Eigenarray numbers

Supplementary Fig. 9. Cell-line- and drug-selective effects are captured by different eigenarrays. (A) For each eigenarray and drug, we analyzed if the coefficients that are related to the gene expression profiles for that drug on that eigenarray significantly differ from all other coefficients on that eigenarray. Consequently, we calculated one p-value for each drug-eigenarray combination. Similarly, we calculated one p-value for each cell line-eigenarray combination. **(B)** All p-values were transformed into $-\log_{10}(\text{p-values})$ and used to calculate pairwise correlation coefficients between all drugs and cell lines, followed by hierarchical clustering. The initial heatmap of $-\log_{10}(\text{p-values})$ was rearranged according to the clustering results. Grouping of the six cell lines into a single separated cluster (boxed) suggests that the eigenarray decomposition allows differentiation of cell-line-specific effects from drug-specific effects.





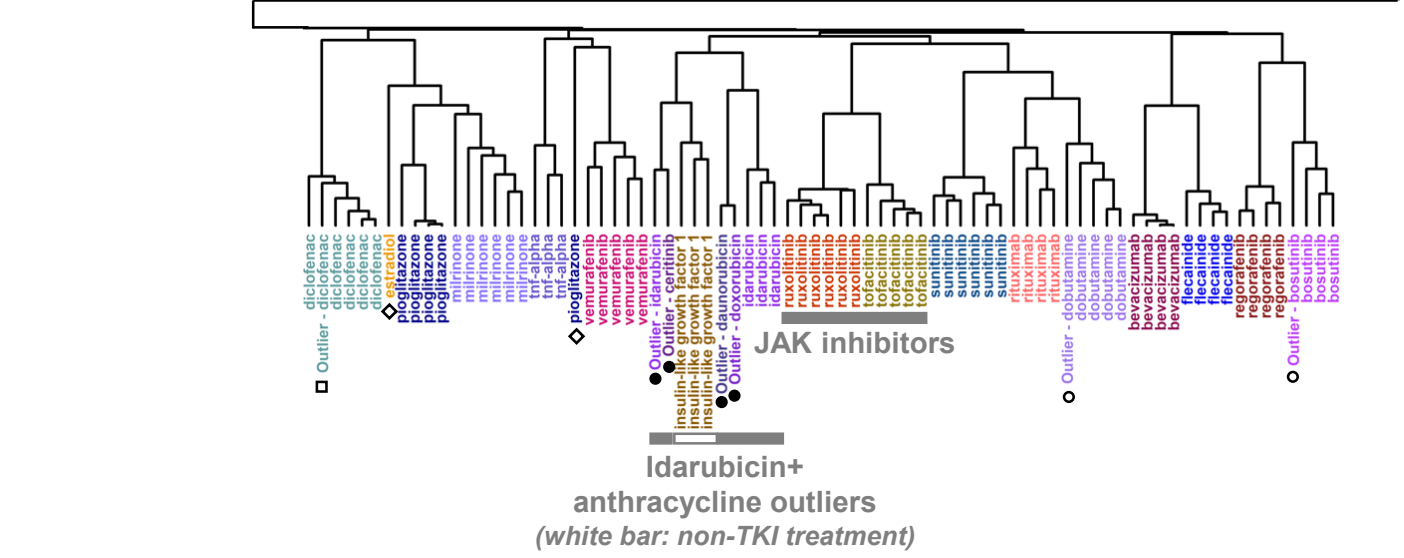
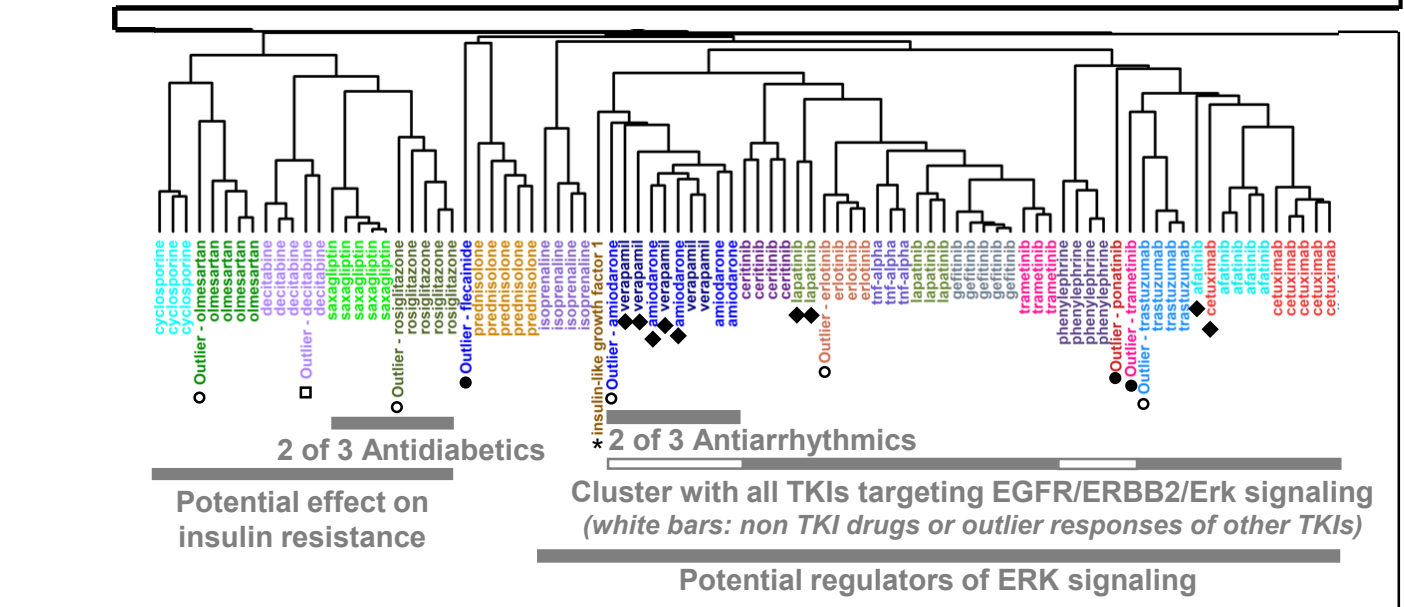
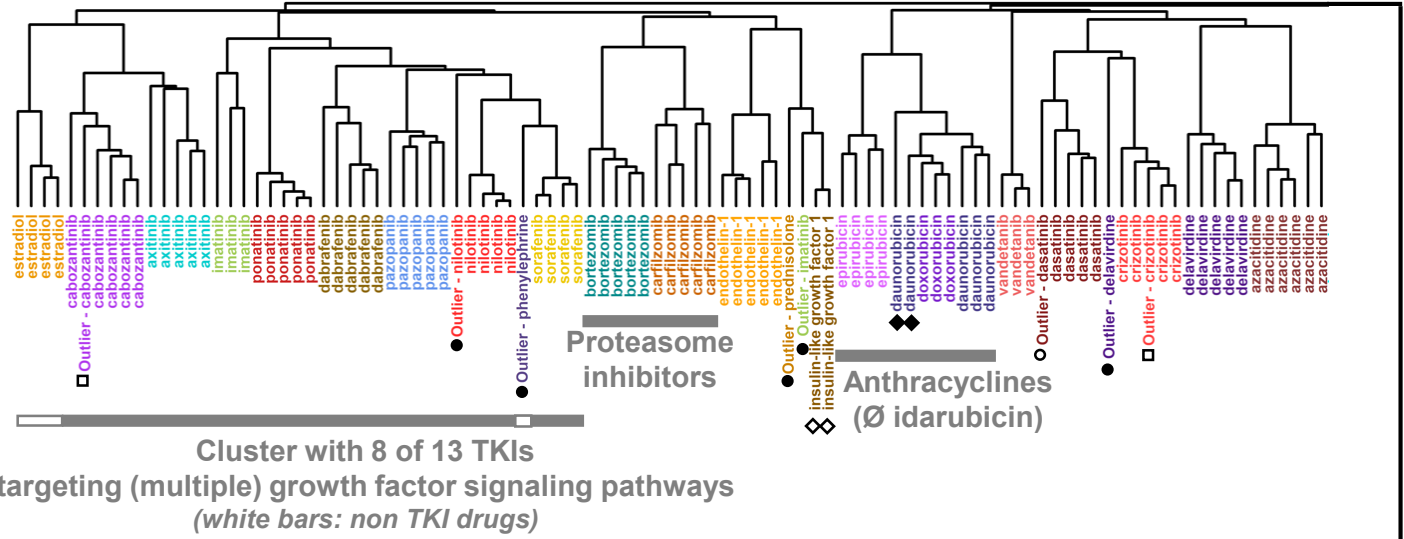
Supplementary Fig. 10

Supplementary Fig. 10. Identification of drug-selective gene expression profiles and outlier responses. (A) For each drug, we ranked all eigenarrays by their ability to separate the coefficients associated with cell line/drug combinations treated with that drug from all other coefficients, i.e., we ranked them by increasing p-values. The top 3 to 266 eigenarrays were combined to yield 264 potential drug-selective subspaces. Gene expression profiles after removal of the first eigenarray were projected into the subspaces, followed by pairwise correlation, hierarchical clustering and F1 score calculation for the drug

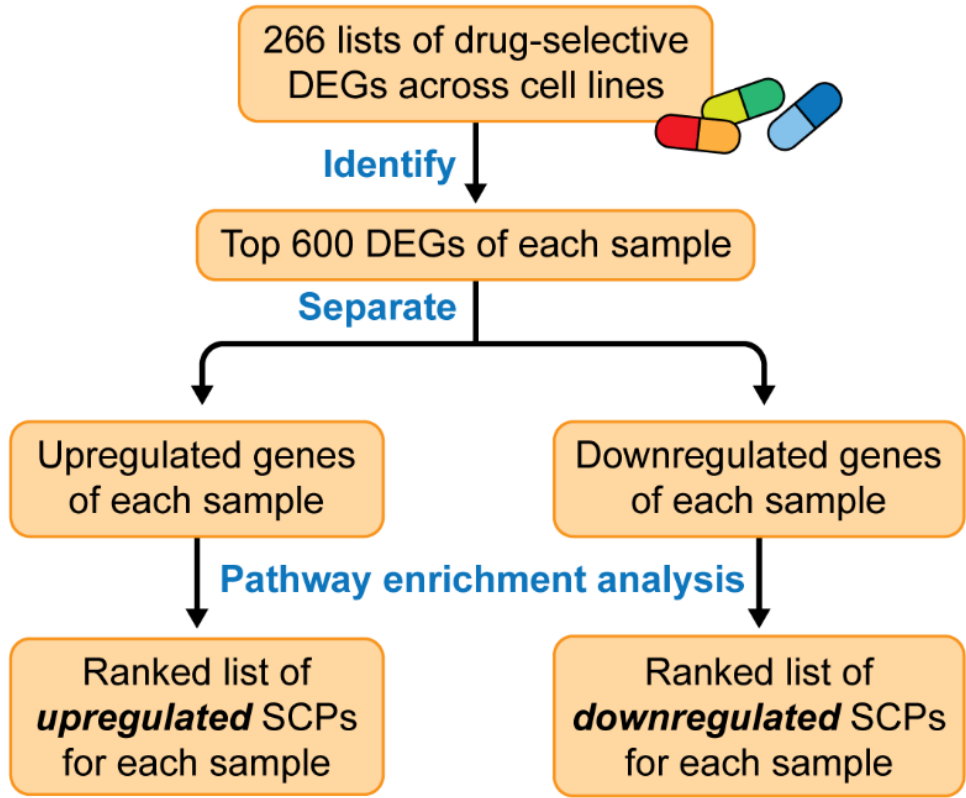
of interest. The example shows the F1 score calculation for imatinib after projection of the data into one of the potential imatinib-selective subspaces. **(B/C)** Cosine similarities between the projected gene expression profiles and the gene expression profiles after removal of the first eigenarray were calculated for each drug. For each potential drug-selective subspace, we calculated weighted averages between the F1 score and the median cosine similarity with changing relative contributions as defined by 20 different F1 score weights (ranging from 0.00 to 0.95 in steps of 0.05). Each F1 score weight allowed us to select one drug-selective subspace, i.e., that subspace with the highest weighted mean or selection score. Shown are **(B)** F1 scores and **(C)** single (green dots) as well as median (bars) cosine similarities obtained based on an F1 score weight of 0.95. Blue lines indicate median heights of all bars. Numbers of treated cell lines are shown below the bars. **(D)** For each drug, we screened all 20 potential drug-selective subspaces (that are defined by different F1 score weights) for subspaces where one cell line/drug combination shows a different transcriptomic response to the drug of interest than all other cell line/drug combinations. We calculated cell line/drug combination-specific F1 scores, using the same approach described above, except that the cell line/drug combination of interest has to be part of the corresponding cluster. Dixon's Q test applied to cell line/drug combination-specific F1 scores was used to identify outliers (adj. p-value ≤ 0.05). **(E)** F1-scores of non-outlier cell line/drug combinations in the final drug-selective subspaces were averaged. Blue and dark gray bars indicate averaged F1 scores for drugs with and without identified outliers, respectively. Error bars show standard deviations for non-outlier cell line/drug combinations. F1 scores identified for outlier cell line/drug combinations are visualized separately (light gray bars). Green dots show individual drug-selective F1-scores. The larger the difference between the top of the blue and light gray bars, the larger the difference in F1 scores between regular and outlier responses. The blue line indicates the median height of blue and dark gray bars. Numbers of treated cell lines are shown below the bars. **(F)** Projection of gene expression profiles into the final drug-selective subspaces leads to a great increase in drug-specific F1 scores. Notice that the F1 scores are the maximum cell line/drug combination-specific F1-scores shown in E. This figure is the same as figure 1D. **(G)** Cosine similarities (green dots) and median cosine similarities (bars) between complete DEG profiles and DEG profiles in final drug-selective subspaces are shown. The blue line shows the median height of all bars.

Supplementary Fig. 11: Clustering results for each drug after removal of the first eigenarray and in the final drug-selective subspaces. See pages 79 - 93.

Supplementary Fig. 12: Identification of outlier responses. See pages 94 - 97.



Supplementary Fig. 13. Clustering of merged drug-selective gene expression profiles. Drug-selective gene expression profiles obtained after projection of the complete gene expression matrix into drug-selective subspaces were merged, followed by pairwise correlation and hierarchical clustering. Outlier cell line/drug combinations are labeled with 'Outlier'. Closed circles label outlier responses that show great outlier characteristics in this dendrogram as well, and do not cluster together with the other cell line/drug combinations treated with the same drugs. Open circles label outlier responses with minor outlier characteristics in this dendrogram, i.e., those outliers that are grouped together with the cell line/drug combinations treated with the same drug in a larger cluster, but get separated from them after sub-clustering. Closed squares label outlier responses that are grouped together with the cell line/drug combinations treated with the same drug. Asterisks label cell line/drug combinations that do not cluster together with the other cell line/drug combinations treated with the same drug and were not identified as outlier responses. Bars label clusters that are composed of cell line/drug combinations from different drugs with closely related potential mechanisms. Fig. 1E shows the same dendrogram, drug labels and most of the bars.

A**Supplementary Fig. 14**

Supplementary Fig. 14. Top Subcellular Processes predicted from complete gene expression profiles, after removal of first eigenarray and from drug-selective gene expression profiles. (A) Complete, decomposed gene expression profiles and gene expression profiles after removal of the first eigenarray were subjected to pathway enrichment analysis using the Molecular Biology of the Cell Ontology and Fisher’s Exact Test to identify up- and downregulated subcellular processes (SCPs). Flow chart is used with permission from Mount Sinai Health System, licensed under CC BY.

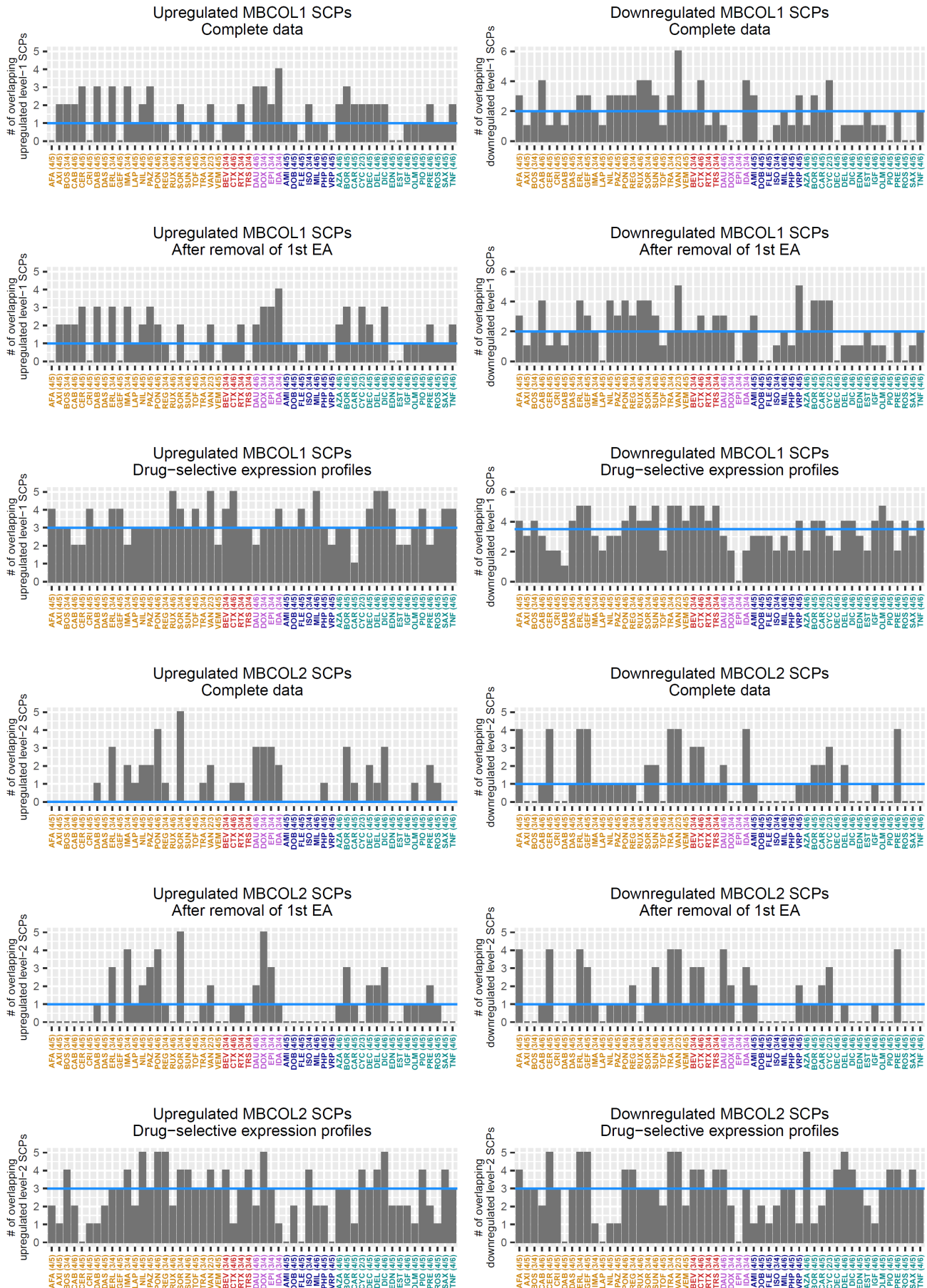
Supplementary Figs. 14B-E: Top Subcellular Processes predicted from complete gene expression profiles, after removal of first eigenarray and from drug-selective gene expression profiles.

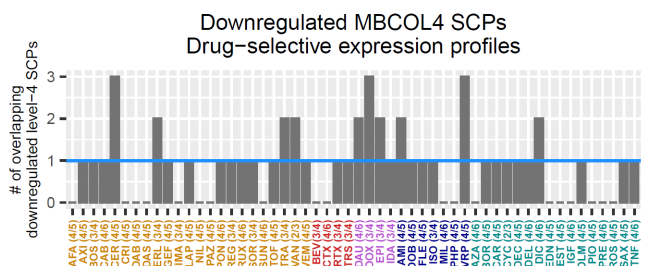
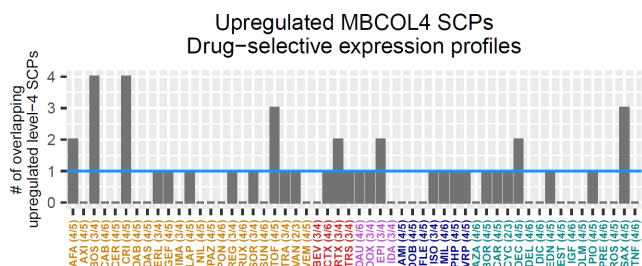
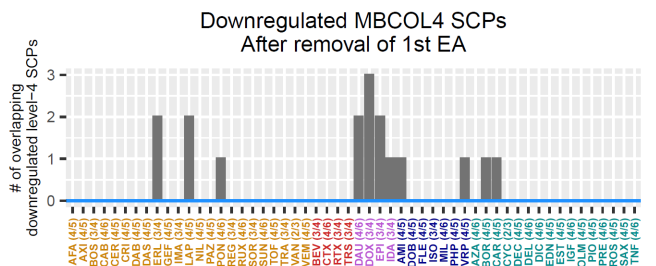
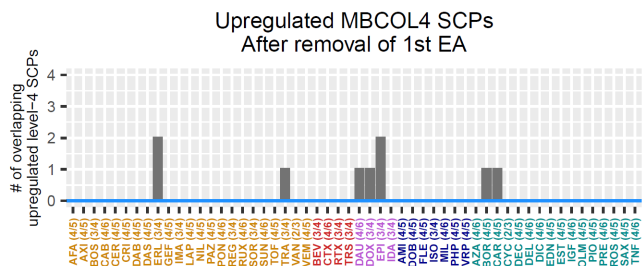
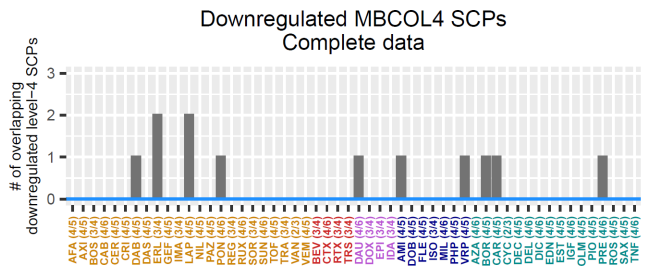
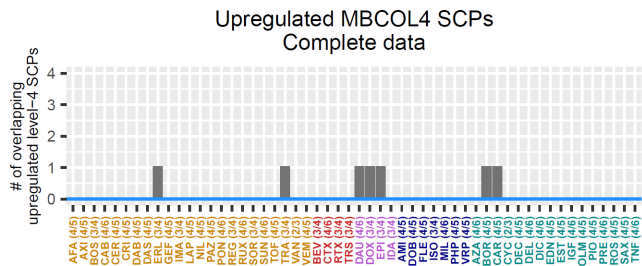
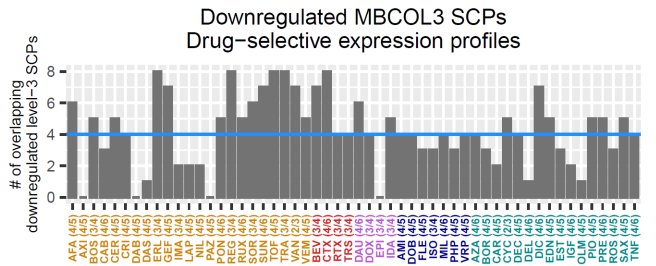
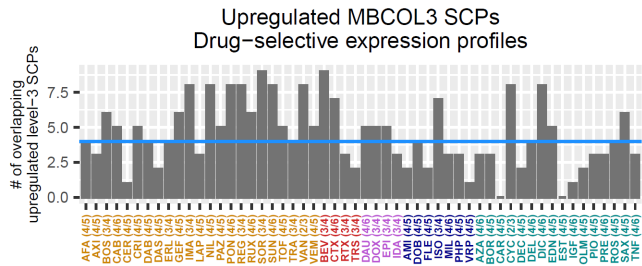
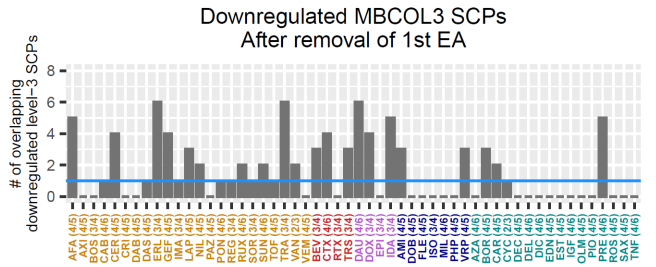
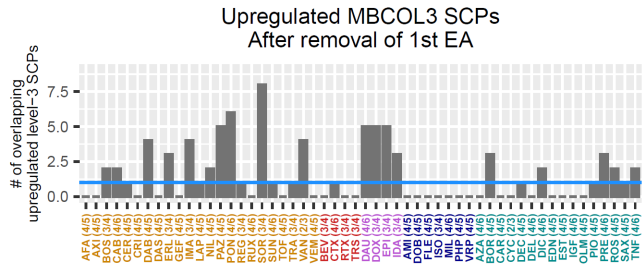
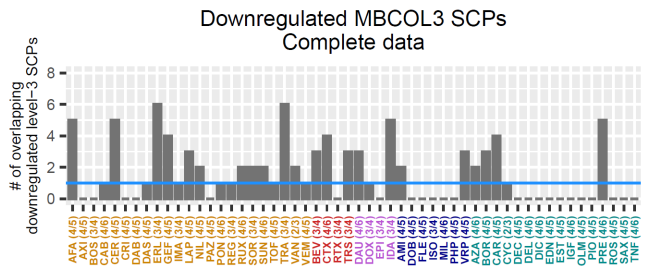
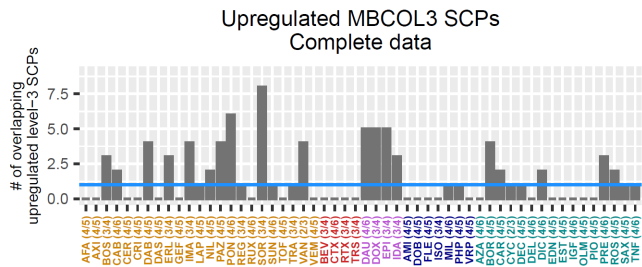
14B: MBCO level-1 SCPs: pages 98 - 111

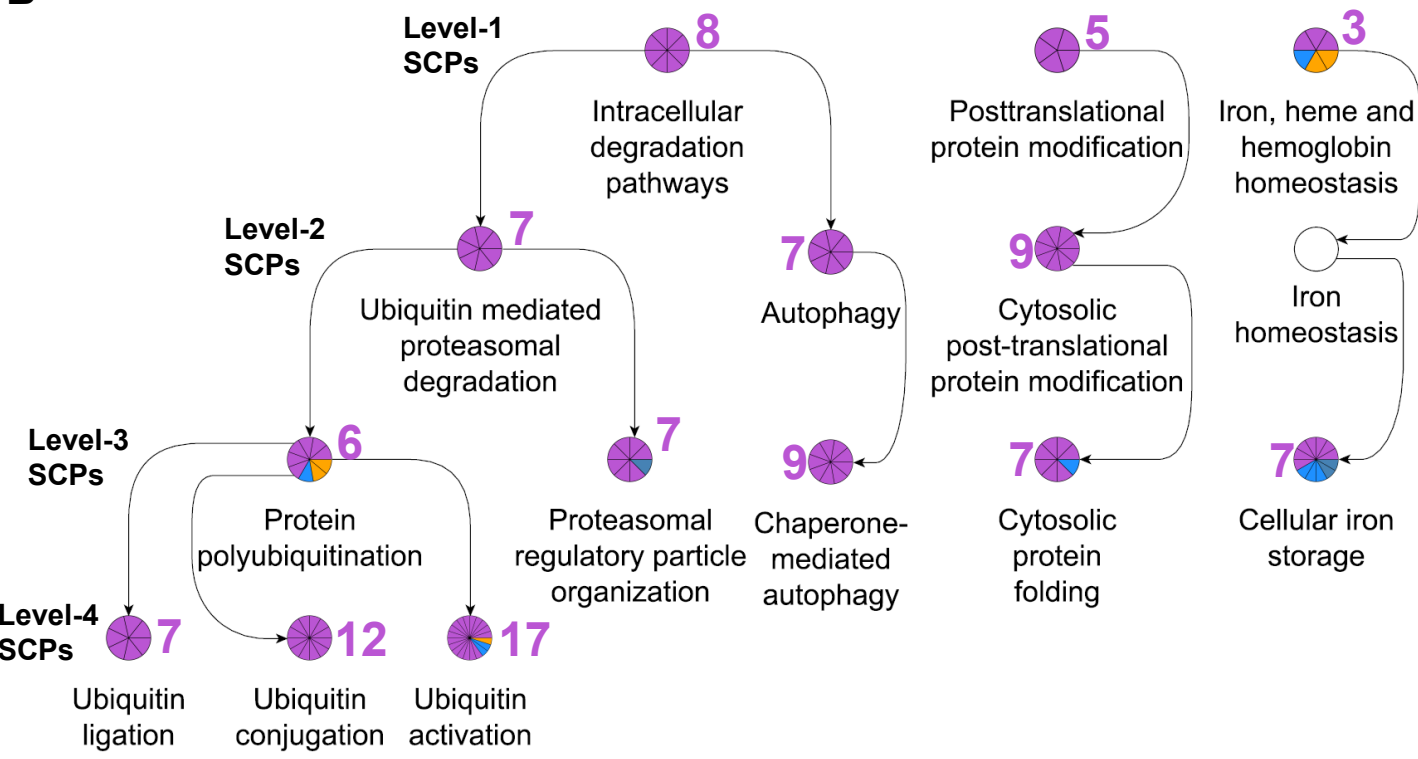
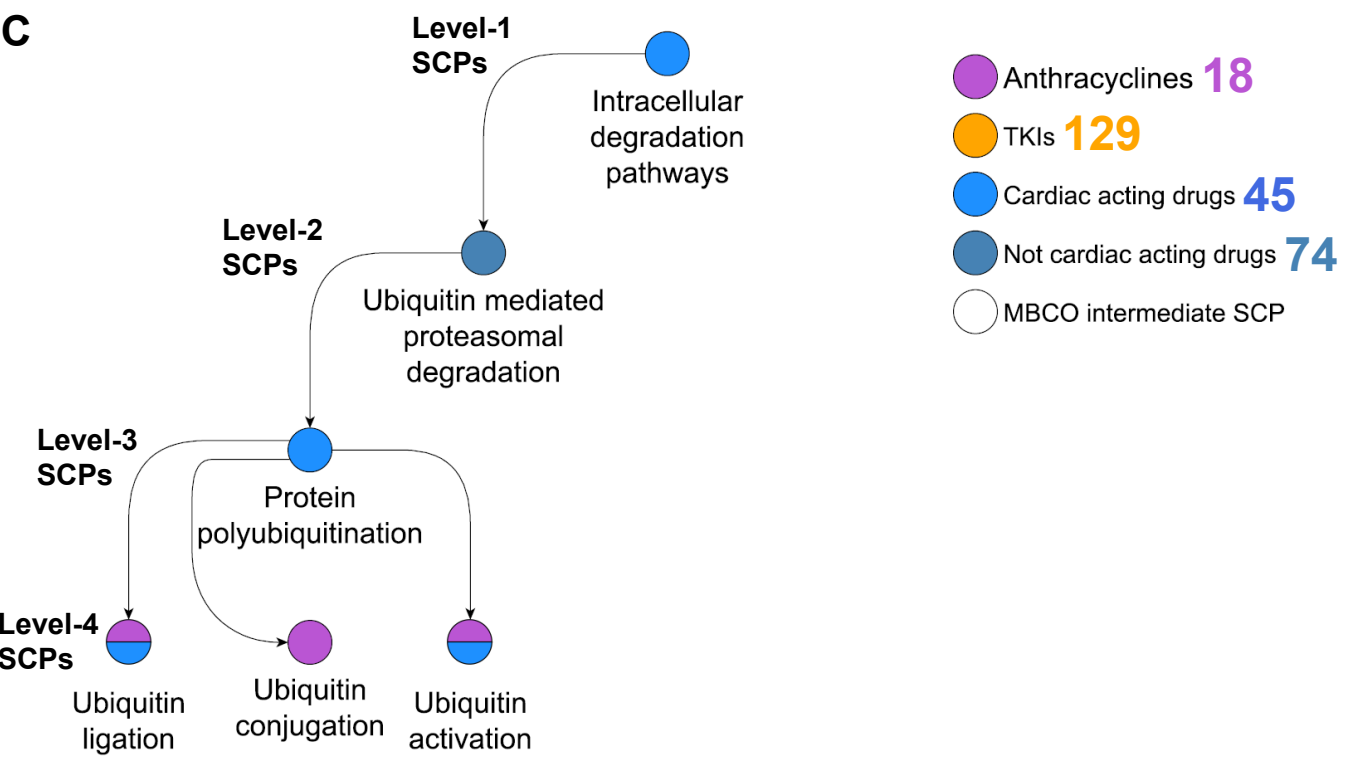
14C: MBCO level-2 SCPs: pages 112 - 125

14D: MBCO level-3 SCPs: pages 126 - 139

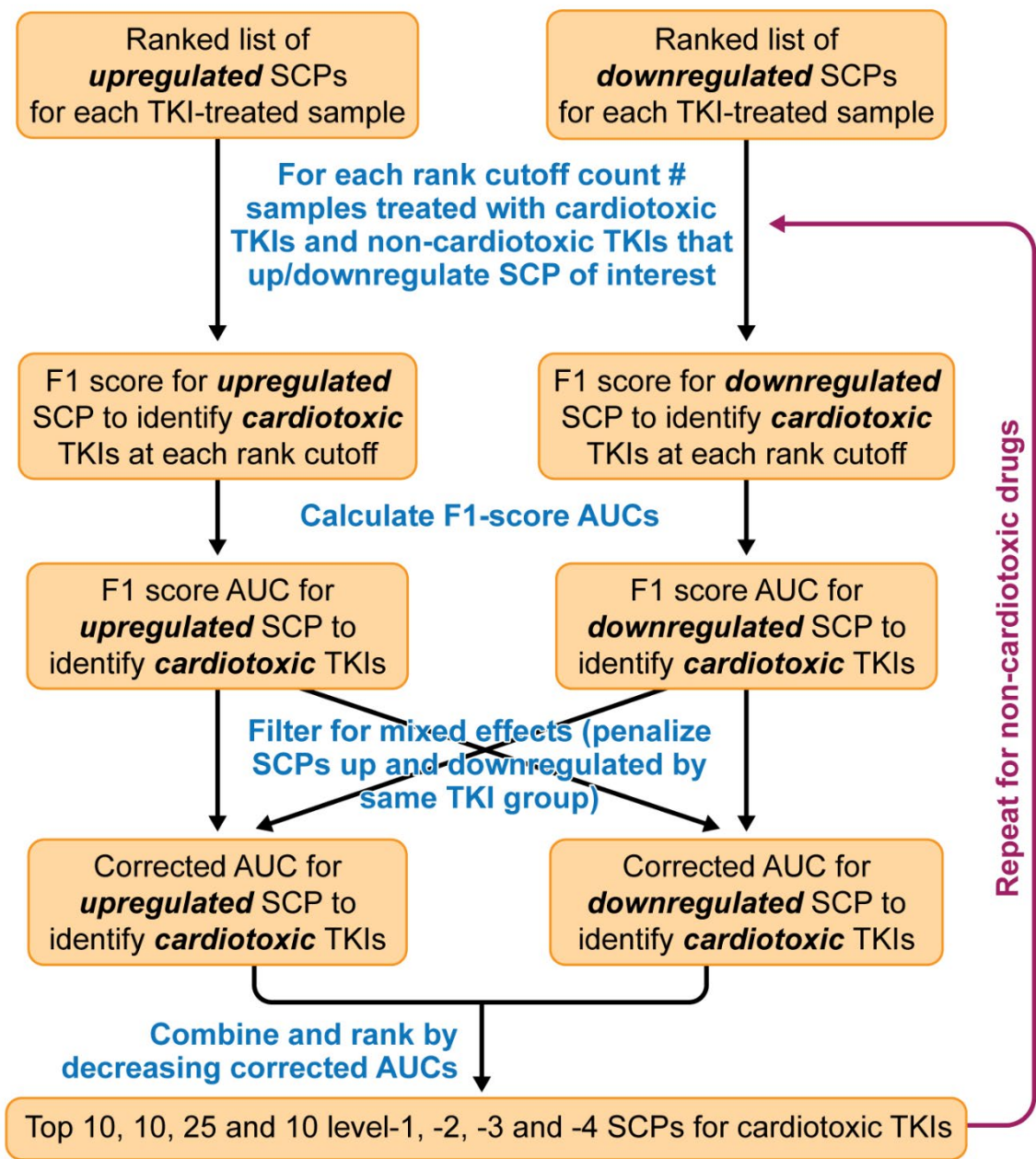
14E: MBCO level-3 SCPs: pages 140 - 154

A



B**C**

Supplementary Fig. 15. SVD decomposition increases the consistency of identified SCPs by the same drug across different cell lines and reveals potentially cardiotoxic SCPs. (A) We analyzed, for each drug, how many up- or downregulated level-1, -2, -3 and -4 SCPs were predicted in at least 66% of all treated cell lines with a maximum rank of five, five, ten and five, respectively. The minimum numbers that equal or exceed 66% and the total numbers of treated cell lines are given as nominators and denominators, respectively, in brackets after the drug abbreviations. The blue line documents the median of overlapping SCP counts. For drug abbreviations see Supplementary Data 3. **(B)** The top five, five, ten and five level-1, -2, -3 and -4 SCPs predicted from downregulated genes in the drug-selective gene expression profiles were integrated into the MBCO hierarchy. Selected SCPs in parent-child relationships (arrows) are shown. Any drug that downregulates an SCP is added as a new pie slice colored according to the drug's class. Purple numbers next to the SCPs indicate the number of anthracycline-treated cell line/drug combinations for which the SCP was predicted (i.e., the number of purple slices). Numbers next to the drug classes in the legend indicate how many cell line/drug combinations were treated with drugs of that class in total. **(C)** The top five, five, ten and five level-1, -2, -3 and -4 SCPs predicted from downregulated genes in the complete gene expression profiles were integrated into the MBCO hierarchy, as described in B. The same SCPs are shown, if predicted.



Supplementary Fig. 16

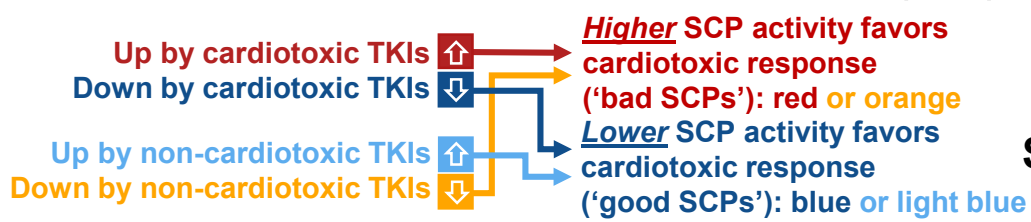
Supplementary Fig. 16. Identification of SCPs associated with cardiotoxic and non-cardiotoxic TKIs. SCPs that were predicted from pathway enrichment analysis of drug-selective gene expression profiles were subjected to our computational pipeline that searches for SCPs associated with a cardiotoxic or non-cardiotoxic response to TKI treatment. See methods for details. Flow chart is used with permission from Mount Sinai Health System, licensed under CC BY.

Supplementary Fig. 17. F1 score and Area Under the Curve statistics. See pages 155 - 173.

Up/Downregulated at higher ranks by
cardiotoxic drugs non-cardiotoxic drugs

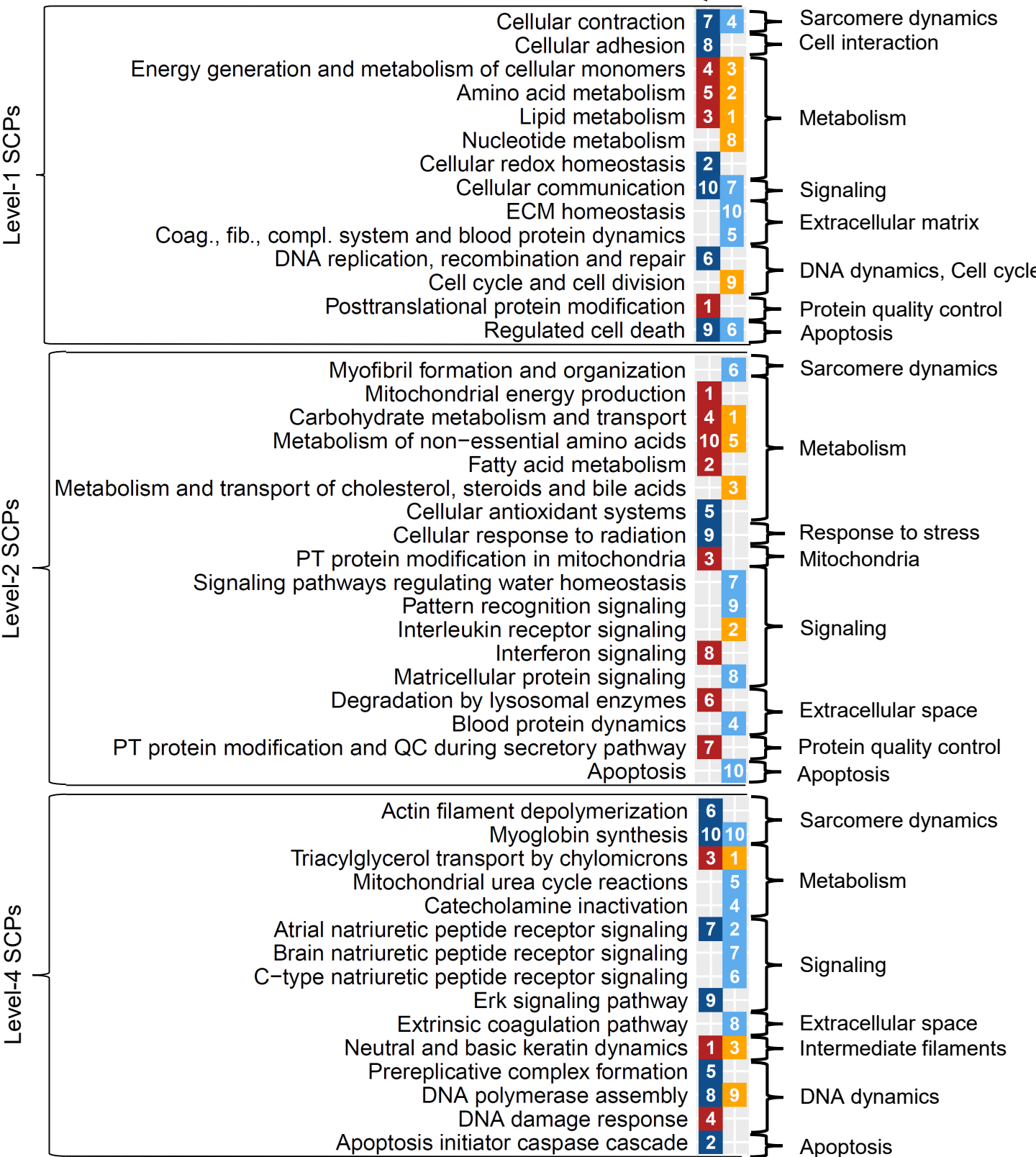
Level-3 SCPs

Biological Process	Upregulated by cardiotoxic drugs	Downregulated by cardiotoxic drugs	Upregulated by non-cardiotoxic drugs	Downregulated by non-cardiotoxic drugs
Thin myofilament organization	21	19		
Myofibril formation	6	6		
Potassium TM transport	7			
Gap junction organization	24			
Chloride TM transport	17			
Water TM transport	9	2		
Citric acid cycle	1			
Glycolysis and Gluconeogenesis			25	
Polyol pathway	4			
Serine and glycine metabolism	19	5		
Aspartate and arginine metabolism			12	
Transamination pathways	25			
GABA metabolism			18	
Desaturation of fatty acids	11			
Cholesterol-sensitive control of SREBP activation	15	24		
Cholesterol synthesis	22	3		
Cellular cholesterol uptake and efflux	23			
Cellular iron uptake and export			23	
Natriuretic peptide receptor signaling			15	
Prostaglandin E2 receptor signaling			21	
Adrenergic receptor signaling	8			
Hippo signaling	13			
Thyroid hormone receptor signaling	10			
PDGF receptor signaling	14			
VEGF receptor signaling	12	9		
HIF-1 receptor signaling pathway	20			
Leptin receptor signaling	5	1		
GCSF receptor signaling	16	8		
Oncostatin-M receptor signaling			10	
Collagen fiber crosslinking			7	
Collagen fibril organization by fibril-associated bridges			17	
Elastin cross-linking and assembly			16	
Biglycan synthesis	18	13		
Amyloid degradation, uptake and aggregation inhibition			11	
Lysosomal glycoprotein degradation	2			
Epithelial intermediate filament dynamics			20	
Axonal intermediate filament dynamics			14	
Restriction point	3	4		
Inhibition of apoptosis			22	



Supplementary Fig. 18

Up/Downregulated at higher ranks by
cardiotoxic drugs **non-cardiotoxic drugs**

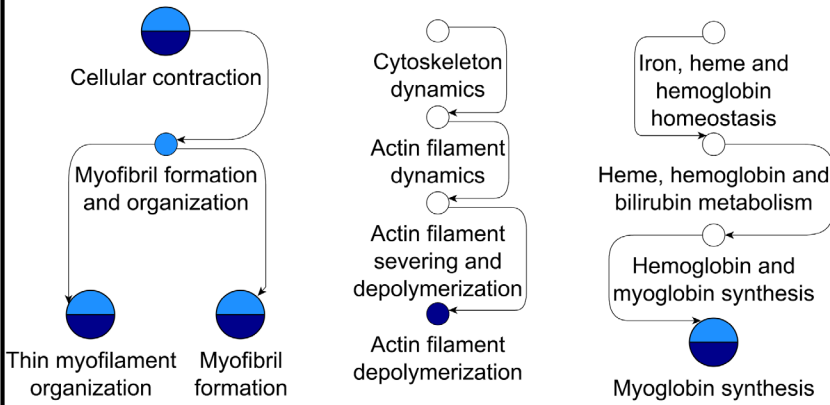


Up by cardiotoxic TKIs ↑ **Down by cardiotoxic TKIs** ↓
Up by non-cardiotoxic TKIs ↑ **Down by non-cardiotoxic TKIs** ↓

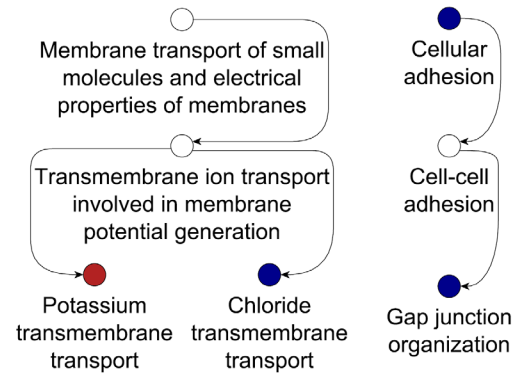
Higher SCP activity favors cardiotoxic response ('bad SCPs'): red or orange
Lower SCP activity favors cardiotoxic response ('good SCPs'): blue or light blue

Supplementary Fig. 18. SCPs associated with cardiotoxic and non-cardiotoxic responses. Predicted up- and downregulated subcellular processes (SCPs) of the same level were ranked by significance for each drug and cell line. We searched for those SCPs that are up- or downregulated at higher significance ranks by cardiotoxic or non-cardiotoxic TKIs. Identified SCPs were ranked by their selectivity for either cardiotoxic or non-cardiotoxic drugs (white numbers). To simplify our findings, we defined that SCPs that are upregulated by cardiotoxic drugs (red) or downregulated by non-cardiotoxic drugs (orange) are associated with a cardiotoxic response after upregulation or at baseline level, respectively. For these SCPs a higher activity favors a cardiotoxic response. Similarly, we defined that SCPs downregulated by cardiotoxic (dark blue) or upregulated by non-cardiotoxic drugs (light blue) are associated with a non-cardiotoxic response after downregulation or at baseline level, respectively. For these SCPs a lower activity favors a cardiotoxic response. Shown are the top 25, 10, 10 and 10 predicted level-3, -1, -2 and -4 SCPs for cardiotoxic and non-cardiotoxic TKIs. The level-3 SCPs that are up- or downregulated by cardiotoxic TKIs are also shown in Fig. 2B.

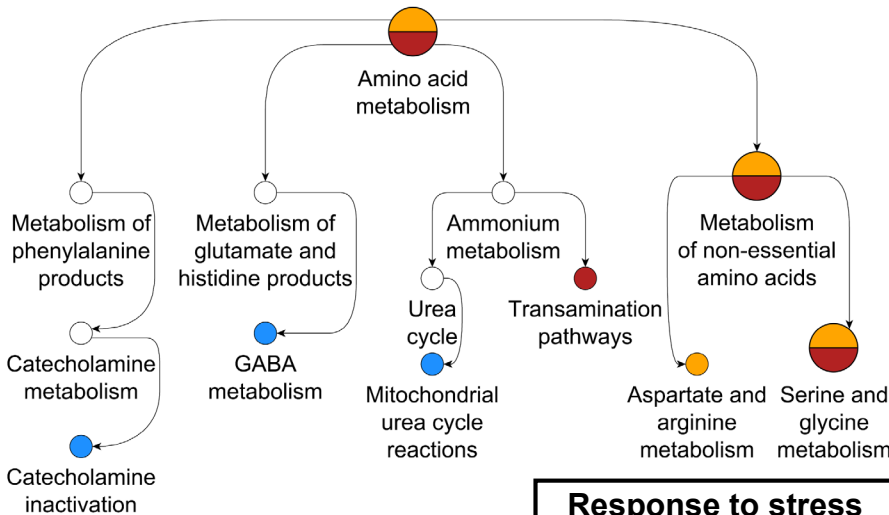
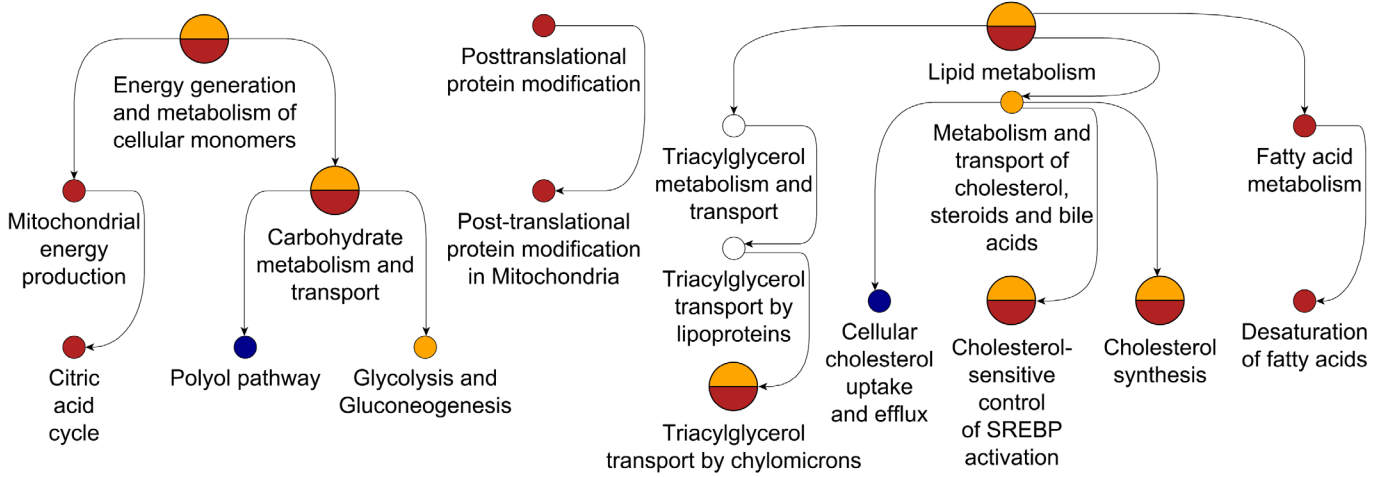
Muscle contractility



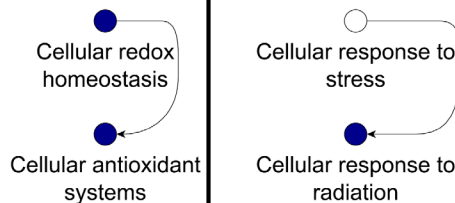
Electric transmission



Metabolism



Response to stress



Up by cardiotoxic TKIs (red up arrow)

Down by cardiotoxic TKIs (blue down arrow)

Up by non-cardiotoxic TKIs (blue up arrow)

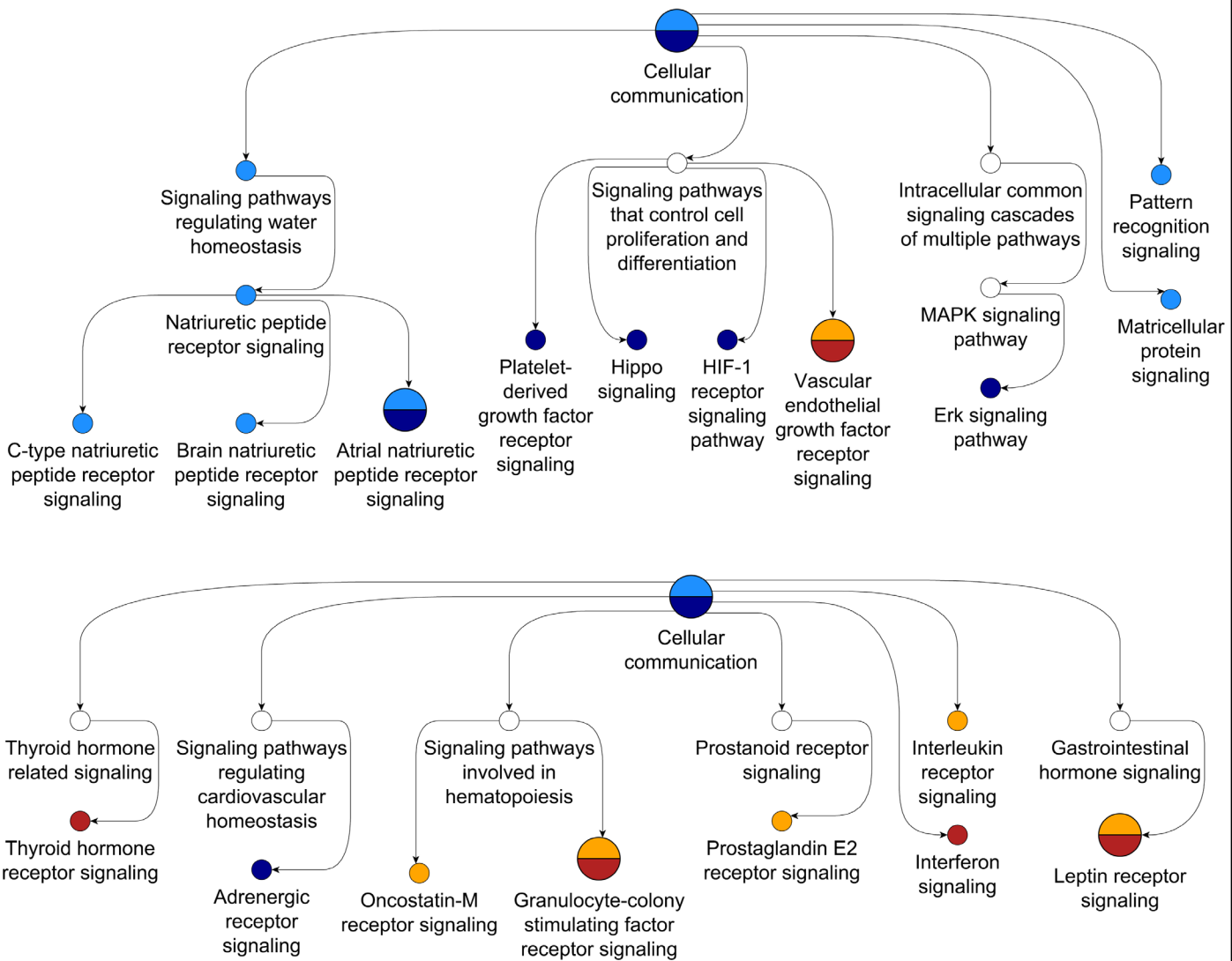
Down by non-cardiotoxic TKIs (yellow down arrow)

MBCO Intermediate SCP (white circle)

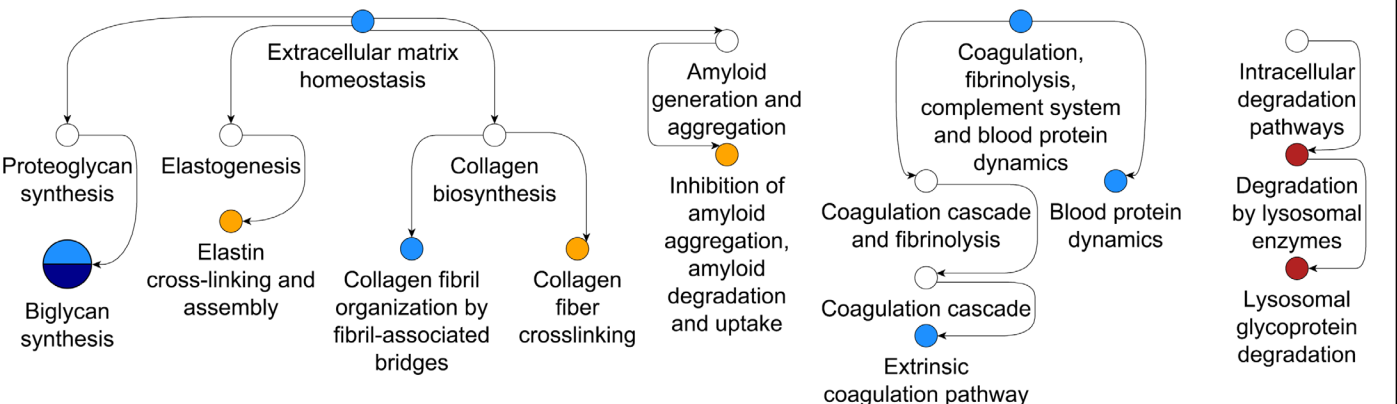
Higher SCP activity favors cardiotoxic response ('bad SCPs'): red or orange

Lower SCP activity favors cardiotoxic response ('good SCPs'): blue or light blue

Signaling



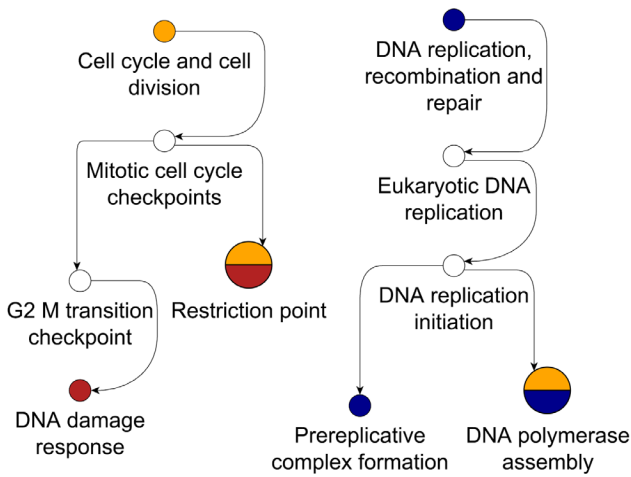
Extracellular matrix and intracellular degradation



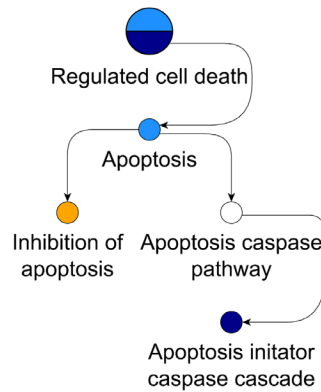
Up by cardiotoxic TKIs
Up by non-cardiotoxic TKIs
MBCO Intermediate

Down by cardiotoxic TKIs
Down by non-cardiotoxic TKIs

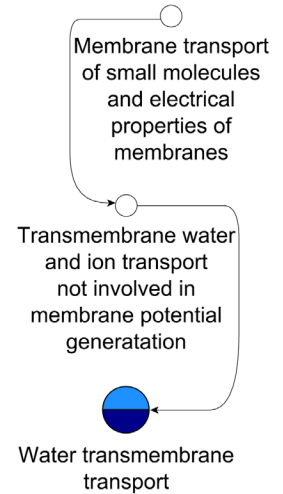
Cell cycle, DNA dynamics



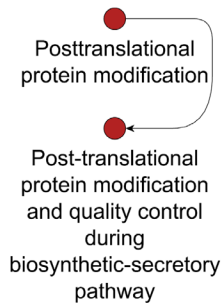
Apoptosis



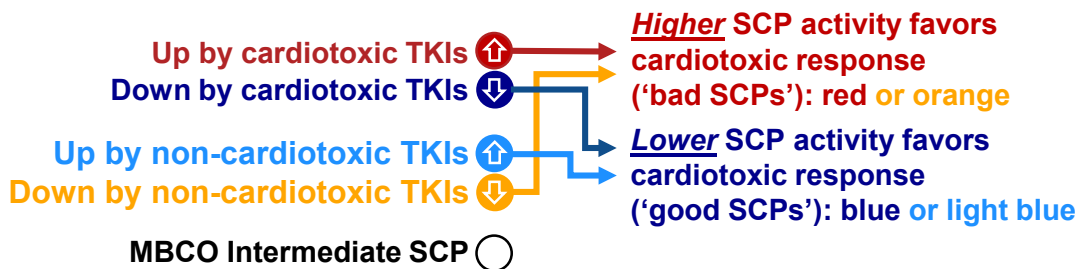
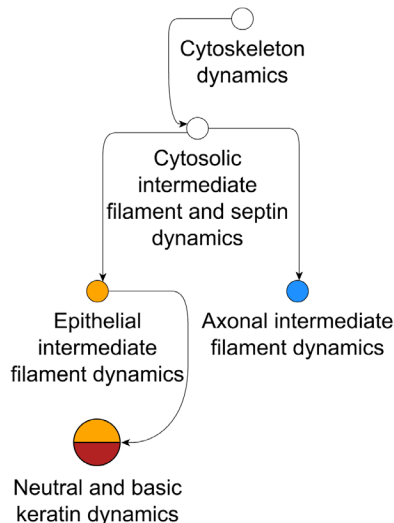
Transmembrane transport



Posttranslational modification



Intermediate filaments



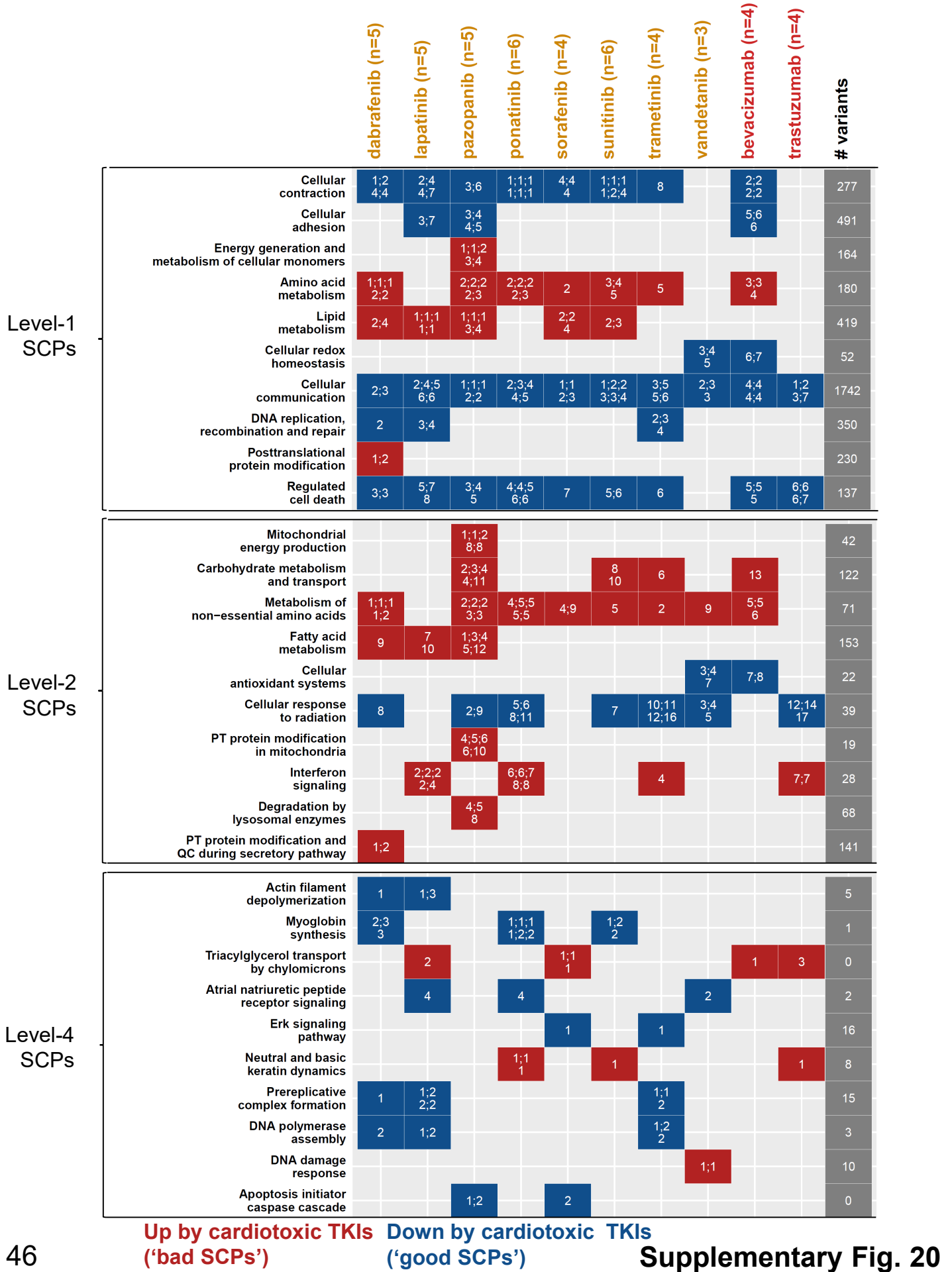
Supplementary Fig. 19. Integration of identified SCPs into the MBCO hierarchy. Up- and downregulated SCPs associated with a cardiotoxic or non-cardiotoxic response were integrated into the MBCO hierarchy. Arrows point from parent to child SCPs. Each tree starts with a level-1 SCP and then consecutively connects it to predicted level-2, -3 and -4 SCPs. Not predicted SCPs that are ancestors of predicted SCPs are in white. Red/orange: SCPs whose higher activity favors a cardiotoxic response, Dark blue/light blue: SCPs whose lower activity favors a cardiotoxic response. The muscle contractility SCPs, and selected SCPs involved in Energy metabolism are also shown in Fig. 2C.

Level-3
SCPs

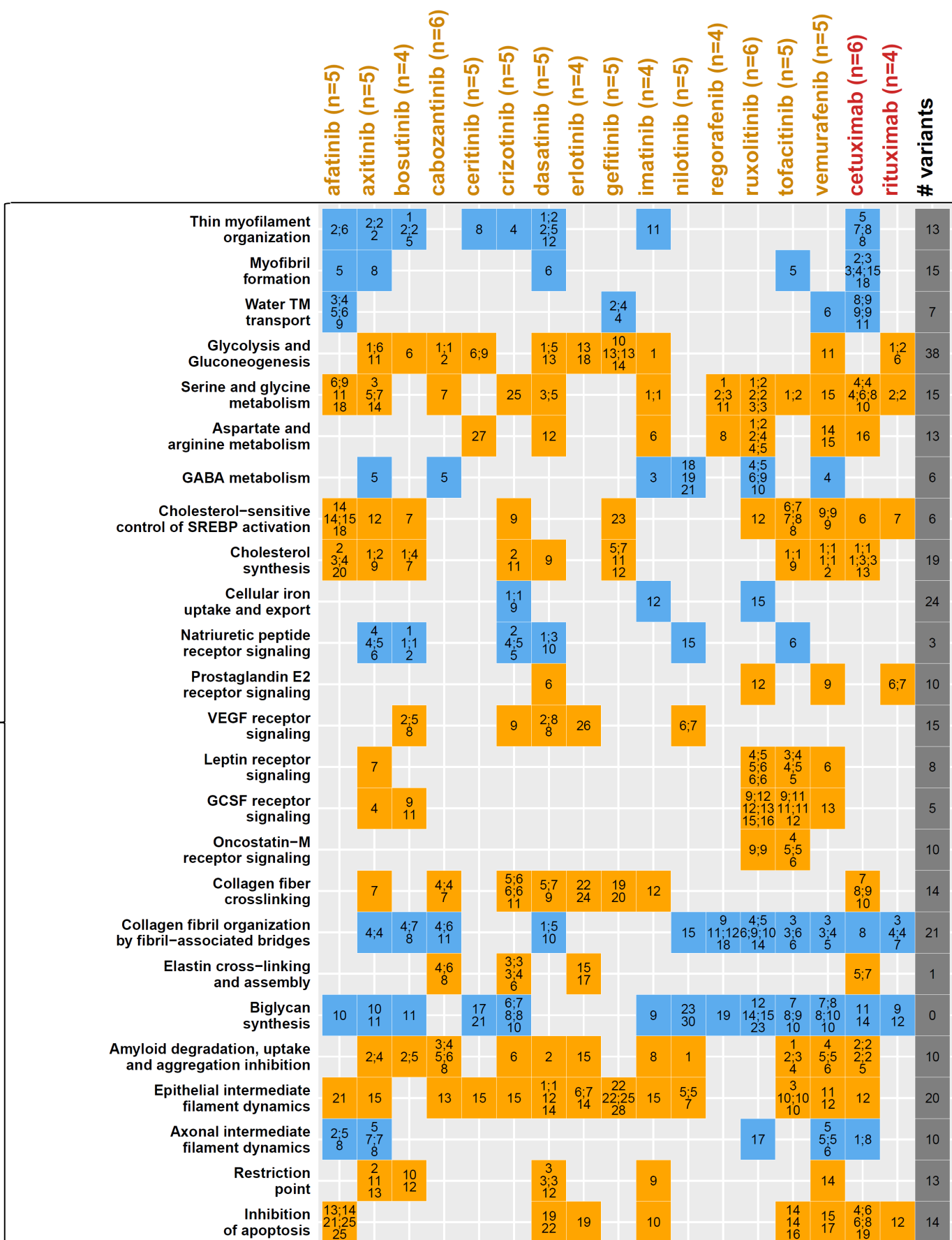
	dabrafenib (n=5)	lapatinib (n=5)	pazopanib (n=5)	ponatinib (n=6)	sorafenib (n=4)	sunitinib (n=6)	trametinib (n=4)	vandetanib (n=3)	bevacizumab (n=4)	trastuzumab (n=4)	# variants
Thin myofilament organization	5	7;12 17		1;1;1 1;1		3;3;4 7;7;7	22		3;3 5;7		13
Myofibril formation	10 10		9	3;4;8 12;12	8				8		15
Potassium TM transport		7 10					2;3 9		17	7 10	44
Gap junction organization	24		1;3	15;16 17				9	13;14 14;15		21
Chloride TM transport				14;14 16		12 12		8			21
Water TM transport	6;7		4	6;9							7
Citric acid cycle			1;1 2;3								15
Polyol pathway									1;1 1;1		2
Serine and glycine metabolism	1;1;1 2;3		1;1;3 4;5	5;5;5 5;6	2;11 19;21	12	4	12 14			15
Transamination pathways			6;10 10;11								8
Desaturation of fatty acids	3	3;4	2;7 10		7;8 14;14						8
Cholesterol-sensitive control of SREBP activation		2;3;4 5;6	4;5;8 8;8	15 15	14	7					6
Cholesterol synthesis	1;4 5	1;1;1 1;1	2;2 13		2;4	1;1 3;8		2			19
Cellular cholesterol uptake and efflux	4	4 22				3;3 7		1 15			43
Adrenergic receptor signaling	9	9		10;13 14					2;6 7;9		44
Hippo signaling			3;5 7								46
Thyroid hormone receptor signaling									4;4 6		9
PDGF receptor signaling		20	9	4;6;6 6;13	5;6 10;15		15 30	9 13		2;4 5;11	18
VEGF receptor signaling	7;7 10		6;10 10;11								15
HIF-1 receptor signaling pathway	8;8		1;6 6								12
Leptin receptor signaling		3;5 5;6								4	8
GCSF receptor signaling		7;8 11;12							15	11	5
Biglycan synthesis	12	18;19 21;28	15	9;10;10 11;12;14	8		26 28	5;8 10		15;17 19	0
Lysosomal glycoprotein degradation			4;4;5 8;8								9
Restriction point						2;3;4 6;11		9			13

Up by cardiotoxic TKIs
(‘bad SCPs’)

Down by cardiotoxic TKIs
(‘good SCPs’)



Supplementary Fig. 20. Regulation of identified SCPs by each cardiotoxic TKI. SCPs that were up- or downregulated at higher ranks by cardiotoxic TKIs were mapped back to the individual drugs that upregulated (red) or repressed (dark blue) them. Numbers indicate significance ranks as shown in Suppl. Figs. 14B/C/D/E for level-1, -2, -3 and -4 SCPs. Only ranks that were below the maximum rank cutoff in our F1 score and AUC statistics are shown (20, 20, 30, 20 for level-1, -2, -3 and -4 SCPs). Numbers in parentheses after drug labels indicate total numbers of treated cell lines for each TKI. Number of genomic variants that are underrepresented in the general population and map to SCP genes are shown in the last column. See methods for details. Note that this representation gives an estimation of the recall for each SCP, but does not allow conclusions about the precision that was favored during identification of SCPs associated with a cardiotoxic response. Drug labels of small molecule kinase inhibitors and monoclonal antibodies are colored orange and red, respectively.



Up by non-cardiotoxic TKIs ('good SCPs')
 Down by non-cardiotoxic TKIs ('bad SCPs')

Level-1 SCPs

	afatinib (n=5)	axitinib (n=5)	bosutinib (n=4)	cabozantinib (n=6)	ceritinib (n=5)	crizotinib (n=5)	dasatinib (n=5)	erlotinib (n=4)	gefitinib (n=5)	imatinib (n=4)	nilotinib (n=5)	regorafenib (n=4)	ruxolitinib (n=6)	tofacitinib (n=5)	vemurafenib (n=5)	cetuximab (n=6)	rituximab (n=4)	# variants
Cellular contraction	1 1,2 3	1,2 3	1 1,2 3		3,5	2,2 6	1,1 1,2 2	2,5 5	2,6 7	4		4		3,7 7	3	1,1 2,2 3		277
Energy generation and metabolism of cellular monomers		6,6 6	6	2 3,6 7	4,5		5		6,8	2					4,8		3,4 5	164
Amino acid metabolism	3 3,3 3	4 5,5 5		2,5 6		5,7	4 4,4 4			1,3 4		2 3,3 4	1,1 2,2 2,2	2,8	2,5 5,6 7	2,2 3,3 3,3	4,5 5	180
Lipid metabolism	2 2,2 4	1,2 7	3 3,4 5	7		2,3 6			3,3 4,4 6					1 1,4 6	2,2 3,3 4	1,2 3,4 4	6,6	419
Nucleotide metabolism			6		5,6			5,7 7										59
Cellular communication	1,2 3,3 6	1,1 2,2 3		1,1 1,2 3,3	1,1 1,2 3	2 3,5 6	2,3 3,4 6		1,1 1,2 3		6	4,5	2,3 3,5 5	2,2 2,2 6	2,2 2,2 3	2,3 4,4 5,5	2,2 5	1742
ECM homeostasis	1 2,4 4	1,2 2,4 5	1 2,2 2	1,4 3	1,1 2,2 4	1,1 1,1 1	1 1,2 2	1,3	1,2 2,2 5	2,3	4	2 2,3 3	1,1 1,1 2,2	1,1 1,1 1	1,1 1,1 3,4	1,1 2,3 3,4	1,1 1	524
Coag., fib., compl. system and blood protein dynamics			5,6	5	4,5	3,4 4	2,3 3,3 5	3,5 8	1 3,3 5	6			2,3 3,3 4	2,3 3	4,4	4,6 6,6 6		94
Cell cycle and cell division	1,1 1,1 2	4,6			1,1 1,1 1			1 1,1 1	1,1 1					7		1,1 1,1 1		532
Regulated cell death	4,4 5	1,3 3,4 5			3,6		3,4 5	2 3,4 4	4 4,5 6		4,5			4 6,6 7		2,4 4,5 5		137

Level-2 SCPs

Myofibril formation and organization	1,2 3,3 13	2,2 2	1 1,4 6		3	1,2 8	1,1 1,2 5	4,5 7	1,7 10	10		10		7 13		1,1 1,1 2		273
Carbohydrate metabolism and transport	11	8 11 12	8	1 1,5 10	6,8 15		2 11	19	6 11,13 14	2					2 11		2,2 9	122
Metabolism of non-essential amino acids	6 6,6 7	7,8 9,10 11	13	6	17	7 14	1,7 13 15			1,1		1 2,4 4	1,1 1,1 1,2	2,4	9,9 11	4,5 6,6,9 11	5,7	71
Metabolism and transport of cholesterol, steroids and bile acids	2,3 4,6 10	1,3 15	4 10 13			1,4 6	10		6 10,13 14				1,1 3,4 12	1,1 1,2 4	1,2 3,3 4	6,8		143
Signaling pathways regulating water homeostasis		9 12,12 14	2 3,4 6	2	13	7,9 10 10	2,2 10				11			11				30
Pattern recognition signaling					7,7 10 15	5 13							7,9 10		4			125
Interleukin receptor signaling													4,6 6,6 7,9	4 5,5 6				21
Matricellular protein signaling	1 4,5 7	2,4 8	2 2,5 7	1,2 2,4 6	1,2 8	1,2 2	1,2 3,4 5		4 5,5 5	6	7 7,7 10	6 7,7 9	2,4 5,6,7 12	1,2 2,3 5	1,1 2,3 4	2,3 4,6 10	3 3,3 4	34
Blood protein dynamics		7											5,6 6,10 10	3,3 3,3 6	5			10
Apoptosis	3,5 6	1,1 4,6 9			4 12		3,6 7	2 3,3 4	4 5,7 7	13	11 12		18	4,7 10 10		1,2 2,6,6 13		123

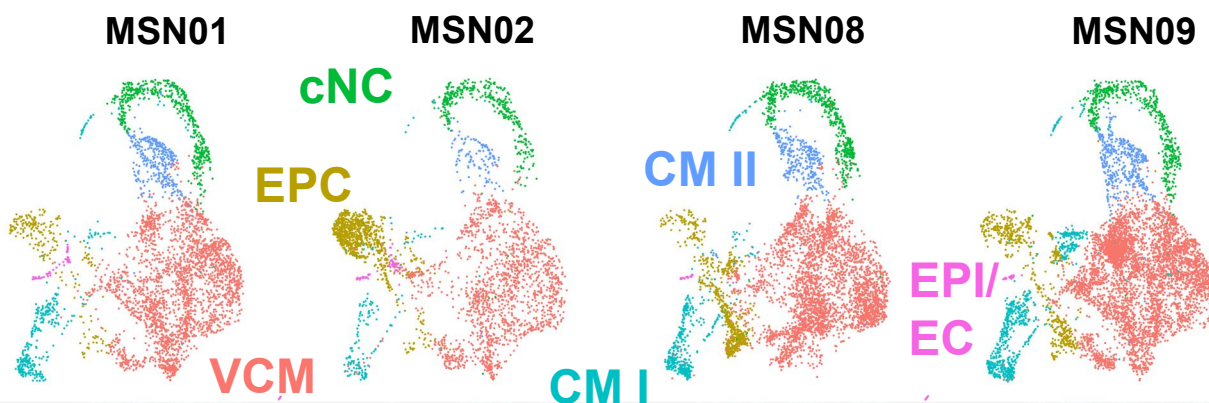
Level-4 SCPs

Myoglobin synthesis	2,3 3,4 4		2				1,2		1,1 1,1 1			1,1	3	1,1 2,2 2	2,2	1,2		1
Triacylglycerol transport by chylomicrons	1	2,3	1,1 1	3,3		1	2,3					2			1,1			0
Mitochondrial urea cycle reactions							2	1,2 2										7
Catecholamine inactivation					1												1,1 2	2
Atrial natriuretic peptide receptor signaling		3	2,2 2			3 3,4 4	4				1		1,2					2
Brain natriuretic peptide receptor signaling		3	2,2 2			3 3,4 4	2,4											3
C-type natriuretic peptide receptor signaling			2,2 2				4											0
Extrinsic coagulation pathway						1,1 1,2 2							1 1,1 6	2 3,3 3				3
Neutral and basic keratin dynamics					1	3		1,1	3,4							1		8
DNA polymerase assembly						2 2,2 4			2 2,2 2	2,3 3								3

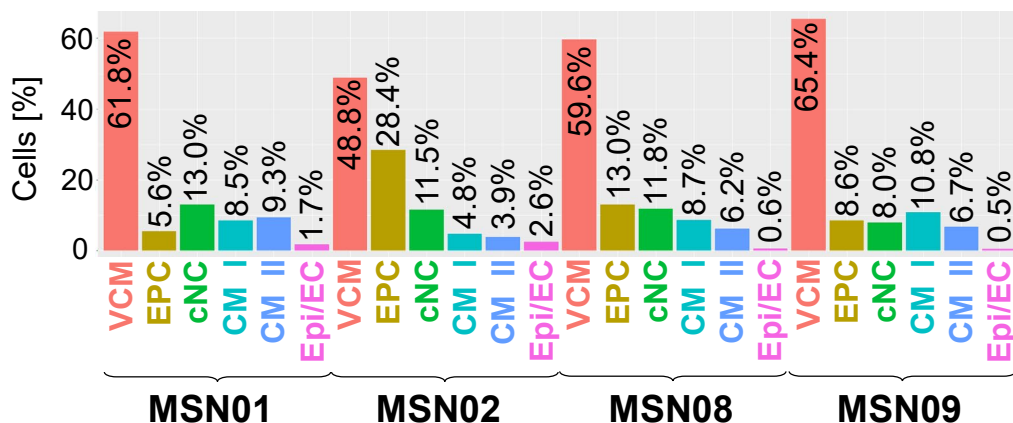
Up by non-cardiotoxic TKIs ('good SCPs')
Down by non-cardiotoxic TKIs ('bad SCPs')

Supplementary Fig. 21. Regulation of identified SCPs by each non-cardiotoxic TKI. SCPs that were up- or downregulated at higher ranks by non-cardiotoxic TKIs were mapped back to the individual drugs that down- (orange) or upregulated (light blue) them. Numbers indicate significance ranks as shown in Suppl. Figs. 14B/C/D/E for level-1, -2, -3 and -4 SCPs. Only ranks that were below the maximum rank cutoff in our F1 score and AUC statistics are shown (20, 20, 30, 20 for level-1, -2, -3 and -4 SCPs). Numbers after drug indicates total numbers of treated cell lines for each TKI. Number of genomic variants that are underrepresented in the general population and map to SCP genes are shown in the last column. See methods for details. Note that this representation gives an estimation of the recall for each SCP, but does not allow conclusions about the precision that was favored during identification of SCPs associated with a non-cardiotoxic response. Drug labels of small molecule kinase inhibitors and monoclonal antibodies are colored orange and red, respectively.

A

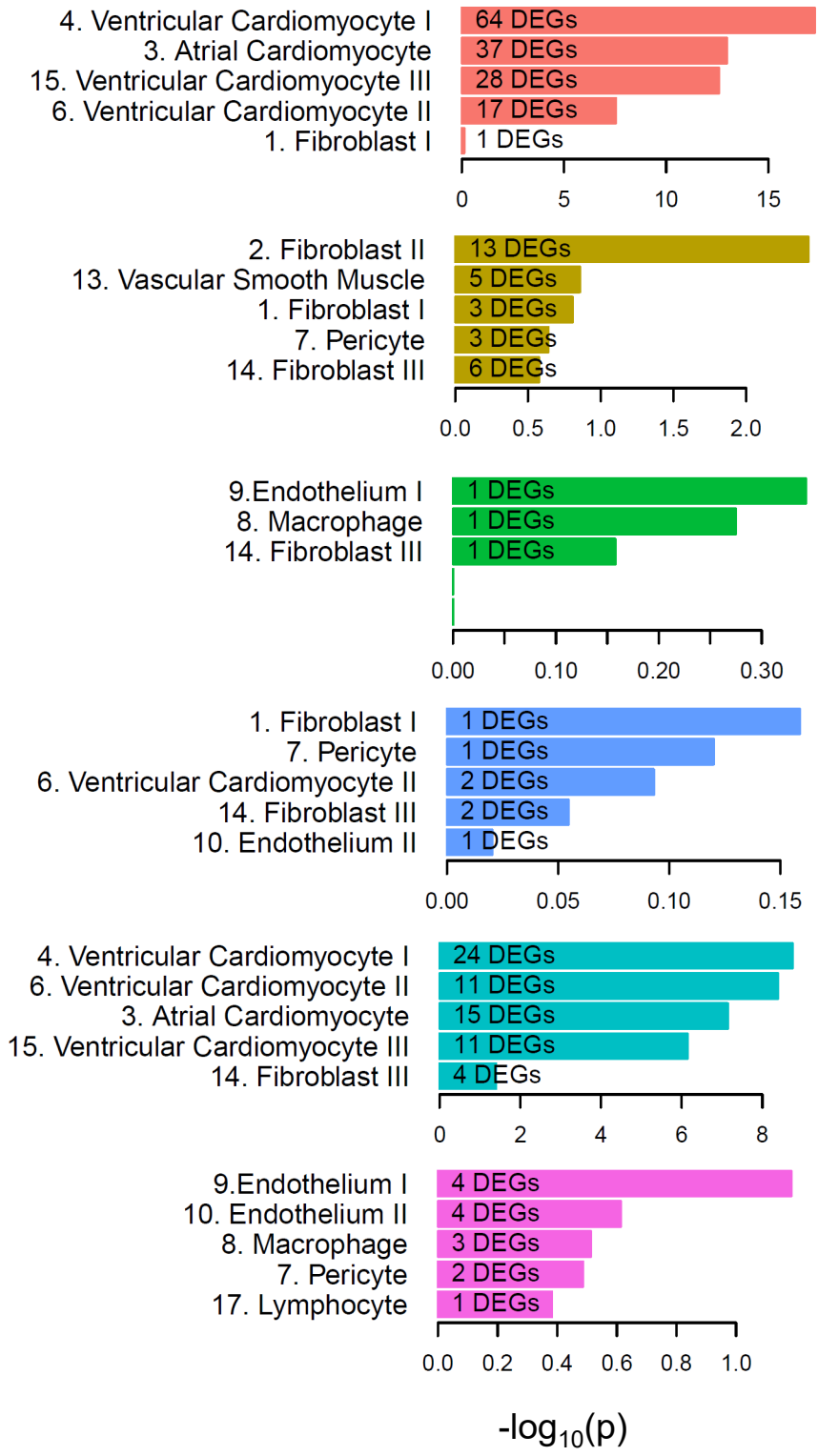


B



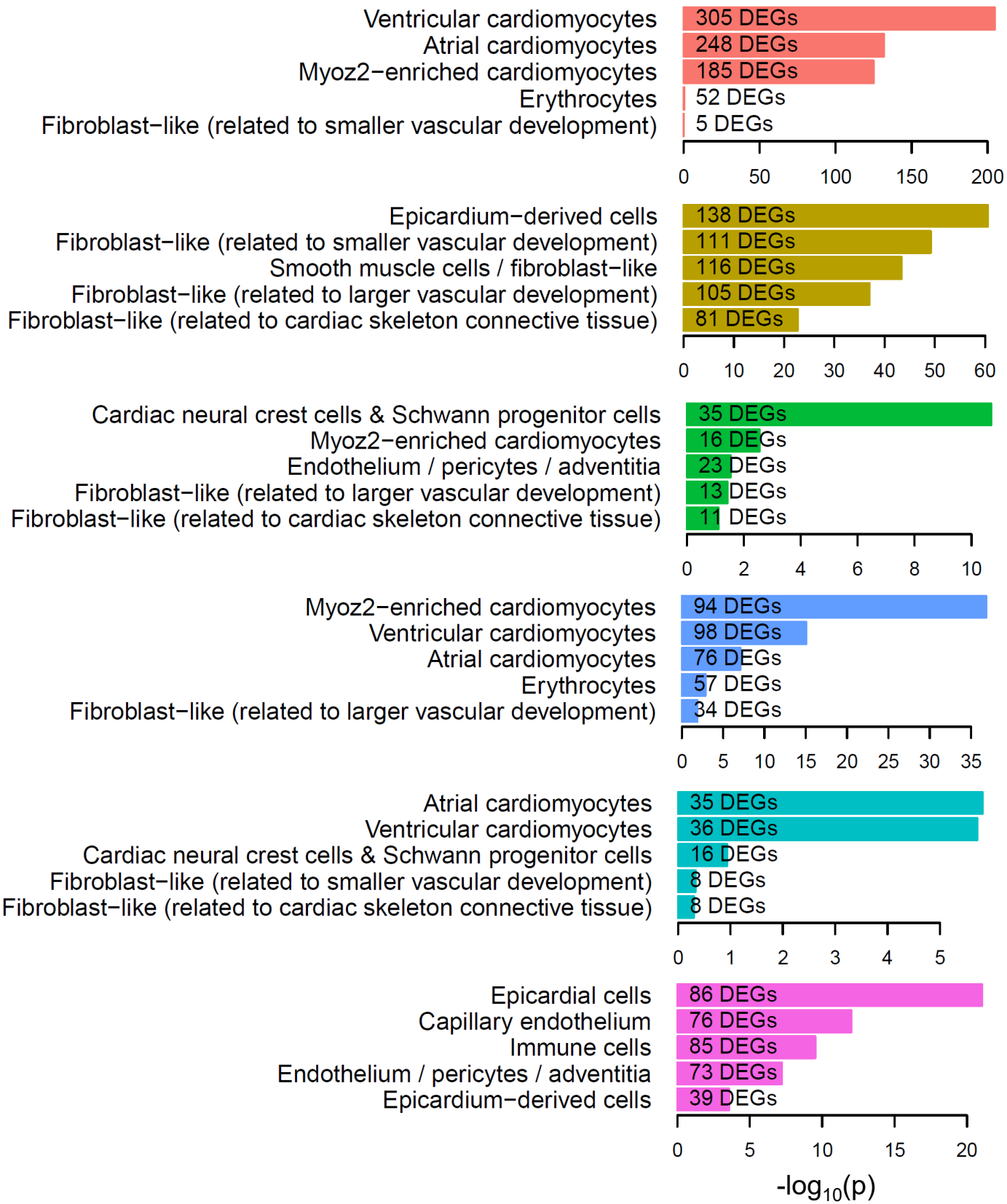
C

Enrichment analysis for marker genes of cell types in the adult heart



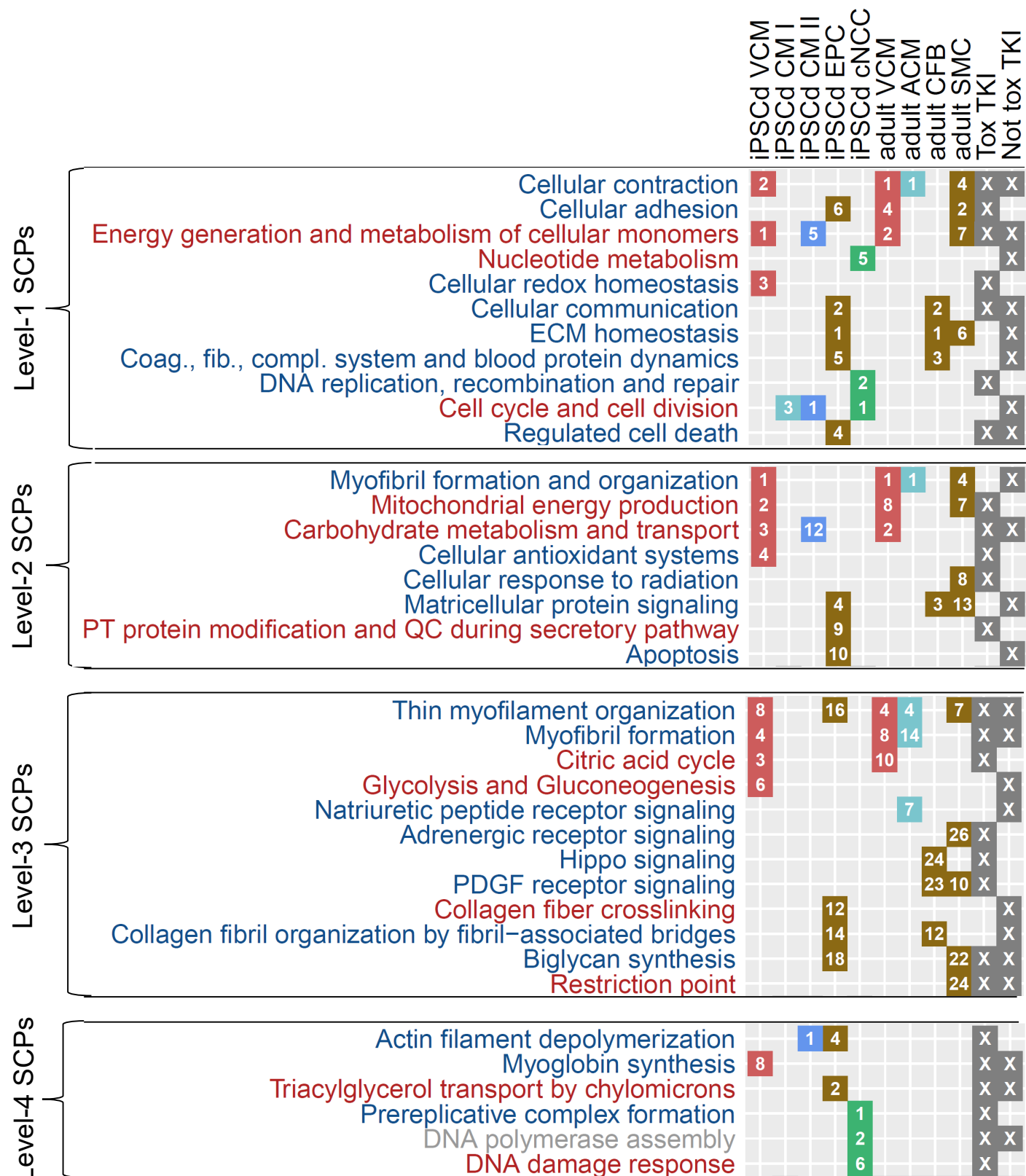
D

Enrichment analysis for marker genes of cell types in the developing heart

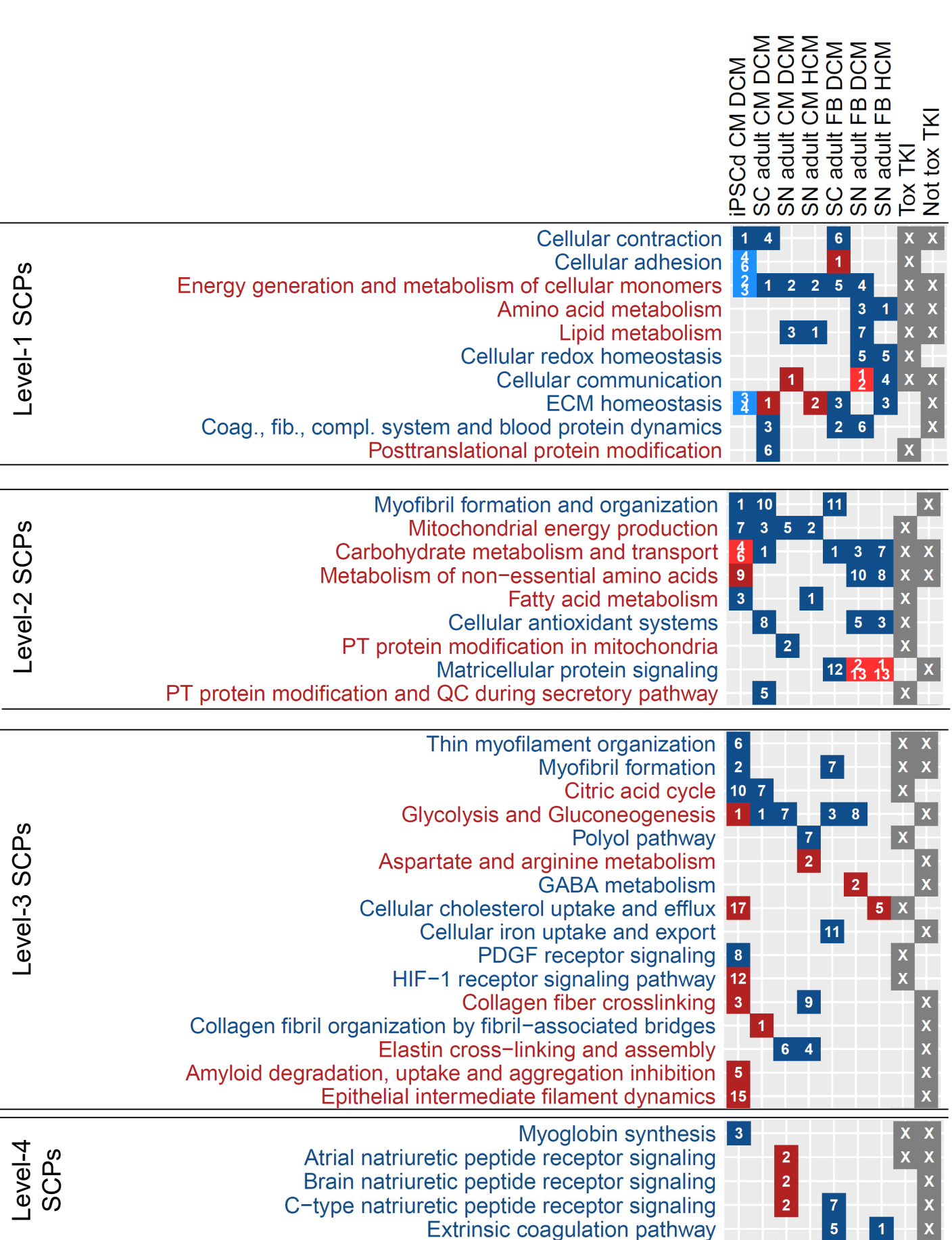


Supplementary Fig. 22

Supplementary Fig. 22. Single cell RNAseq identifies five different cellular subtypes. **(A)** Single cell RNAseq analysis of four of our six different hiPSC-derived cardiomyocyte cell lines identifies one ventricular cardiomyocyte (VCM) subtype, two additional cardiomyocyte subtypes (CM I and CM II), one epicardial-cell-derived subtype (EPC), one cardiac neural crest (cNC) subtype and one epicardial (EPI) or endothelial (EC) cell subtype. **(B)** Cell counts of the identified subtypes document that most of our cells are ventricular cardiomyocytes in all four cell lines. A and B are updated versions of two supplemental figures in our previous publication ¹⁶. **(C)** Subtype-specific marker genes were subjected to pathway enrichment analysis using cell type marker genes identified from single nucleus RNAseq of the human adult heart or **(D)** cell type marker genes identified from single nucleus RNAseq of the human fetal heart. Enrichment results were used for cell type annotations shown in (A).



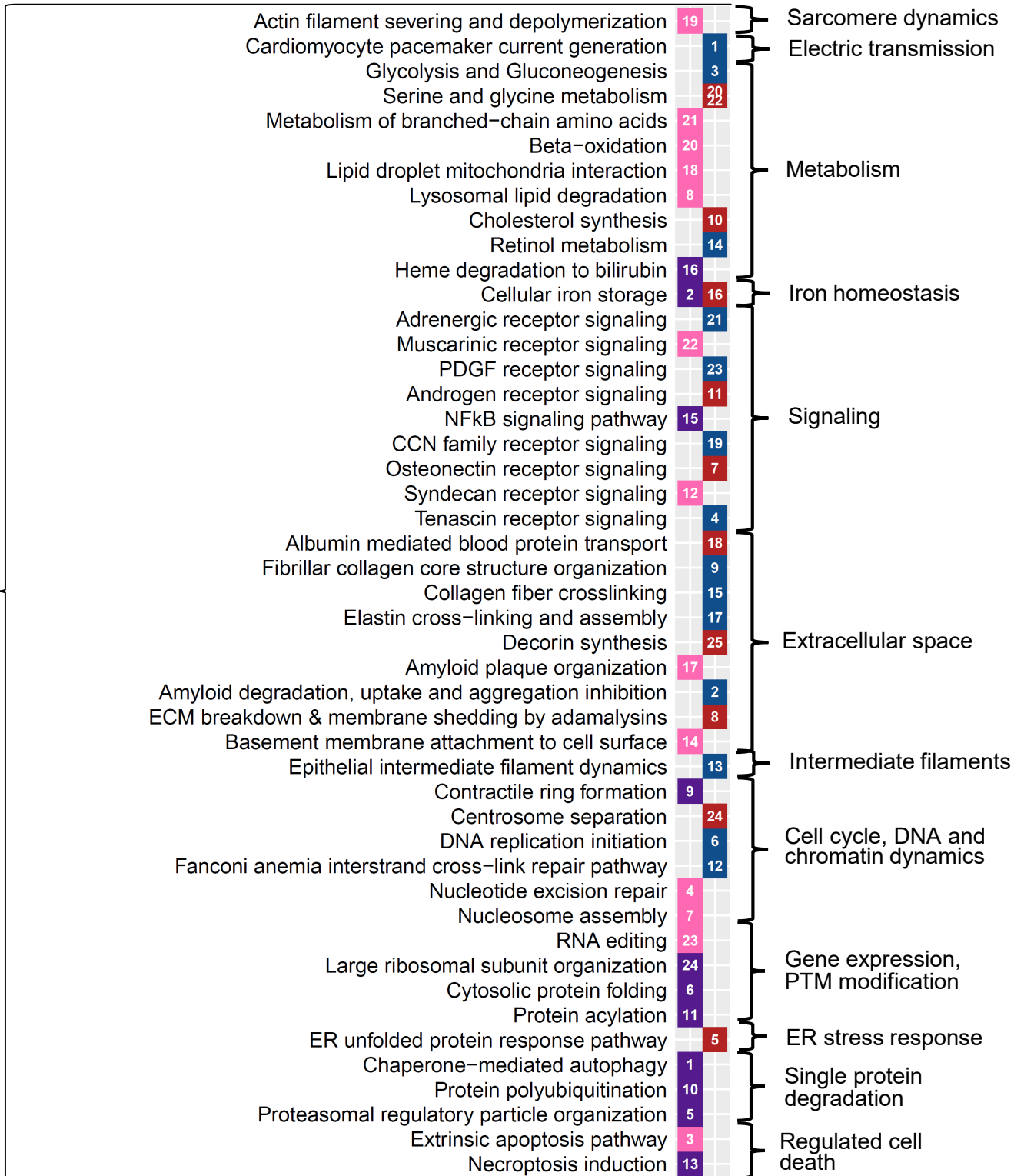
Supplementary Fig. 23. SCPs can be mapped to cellular cardiac cell types. Subtype marker genes identified by single cell RNAseq analysis of our four cell lines ¹⁶ were subjected to enrichment analysis using MBCO and Fisher's exact test. Significant SCPs (nominal p-value ≤ 0.05) were ranked by significance (numbers in the diagram). Similarly, we subjected cell type marker genes obtained from single nucleus RNAseq of the adult human heart ²⁹ to pathway enrichment analysis. The last two columns indicate if the SCP was identified based on cardiotoxic and/or non-cardiotoxic TKIs. SCPs whose higher and lower activity is associated with a cardiotoxic response are in red and blue, respectively. Results for level-3 SCPs identified based on cardiotoxic TKIs are also shown in main figure 3A.



Supplementary Fig. 24. SCPs indicative of TKI-induced cardiotoxicity partially overlap with prior knowledge obtained from single cell and single nucleus RNAseq studies. DEGs in heart cells from patients with DCM or HCM obtained by single cell (SC) ¹³ and nucleus (SN) ¹⁴ RNAseq, respectively, as well as in hiPSC-derived cardiomyocytes from infant DCM patients (GSE184899) were subjected to pathway enrichment analysis using MBO and Fisher's exact test. Significantly up- or downregulated SCPs of each cell type (nominal p-value ≤ 0.05) were ranked by significance (numbers in the diagram). Only SCPs that overlap with SCPs for which higher (red) or lower (blue) activity favors a cardiotoxic response are shown. The last two columns indicate whether the SCP was identified based on cardiotoxic and/or non-cardiotoxic TKIs. iPSCd: iPSC-derived, CM: cardiomyocyte, FB: Cardiac fibroblast. Results for level-3 SCPs that were predicted based on cardiotoxic TKIs are also shown in main Figure 3B.

Up/Downregulated at higher ranks by
anthracyclines TKIs with high cardiotoxicity

Level-3 SCPs



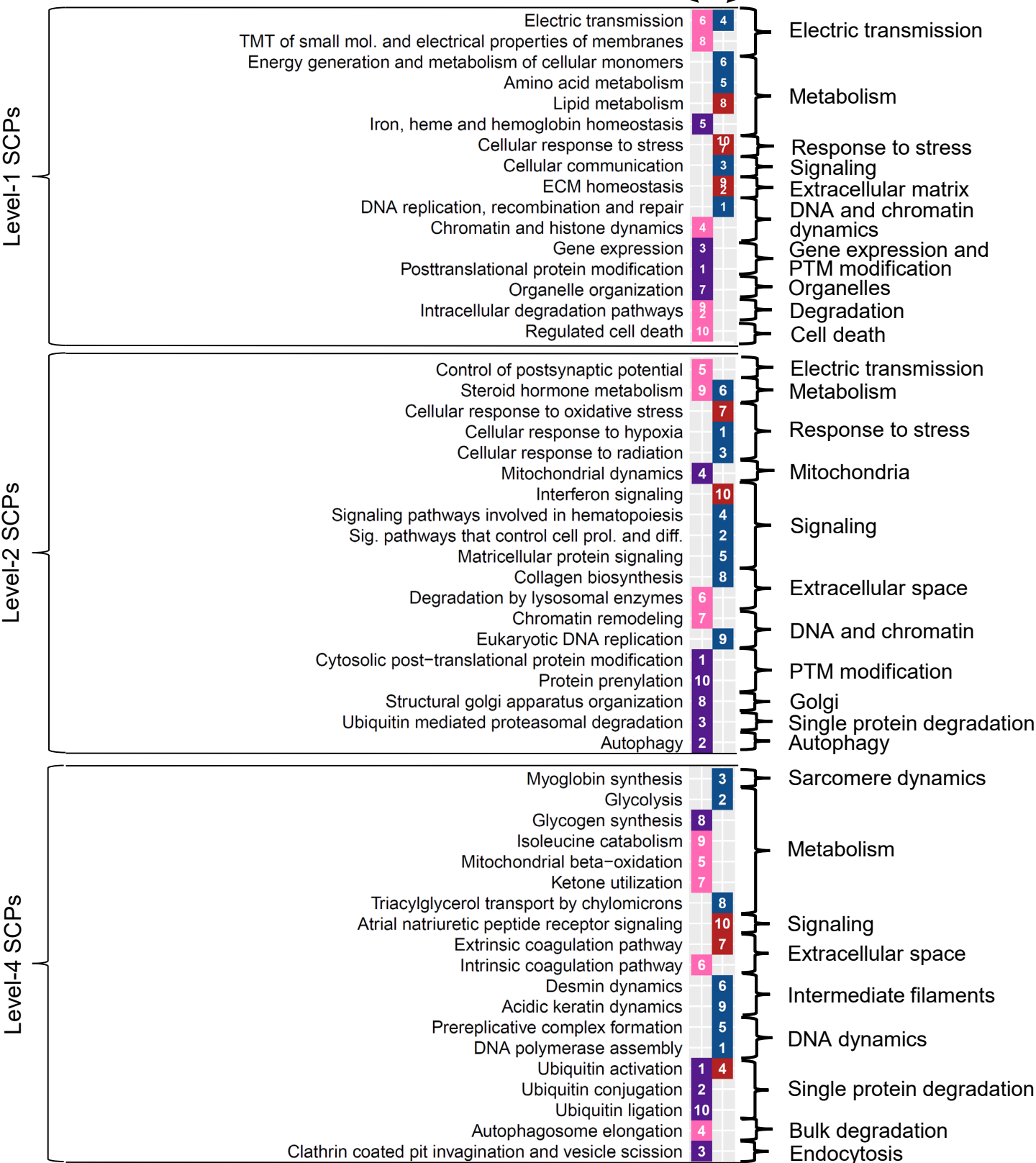
Up by anthracyclines ↑

Down by anthracyclines ↓

Up by very cardiotoxic TKIs ↑

Down by very cardiotoxic TKIs ↓

Up/Downregulated at higher ranks by
anthracyclines **TKIs with high cardiotoxicity**

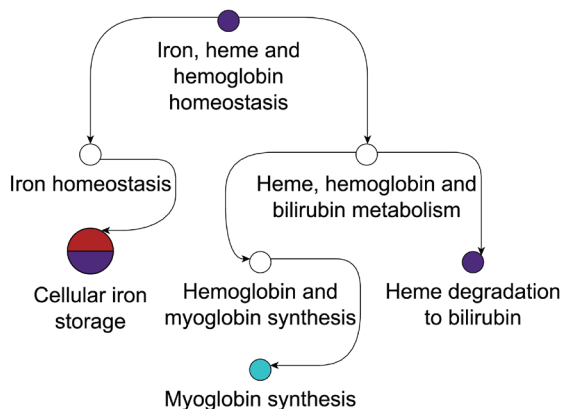


Up by anthracyclines ↑
 Down by anthracyclines ↓

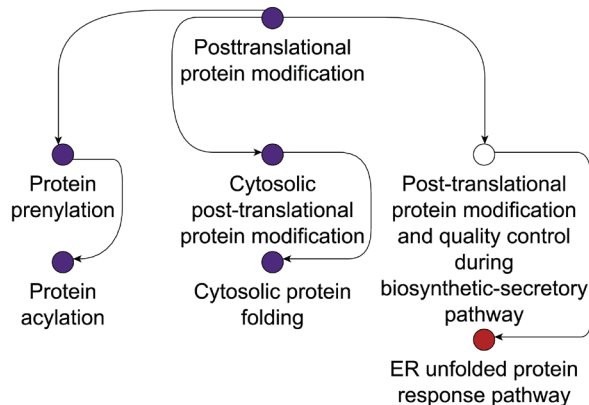
Up by very cardiotoxic TKIs ↑
 Down by very cardiotoxic TKIs ↓

Supplementary Fig. 25. SCPs associated with responses to anthracycline and highly cardiotoxic TKIs. Predicted up- and downregulated subcellular processes (SCPs) of the same level were ranked by significance for each drug and cell line. We searched for those SCPs that are up- or downregulated at higher significance ranks by anthracyclines or highly cardiotoxic TKIs (cardiotoxicity frequency > 10%). Identified SCPs were ranked by their selectivity for either anthracyclines or TKIs (white numbers). Shown are the top 25, 10, 10 and 10 predicted level-3, -1, -2 and -4 SCPs for both drug groups. The level-3 SCPs that are up- or downregulated by anthracyclines are also shown in Fig. 2D. PTM: post-translational modification.

Iron, heme and myoglobin homeostasis



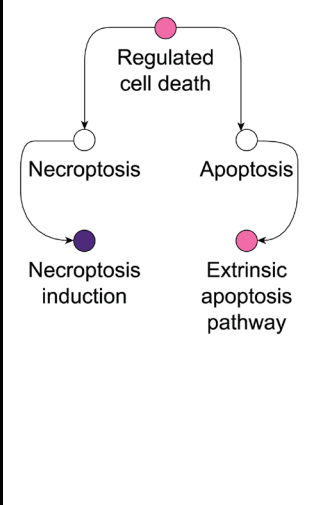
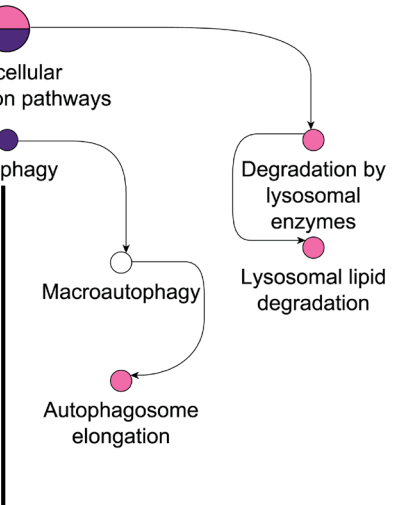
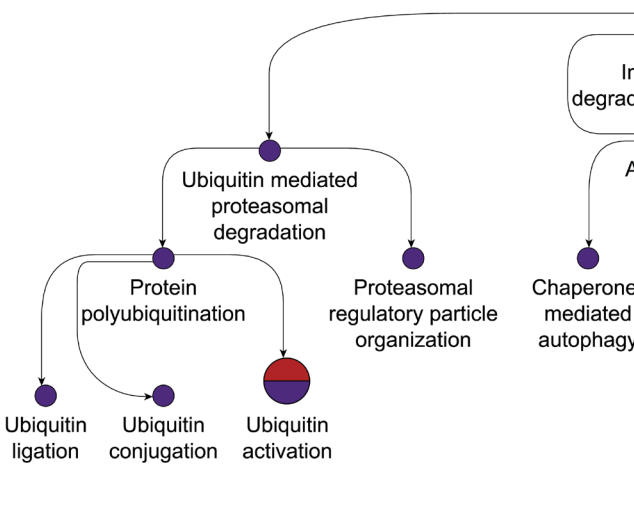
PTM modification



Single protein degradation

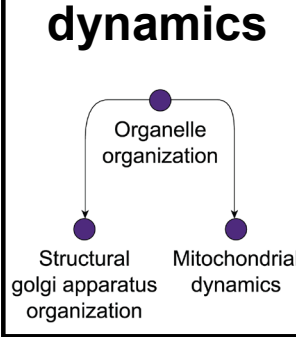
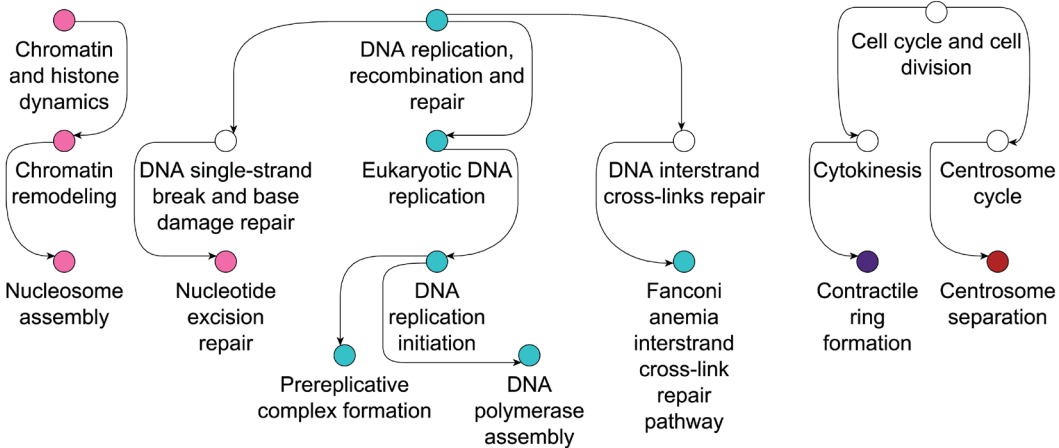
Bulk degradation

Cell death



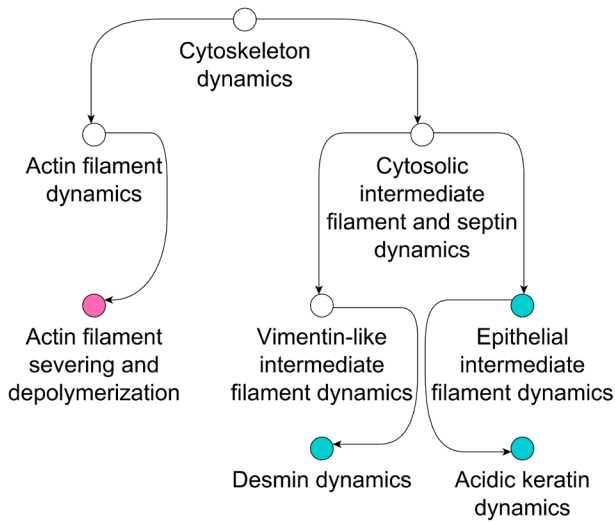
Chromatin, DNA and cell cycle dynamics

Organelle dynamics

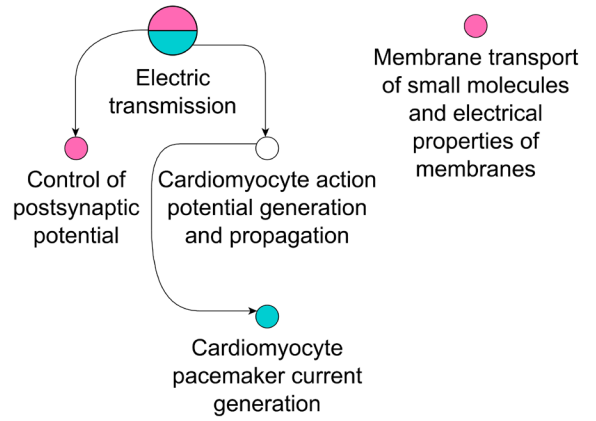


Up by anthracyclines ↑ Up by very cardiotoxic TKIs ↑
 Down by anthracyclines ↓ Down by very cardiotoxic TKIs ↓

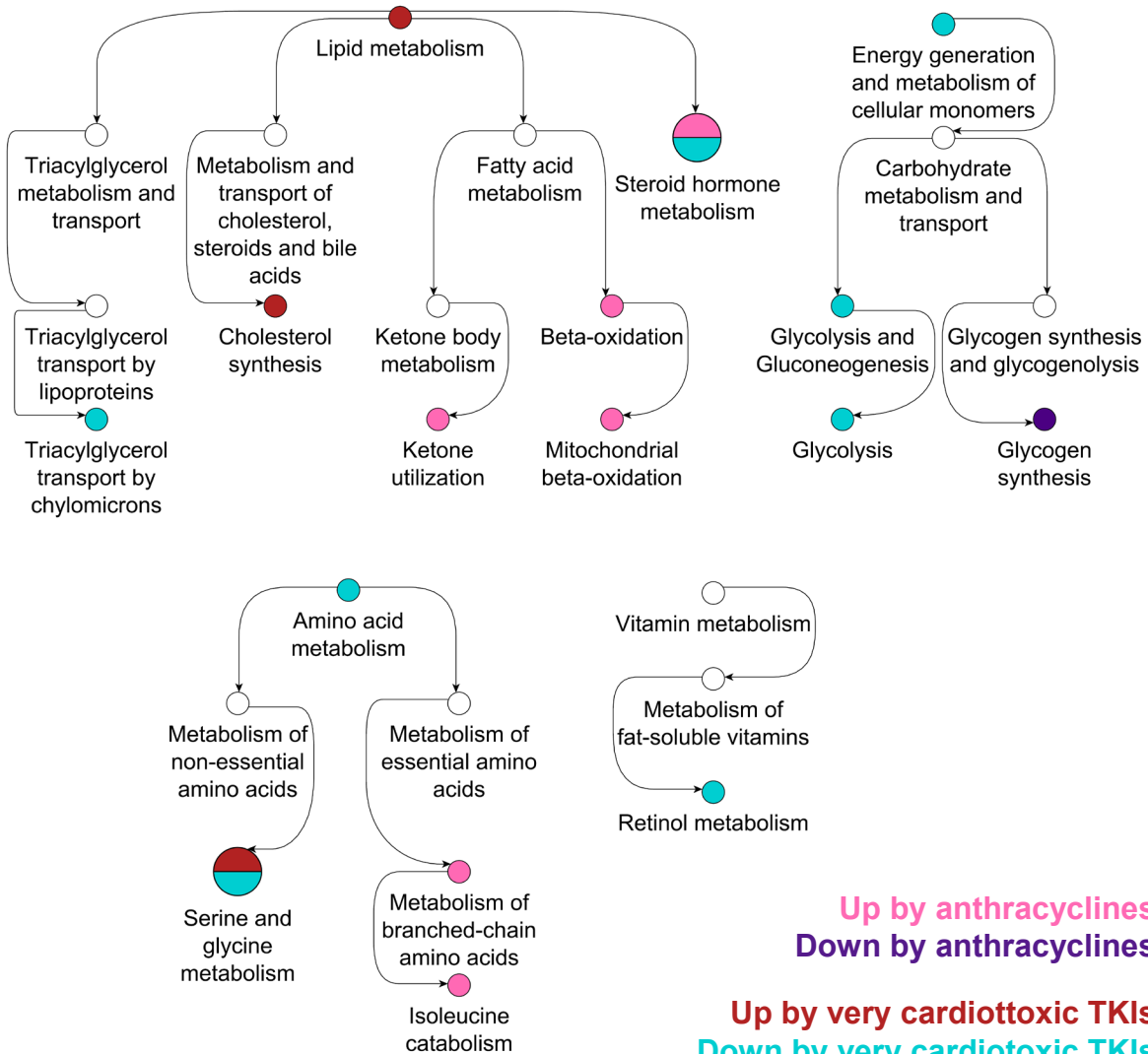
Cytoskeleton dynamics



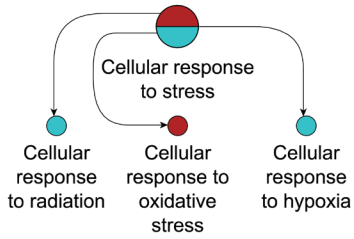
Electric transmission



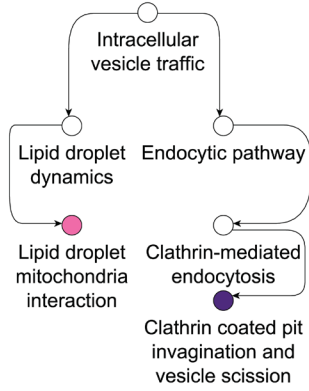
Metabolism



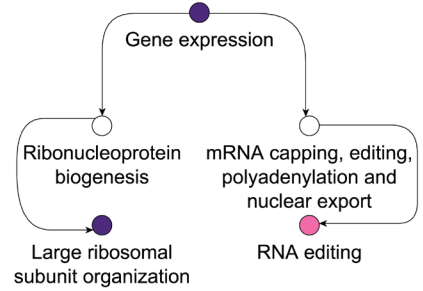
Response to stress



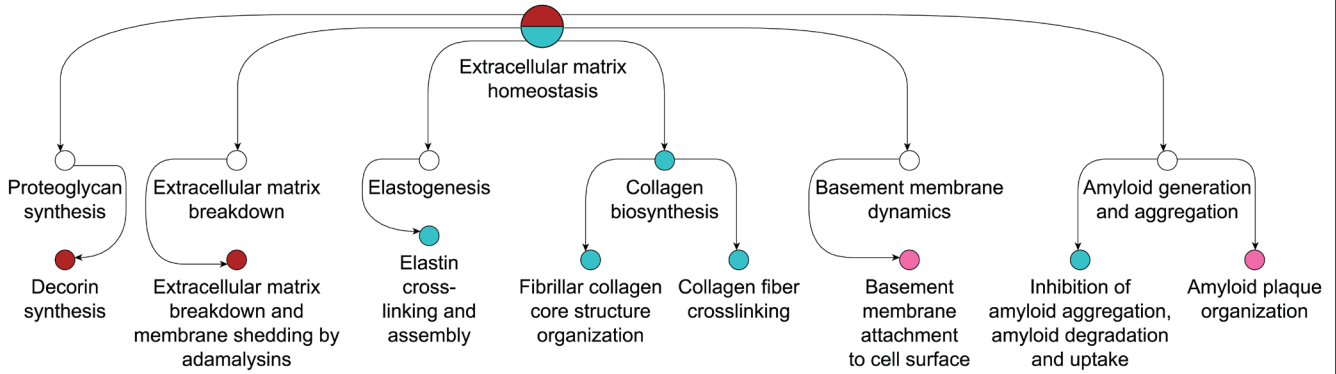
Vesicle traffic



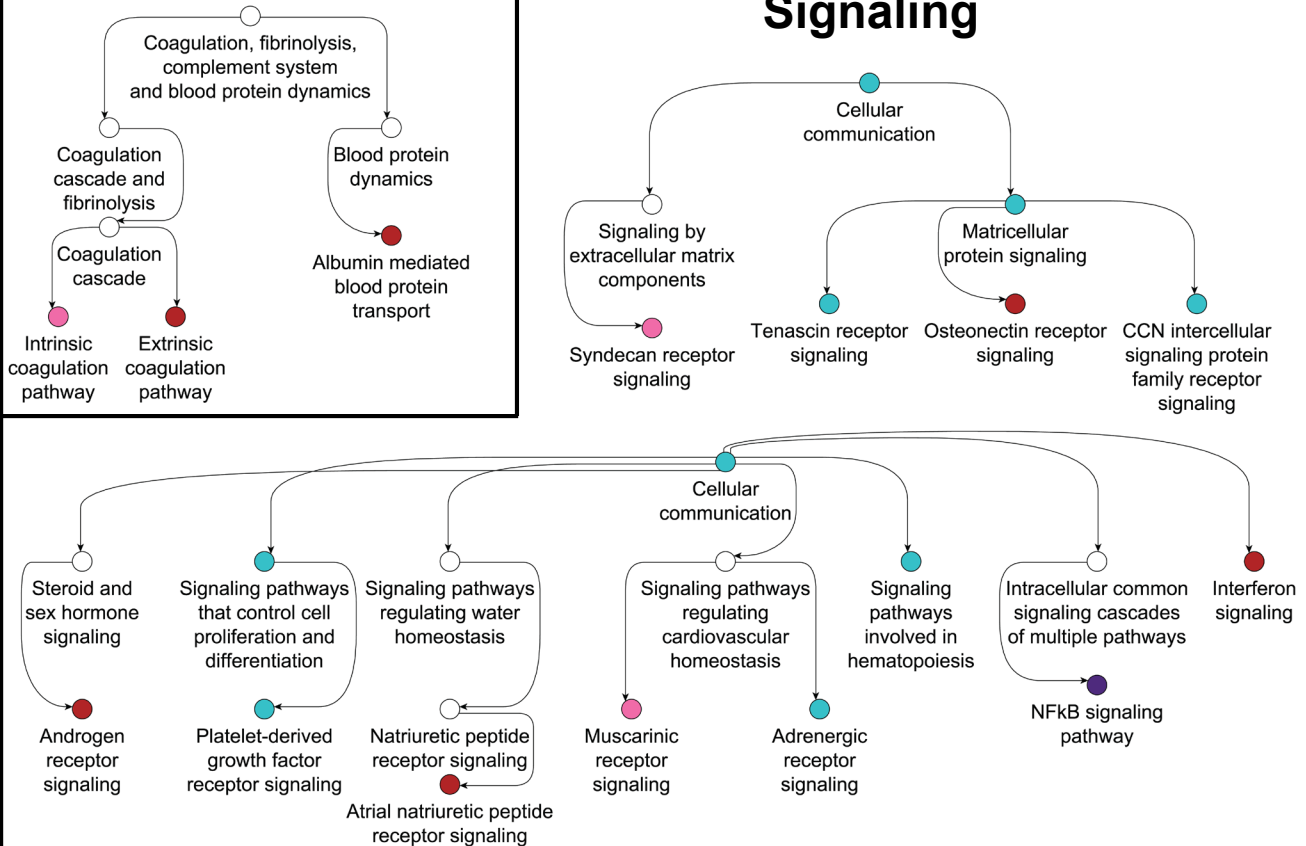
Gene expression



Extracellular space



Signaling



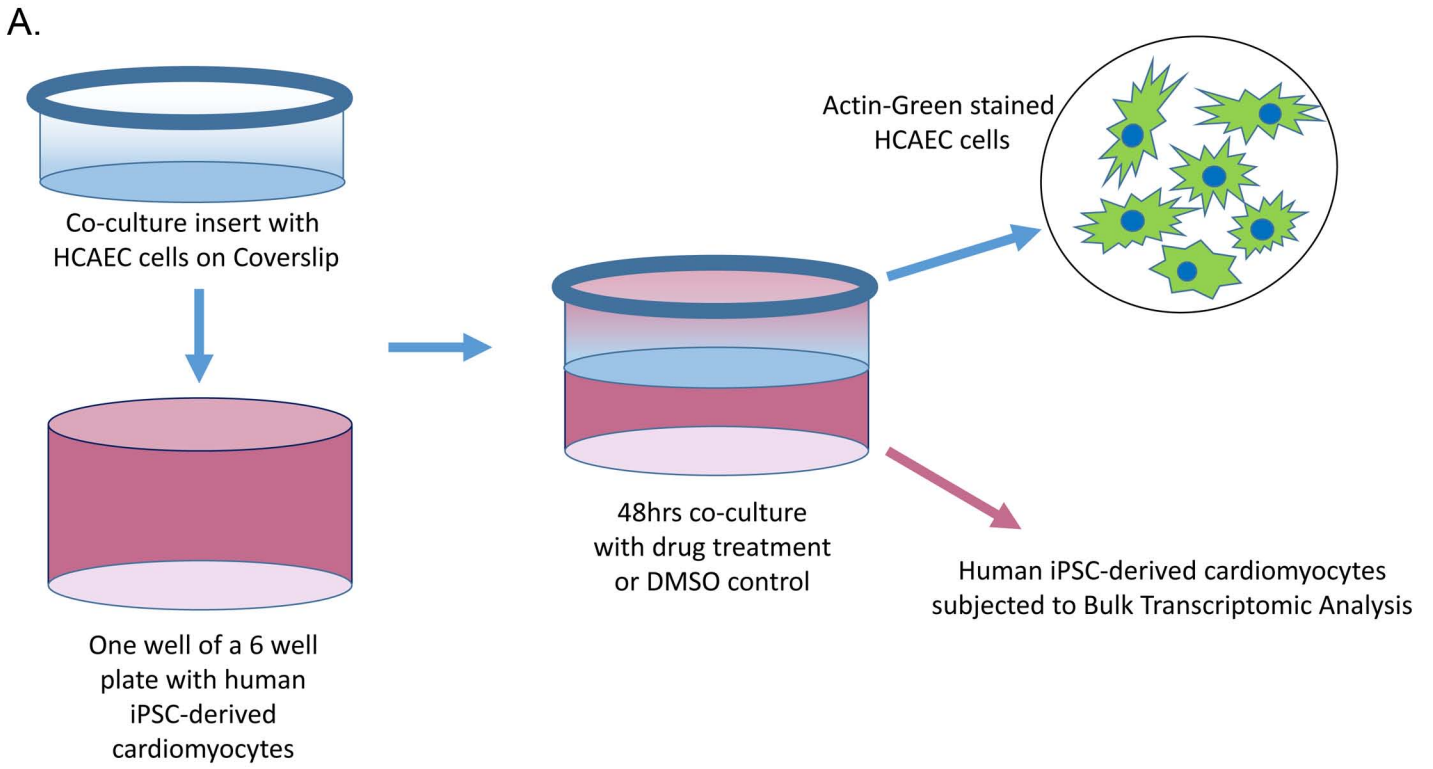
Up by anthracyclines ↑

Up by very cardiotoxic TKIs ↑

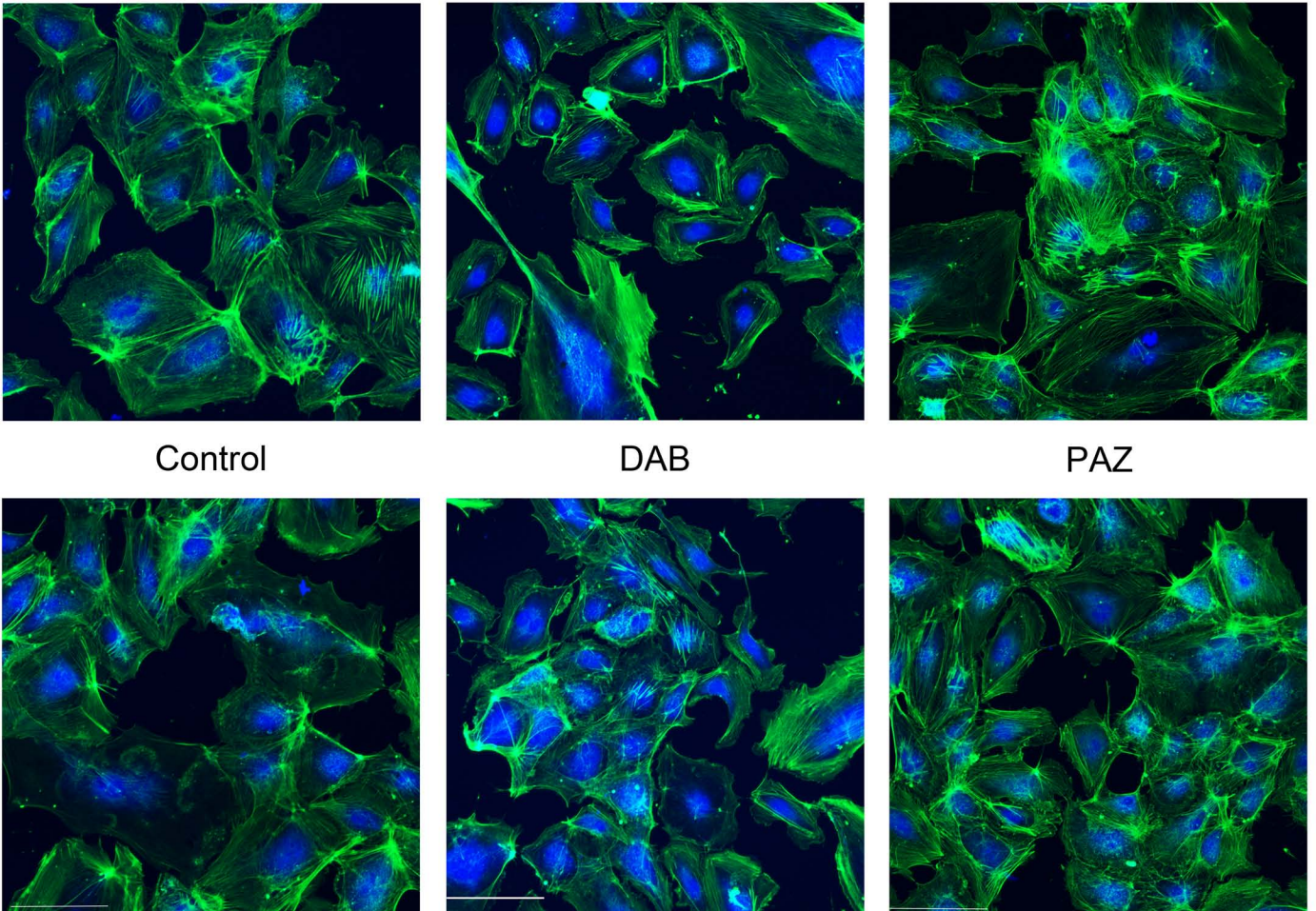
Down by anthracyclines ↓

Down by very cardiotoxic TKIs ↓

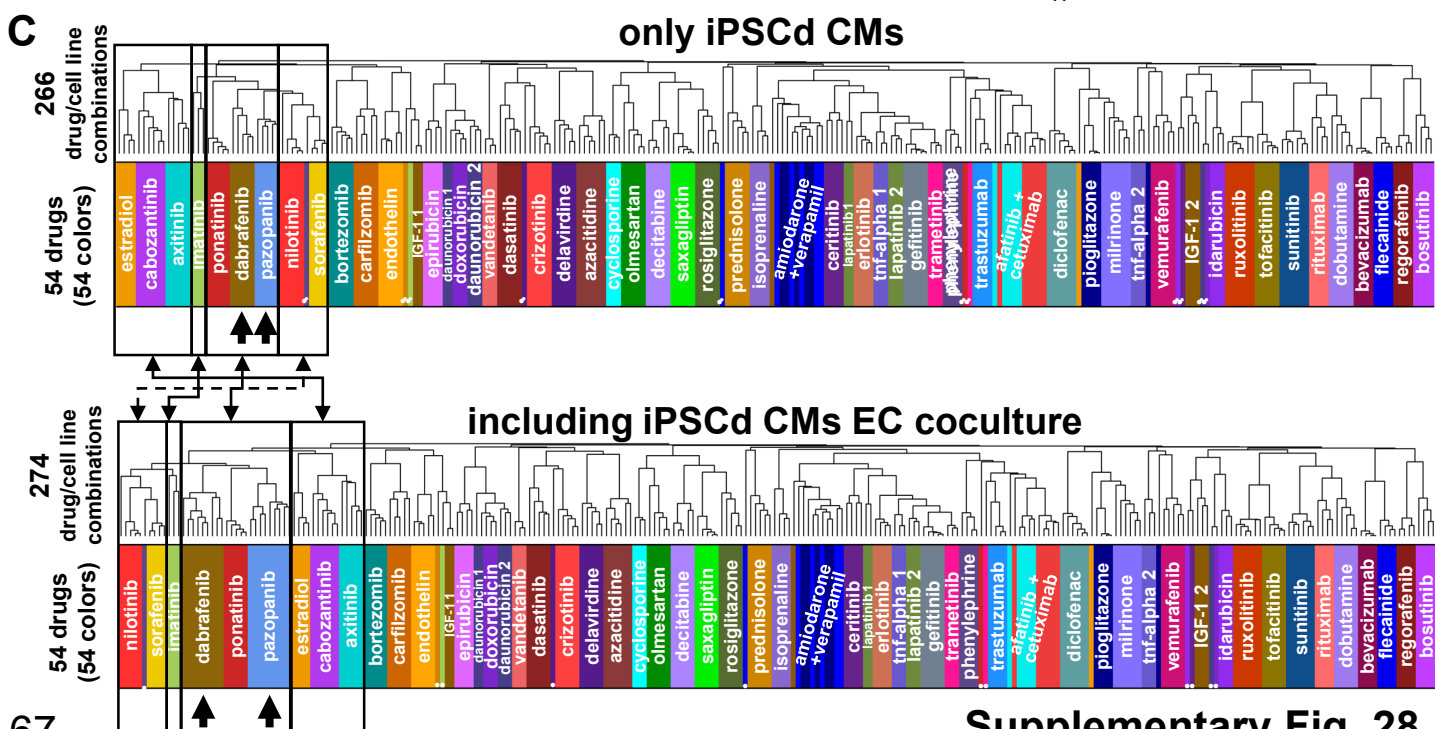
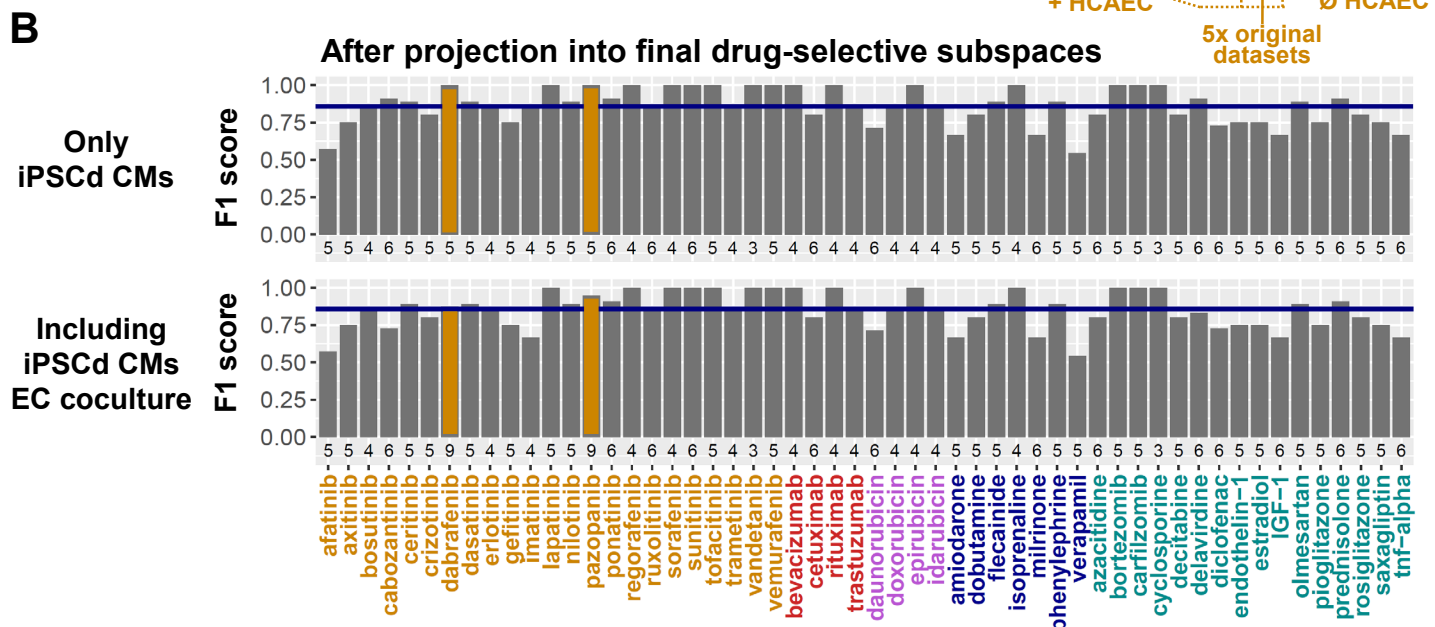
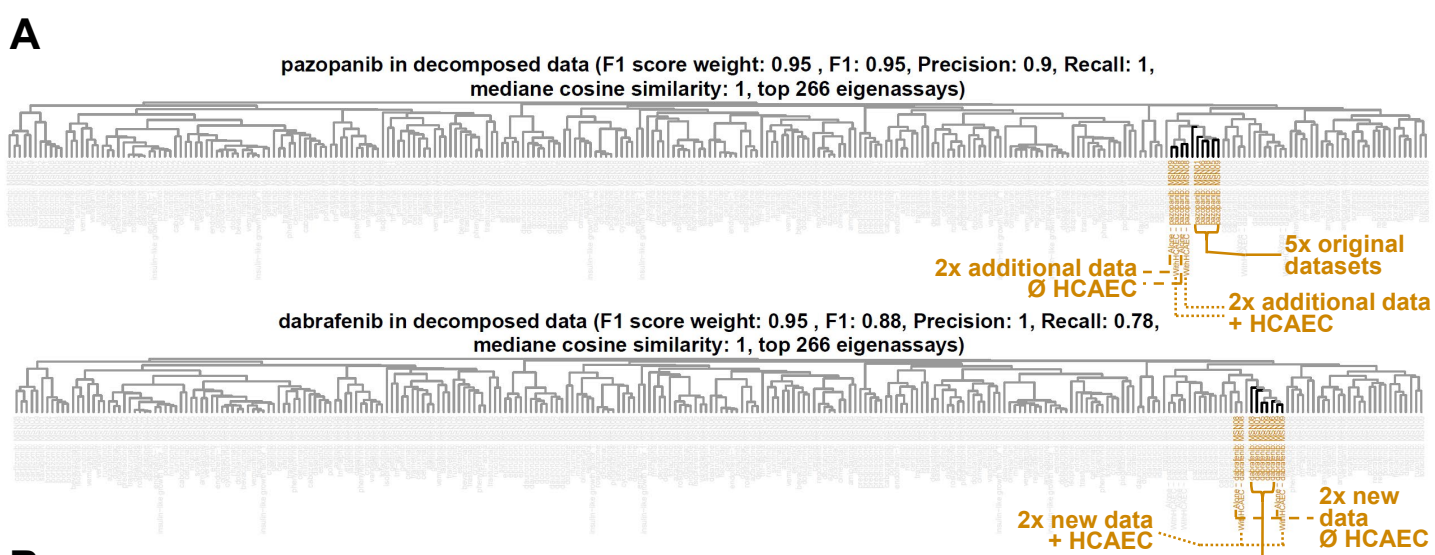
Supplementary Fig. 26. Integration of identified SCPs into the MBCO hierarchy. Up- and downregulated SCPs associated with anthracycline or highly cardiotoxic TKI treatment were integrated into the MBCO hierarchy. Arrows point from parent to child SCPs. Each tree starts with a level-1 SCP and then consecutively connects it to predicted level-2, -3 and -4 SCPs. Non-predicted SCPs that are ancestors of predicted SCPs are in white. Most of the SCPs on the first page are also shown in main figure 2E. PTM: post-translational modification.

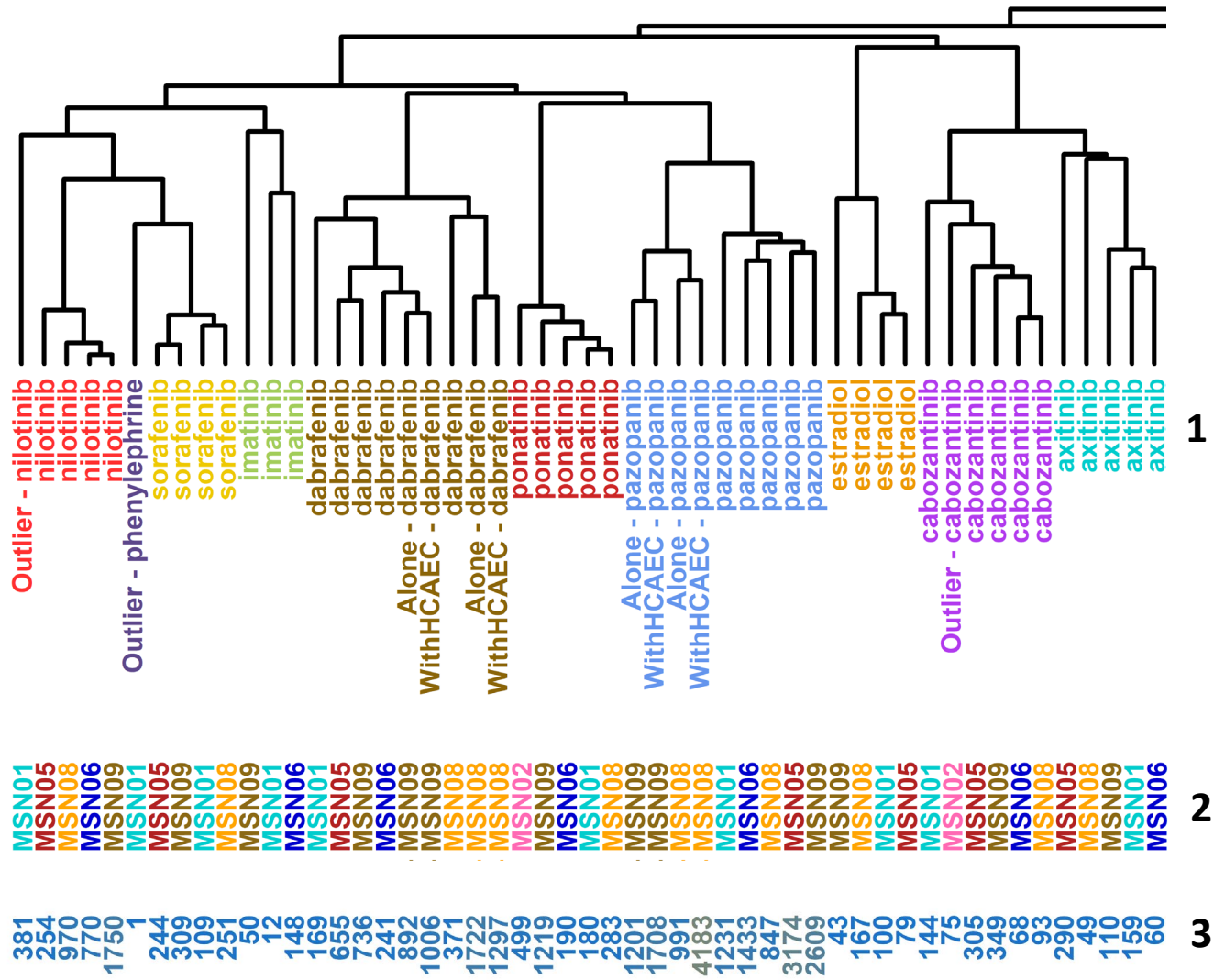


B. Human Coronary Artery Endothelial Cells (HCAEC) stained with Actin-Green



Supplementary Fig. 27. Cardiomyocyte-endothelial cell cocultures. (A) iPSC-derived cardiomyocyte (CM) cell lines MSN08 and MSN09 were incubated for 24 hours with or without human coronary artery endothelial cells (HCAEC). HCAEC were seeded on a well insert consisting of a glass coverslip and a porous filter allowing communication between HCAEC and iPSC-CM. Pazopanib, dabrafenib or control vehicles were added to the media, followed by an additional 48 hours before cardiomyocyte harvesting and HCAEC fixation. Cardiomyocytes were subjected to bulk transcriptomic sequencing. **(B)** ACTIN green staining of HCAEC documents endothelial cell phenotypes.



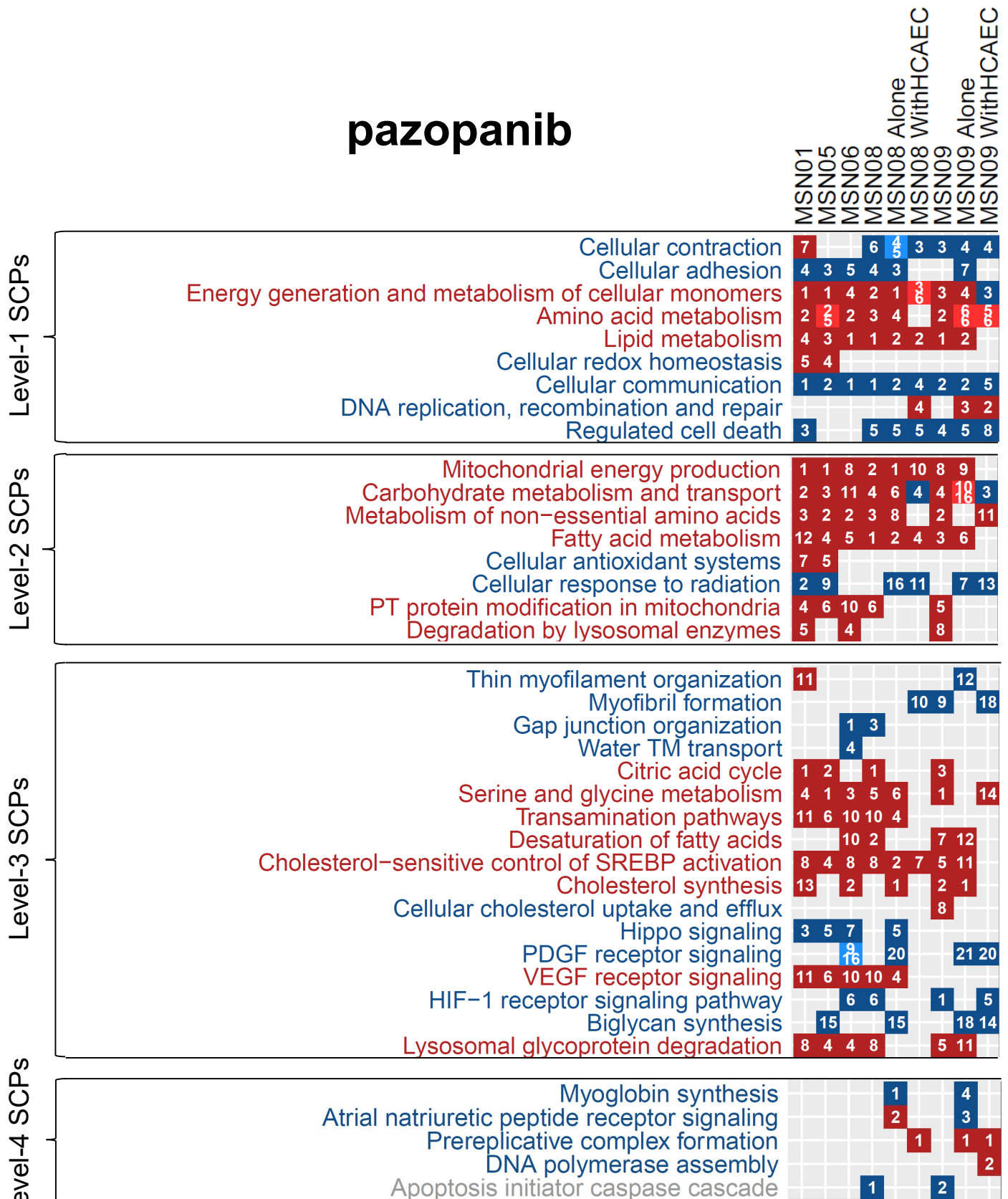


Supplementary Fig. 28. Projection of DEGs from cardiomyocyte-endothelial cell co-culture experiments into drug-selective subspaces. DEGs induced by pazopanib or dabrafenib with or without HCAEC coculture were calculated in cell lines MSN08 and MSN09. The generated additional eight lists of DEGs were merged with the original 266 lists. **(A)** Projection of the combined 274 lists of DEGs into the pazopanib- or dabrafenib-selective subspaces (that were identified using only the original data of 266 lists of DEGs) revealed close clustering of the new pazopanib and dabrafenib-treated cell lines with the existing cell lines treated with the same drugs. A different clustering behavior of the new data generated with or without HCAEC coculture was not observed. **(B)** Comparison of the F1 scores obtained for each drug within its selective subspace, obtained either after projecting the 266 (upper panel) or 274 (lower panel) lists of DEGs, shows only minor differences. Orange bars highlight F1 scores for pazopanib and dabrafenib. The upper panel is identical with the panels shown in Figure 1D and Suppl. Figure 10B. **(C)** All drug-selective DEGs, generated by projecting either the original 266 (upper panel) or the extended 274 (lower panel) lists of DEGs were merged, followed by pairwise correlation and hierarchical clustering. The new data caused small rearrangements in the clustering behavior of nine drugs that cluster close to pazopanib and dabrafenib. Boxes frame treatments that got rearranged against each other. The upper panel is identical with the one shown in Figure 1E. **(D)** The figure shows drug treatments (1), cell lines (2) and number of significant DEGs (3) mapping to the dendrogram area that is framed in C, lower panel.

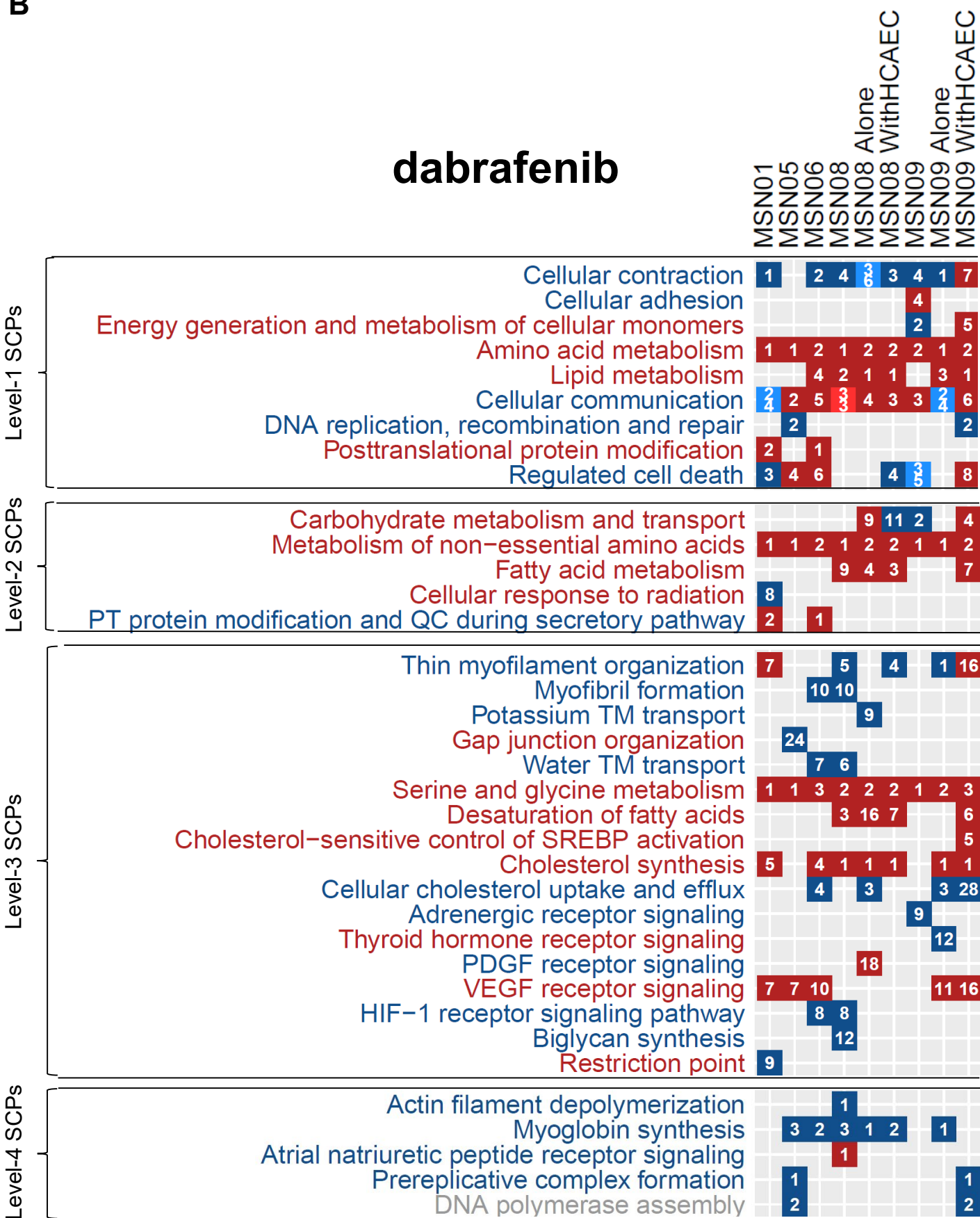
Supplementary Fig. 29. Top Subcellular Processes predicted from complete gene expression profiles, after removal of first eigenarray and from drug-selective gene expression profiles of all dabrafenib or pazopanib-treated samples. See pages 174 - 182.

A

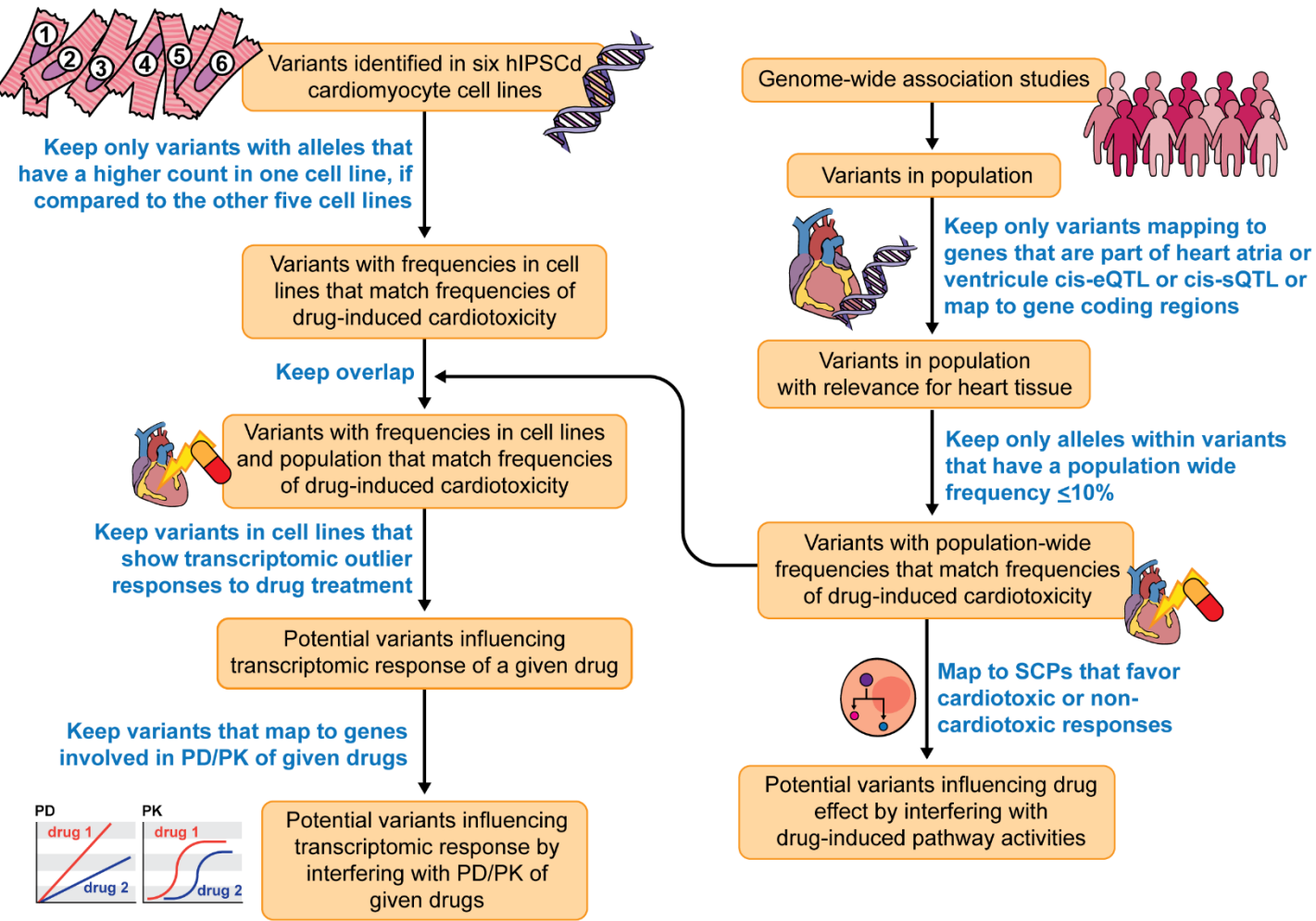
pazopanib



70



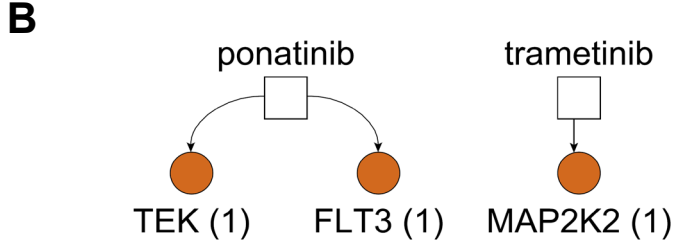
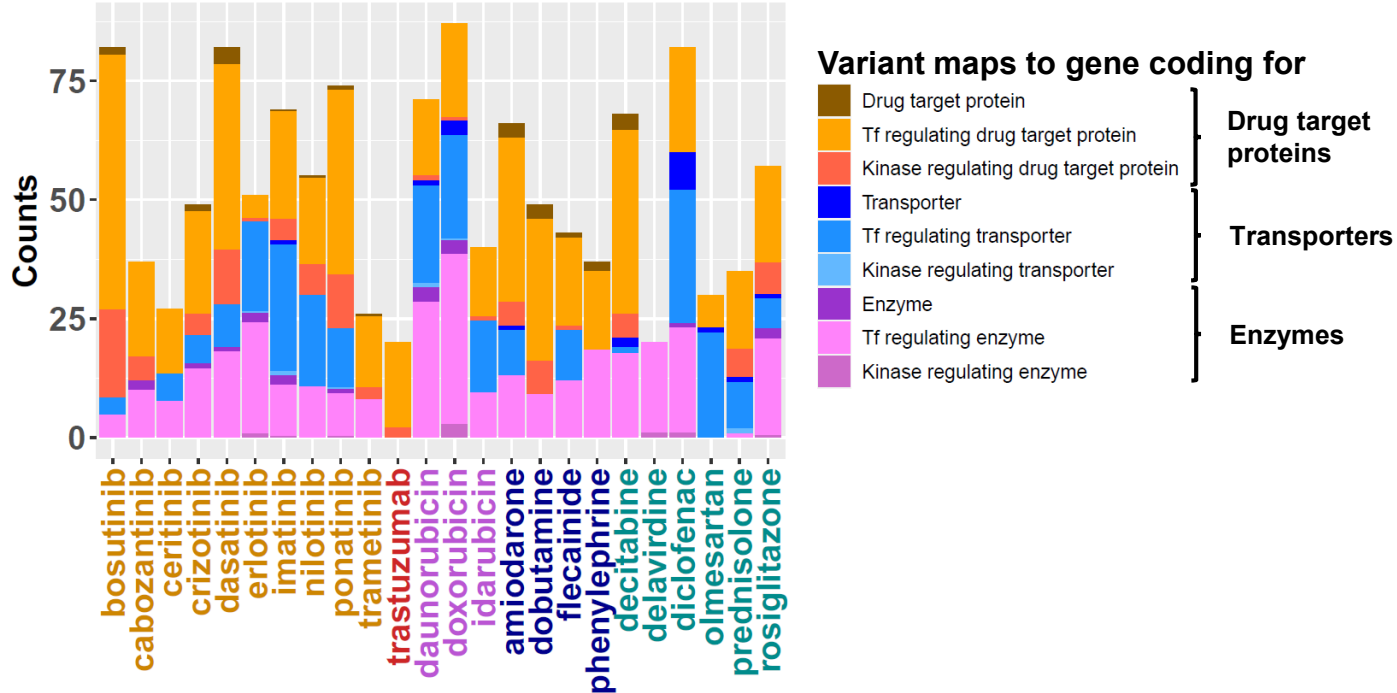
Supplementary Fig. 30. Coculture with HCAEC has only minor influence on up or down regulation of cardiotoxic pathways. (A) Enrichment results (p -value ≤ 0.05) of DEGs induced by pazopanib were filtered for pathways for which a higher (red SCP names) or lower (blue SCP names) activity favors a cardiotoxic response, as predicted from the cardiotoxic drugs. Gray labels an SCP with conflicting results. Since our F1 score and AUC statistics only considered SCPs with a maximum p -value of 0.05 and a maximum significance rank of 20, 20, 30 and 20 for level-1, -2, -3 and -4 SCPs, we filtered the pazopanib-induced pathways using the same criteria. Numbers show enrichment ranks in indicated cell lines. Ranks on a red or blue field indicate up- or downregulation. Bright red fields indicate up- and downregulation with the upper and lower rank in that field, respectively. Reversely, light blue fields indicate down- and upregulation with the upper and lower rank in that field, respectively. Original datasets are only labeled with the stimulated cell lines, additional datasets are further labeled with 'Alone' or 'With HCAEC', if they were obtained from cardiomyocytes cultured without or with HCAEC, respectively. (B) The figure shows described results obtained for dabrafenib treatments.



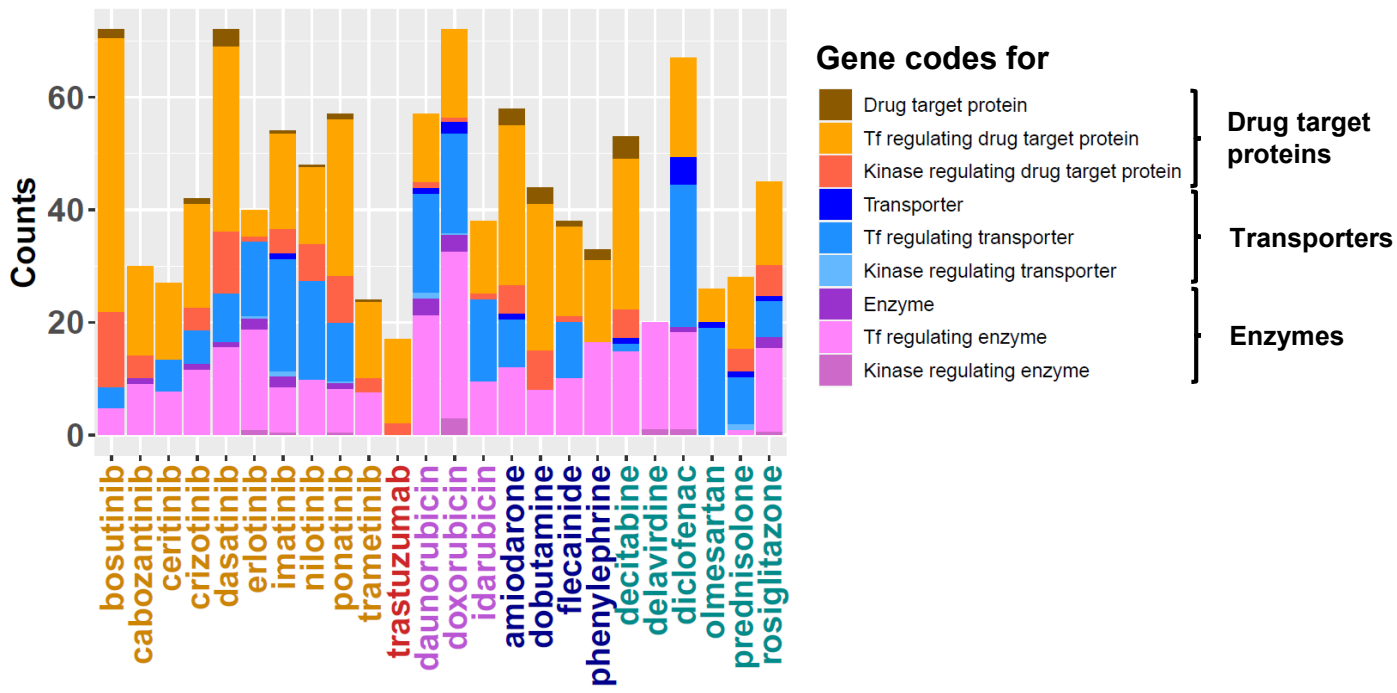
Supplementary Fig. 31

Supplementary Fig. 31. Computational pipeline for the identification of potential genomic variants associated with anthracycline- and TKI-induced cardiotoxicity. The flow chart shows the steps involved in our pipeline for the identification of genomic variant candidates associated with drug-induced cardiotoxicity. See methods for details. Flow chart is used with permission from Mount Sinai Health System, licensed under CC BY.

A Genomic variants associated with outlier responses

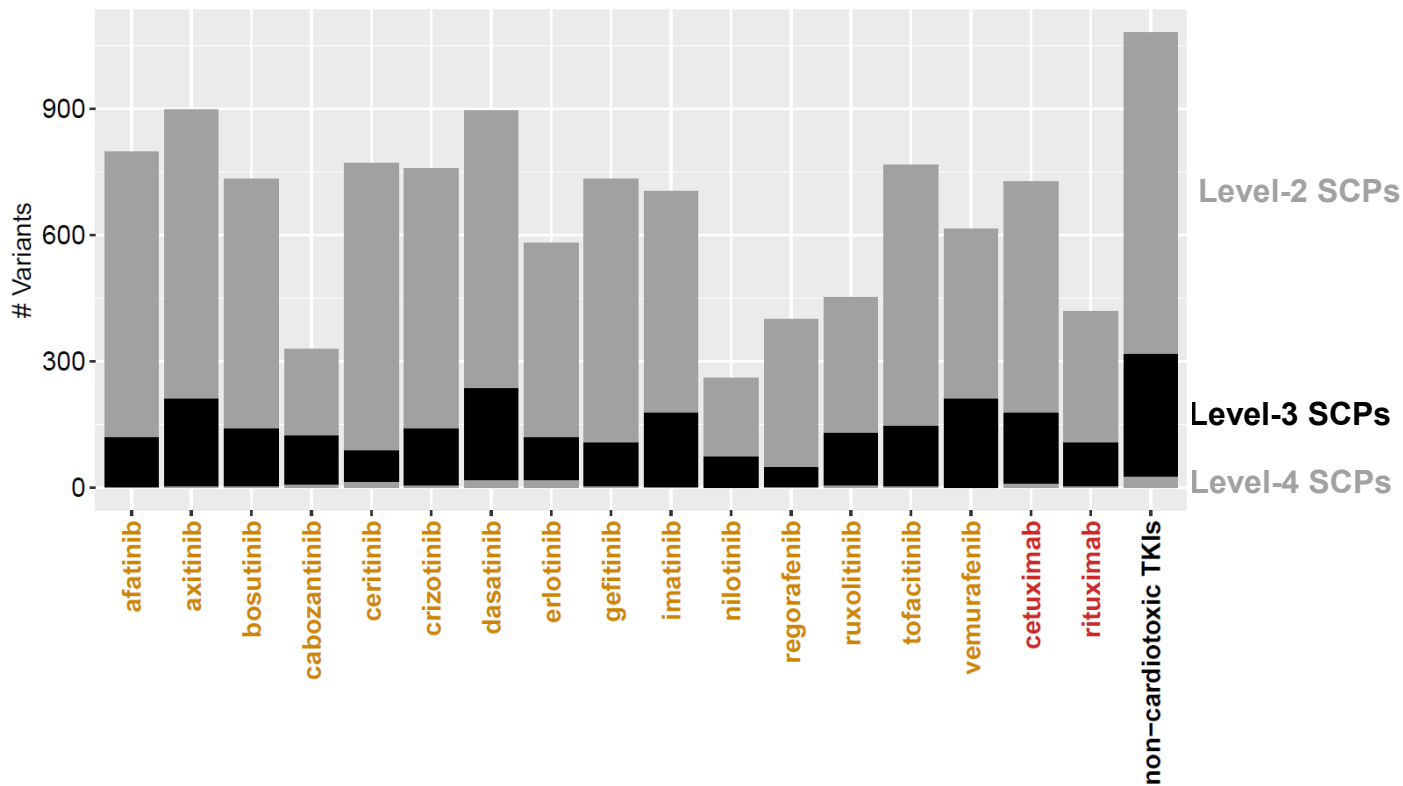


C Genes with genomic variants associated with outlier responses



D

Non-cardiotoxic TKIs



Supplementary Fig. 32

Supplementary Fig. 32. Identification of potential genomic variants associated with anthracycline- and TKI-induced cardiotoxicity. (A) Genomic variants that our algorithm identified as potential regulators of genes involved in a drug's pharmacodynamics (PD) or -kinetics (PK) are shown for all identified small molecule kinase inhibitors (orange), monoclonal antibodies against kinases (red), anthracyclines (purple), cardiac (blue) and non-cardiac (turquoise) acting drugs. The results for the cardiotoxic TKIs and anthracyclines are also shown in Fig. 4E. (B) Three example genes each targeted by one identified variant (numbers in brackets) and code for drug target proteins are shown. (C) Since multiple variants map to the same genes, we also counted the number of genes with at least one variant. (D) Variants passing our population-wide criteria were mapped to up- or downregulated level-2, -3 and -4 SCPs that we predicted to be up- or downregulated at higher ranks by non-cardiotoxic TKIs. Variants that are part of identified SCPs of multiple levels are only counted for the lowest level SCPs (with the highest level numbers) to prevent double counting. See Fig. 4G for results obtained for cardiotoxic TKIs.

(A) Metadata**1. Materials/Reagents:** Company name, Catalogue and lot numbers

PRODUCT	COMPANY NAME	CAT #	Storage	Usable life
DMEM (500 mL)	Life Technologies	11965-118	+4°C	M
IMDM	Life Technologies	12440-053	+4°C	M
DMEM/F12	Life Technologies	11330057	+4°C	M
Penicillin/Streptomycin (100x)	Life Technologies	15140-122	+4°C	M
Sodium-Pyruvate (100 mM)	Life Technologies	11360-070	+4°C	M
L-Glutamine (200 mM)	Life Technologies	25030-081	+4°C	M
Non-Essential Amino Acids (100x)	Life Technologies	11140-050	+4°C	M
Fetal Bovine Serum (FBS; 500 mL)	Corning	35-011-CV	+4°C	M
EDTA	Corning	46-034-CI	RT	M
KnockOut Serum Replacement	Life Technologies	10828-028	-20°C +4°C	M
mTeSR™: 1) mTeSR™ Basal medium 2) mTeSR™ 1.5X Supplement	STEMCELL Technologies	05850	+4°C -20°C	M
2-Mercaptoethanol	MP Biomedicals	194705	RT	N/A
TrypLE Express (1X)	Life Technologies	12605010	+4°C	M
ReLeSR™	STEMCELL Technologies	05872	RT	M
Gelatin	Sigma	G1890	RT	M
Matrigel	Corning	254248	-20°C +4°C	M
Dulbecco's phosphate-buffered saline (DPBS)	Life Technologies	14190-136	+4°C	M
DMSO	Fisher Scientific	BP2311	RT	M
FGF2	R&D Systems	223-FB-10	-20°C +4°C	M
Thiazovivin	Millipore	420220	-20°C +4°C	M
Irradiated MEFs (Mouse Embryonic Fibroblasts)	Global Stem	GSC-6001G	Liquid Nitrogen	M
mRNA Reprogramming Kit	Stemgent	00-0071	-70°C	M
microRNA Booster Kit	Stemgent	00-0073	-70°C	M
B18R	Stemgent	03-0071	-70°C	M
Pluriton Supplement (2500x)	Stemgent	01-0061	-80°C	M
Pluriton Medium (500 mL)	Stemgent	01-0015	-20°C +4°C	M
Stemfect RNA Transfection Kit: 1) Stemfect Transfection Buffer 2) Stemfect Transfection Reagent	Stemgent	00-0069	+4°C	M

PureLink™ Genomic DNA Mini Kit	Life Technologies	K1820-001	RT	N/A
e-Myco™ plus Mycoplasma PCR Detection KIT	iNtRON Biotechnology	25235	-20°C	M
50 ml conical tube	BD FALCON	352098	RT	N/A
15 ml conical tube	BD FALCON	352099	RT	N/A
75 cm ² Cell Culture Flask	Corning	430641	RT	N/A
50 mL Rapid Flow Conical Filter with a 0.2 µm aPES membrane	Thermo Scientific	564-0020	RT	N/A
6 well Tissue Culture (TC) plate	Corning	353046	RT	N/A
2 ml Aspirating pipettes	BD FALCON	357558	RT	N/A
5 ml Serological Pipettes	BD FALCON	357543	RT	N/A
10 ml Serological Pipettes	BD FALCON	357551	RT	N/A
Hemocytometer	Thermo Scientific	0267110	RT	N/A
1 mL filter tips	USA Scientific	1126-7810	RT	N/A
200 µL filter tips	USA Scientific	1120-8810	RT	N/A
20 µL filter tips	USA Scientific	1123-1810	RT	N/A
0.1-10 µL filter tips	USA Scientific	1121-3810	RT	N/A
Cryovials	Nunc	377367	RT	N/A
Cryo 1°C freezing container	Nalgene	5100-0001	RT	N/A
2-Propanol	Thermo Scientific	A417-4	RT	N

M; according to manufacture's shelf-life information; RT, room temperature

2. Subject(s): subject ID (de-identified), age, gender/sex, race/ethnicity

3. Fibroblast(s): subject ID (de-identified), passage number, dates of each passage, date of biopsy, date of initial plating, date of freezing.

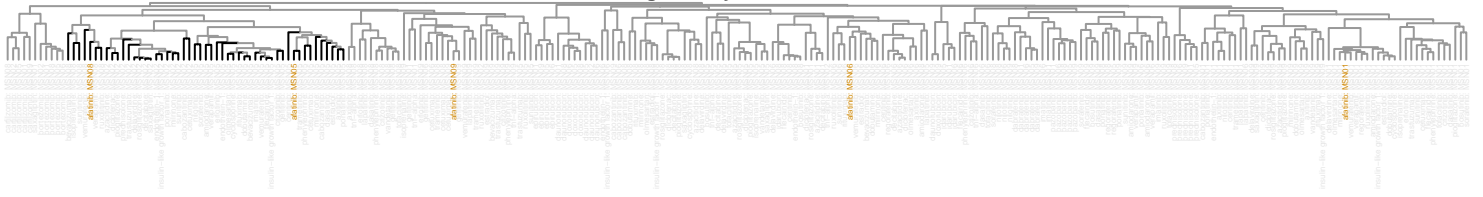
4. Microscopy pictures: subject ID (de-identified), passage number, date, microscope name (company, catalogue number), magnification.

(B) Materials used for co-culture experiments

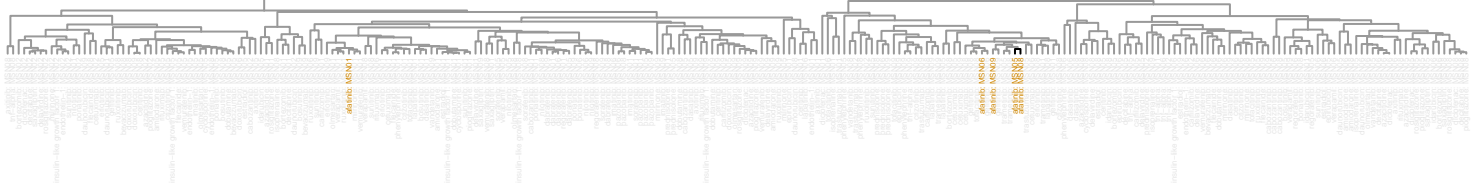
HCAEC	PromoCell	Catalog# C-12221
Endothelial Cell Growth Medium MV Kit	PromoCell	Catalog# C-22120
DetachKit (Trypsin/EDTA)	PromoCell	Catalog# C-41210
ActinGreen 488 Ready Probes Reagent	ThermoFisher	Catalog# R37110
Poly-L-lysine hydrobromide	Sigma-Aldrich	Catalog# P1274
Glass circular coverslips (18mm)	FisherScientific	Catalog# 12-545-86
Nunc Polycarbonate Cell Culutre Inserts in 6-well plates – Pore size of 0.4µm	ThermoFisher	Catalog# 140640
Paraformaldehyde 32% aqueous solution	Electron Microscopy Services	Catalog# 15714S
ProLong Gold Antifade Mountant with DAPI	ThermoFisher	Catalog# P36931

Supplementary Table 1. Description of materials used in this study. **(A)** This table lists the materials used for the initial experiments. It is taken from the Supplementary Information for Schaniel et al. (Stem Cell Reports. 2021 Dec 14;16(12):3036-3049, pages 9 and 10) ¹⁶, since the two studies were conducted concurrently. © 2021 The Author(s), released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license. **(B)** This table lists additional materials used for the coculture experiments.

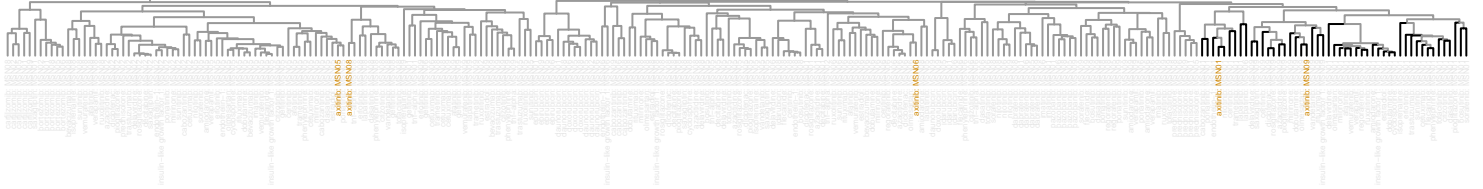
afatinib after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.4



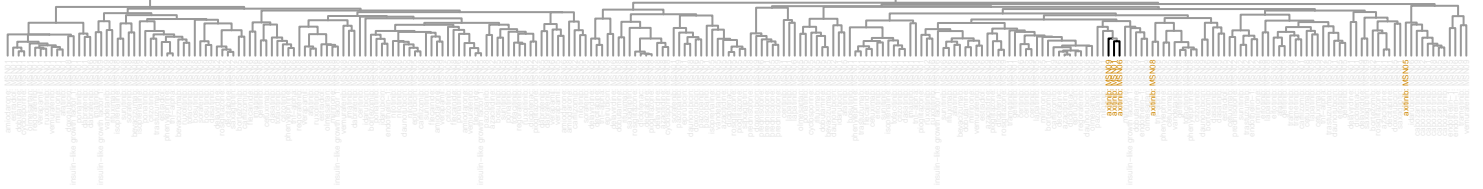
afatinib in decomposed data (F1 score weight: 0.95 , F1: 0.57, Precision: 1, Recall: 0.4, mediane cosine similarity: 0.41, top 23 eigenarrays)



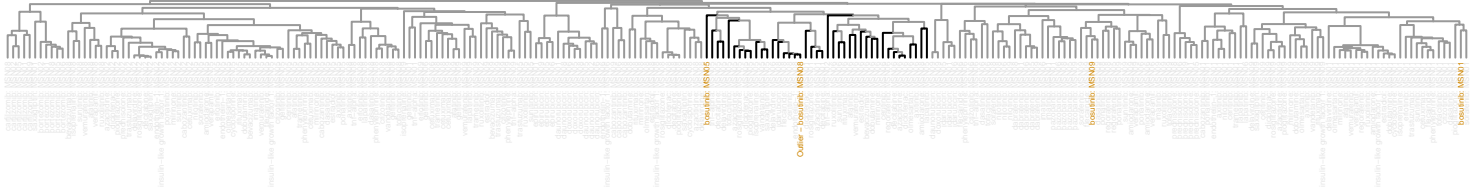
axitinib after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.4



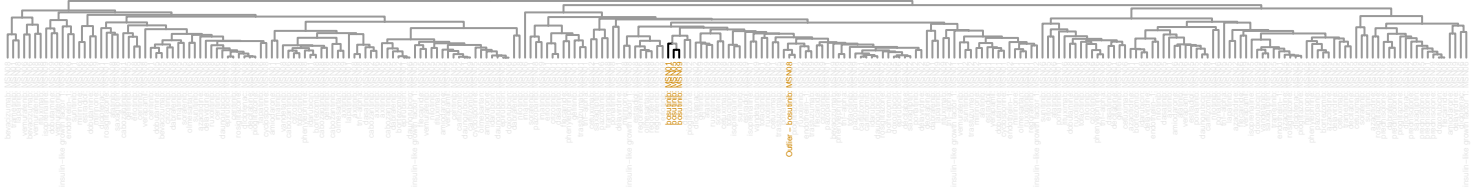
axitinib in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, mediane cosine similarity: 0.39, top 50 eigenarrays)



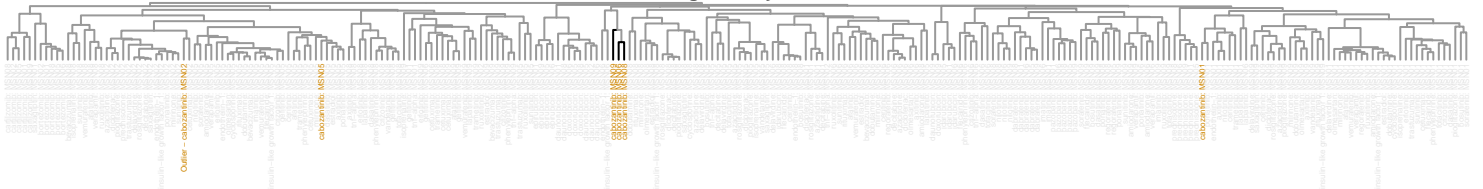
bosutinib after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.5



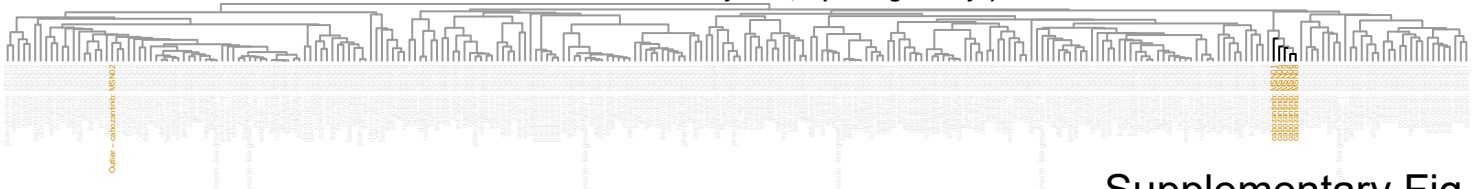
bosutinib in decomposed data (F1 score weight: 0.65 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 0.22, top 24 eigenarrays)



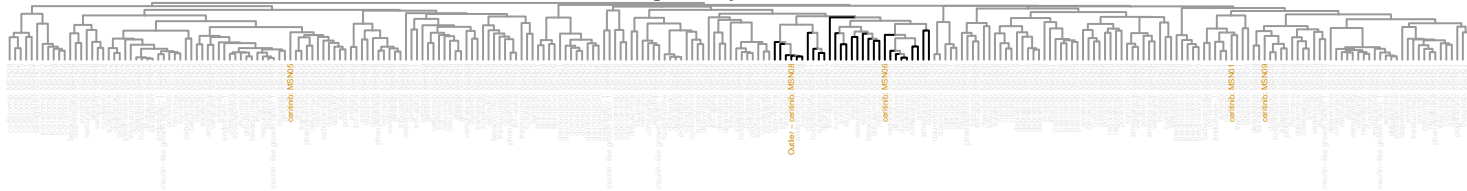
cabozantinib after removal of 1st eigenarray , F1: 0.67 , Precision: 1 , Recall: 0.5



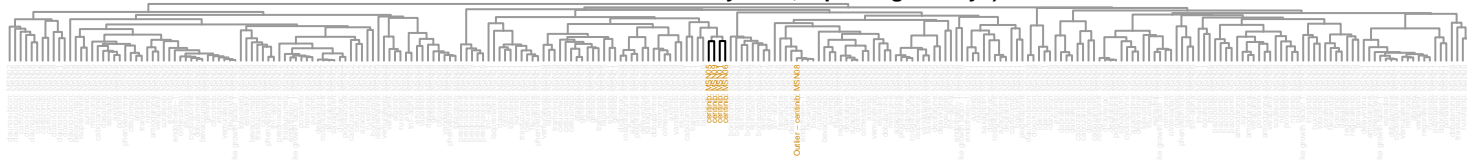
cabozantinib in decomposed data (F1 score weight: 0.5 , F1: 0.91, Precision: 1, Recall: 0.83, mediane cosine similarity: 0.76, top 57 eigenarrays)



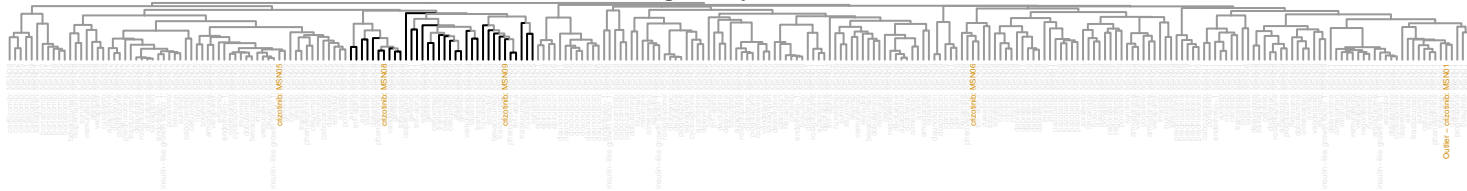
ceritinib after removal of 1st eigenarray , F1: 0.12 , Precision: 0.07 , Recall: 0.4



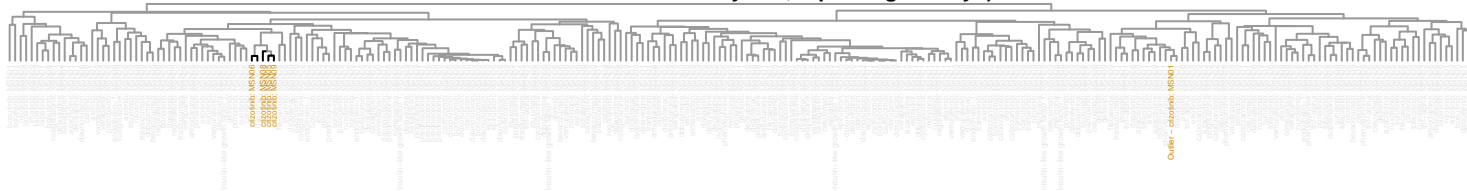
ceritinib in decomposed data (F1 score weight: 0.15 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.88, top 86 eigenarrays)



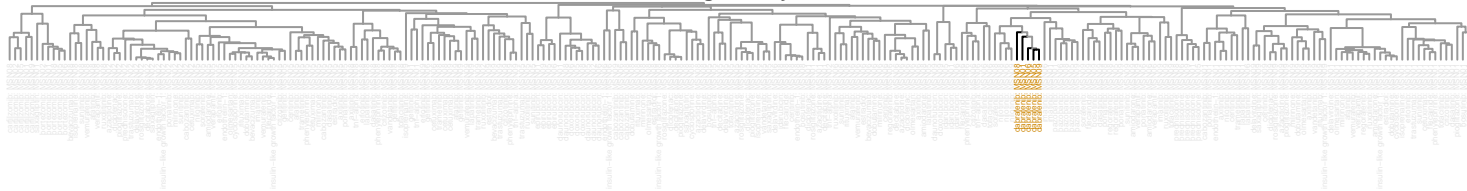
crizotinib after removal of 1st eigenarray , F1: 0.1 , Precision: 0.06 , Recall: 0.4



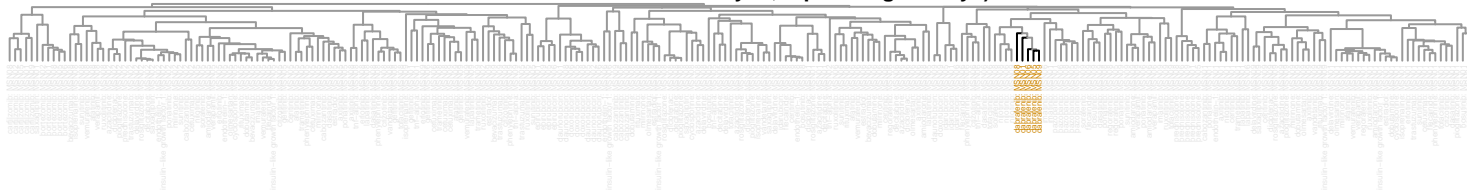
crizotinib in decomposed data (F1 score weight: 0.6 , F1: 0.8, Precision: 0.8, Recall: 0.8, mediane cosine similarity: 0.3, top 23 eigenarrays)



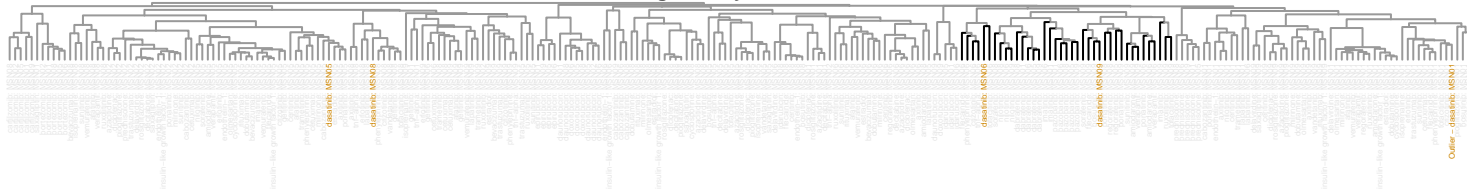
dabrafenib after removal of 1st eigenarray , F1: 1 , Precision: 1 , Recall: 1



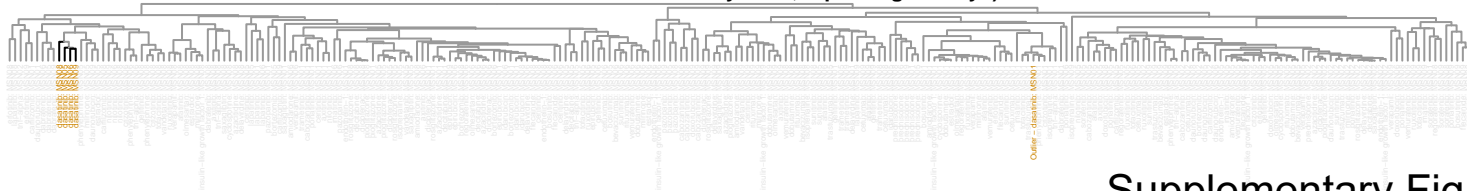
dabrafenib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 1, top 266 eigenarrays)



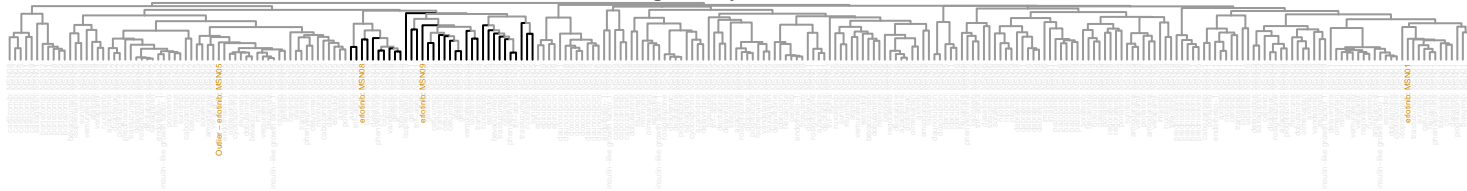
dasatinib after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



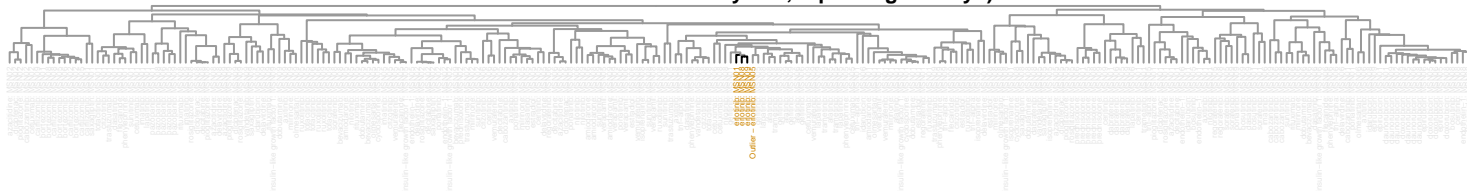
dasatinib in decomposed data (F1 score weight: 0.6 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.58, top 43 eigenarrays)



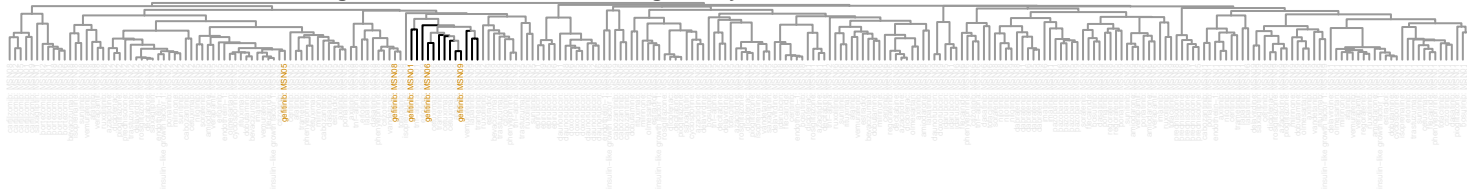
erlotinib after removal of 1st eigenarray , F1: 0.11 , Precision: 0.06 , Recall: 0.5



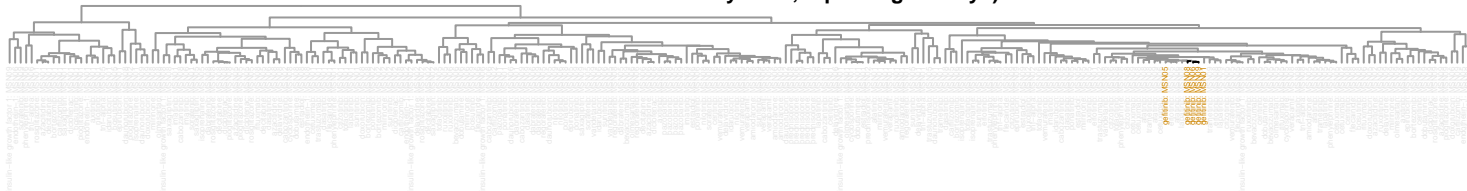
erlotinib in decomposed data (F1 score weight: 0.55 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 0.7, top 25 eigenarrays)



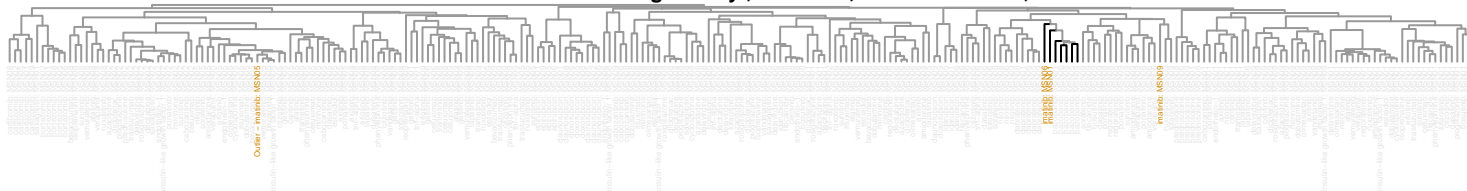
gefitinib after removal of 1st eigenarray , F1: 0.33 , Precision: 0.23 , Recall: 0.6



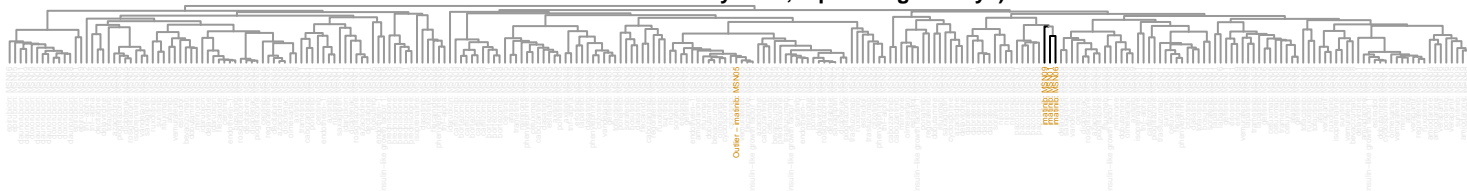
gefitinib in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, mediane cosine similarity: 0.61, top 16 eigenarrays)



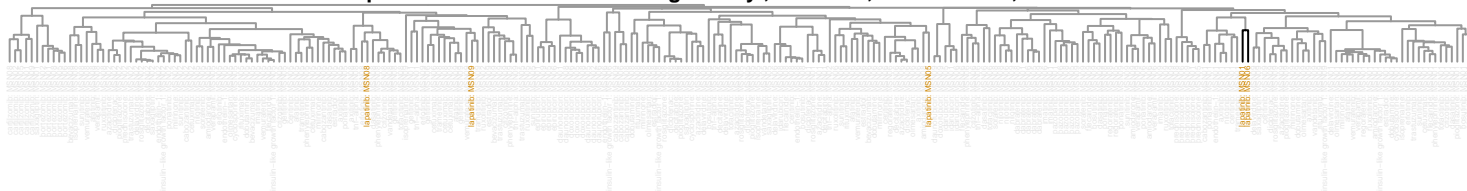
imatinib after removal of 1st eigenarray , F1: 0.36 , Precision: 0.29 , Recall: 0.5



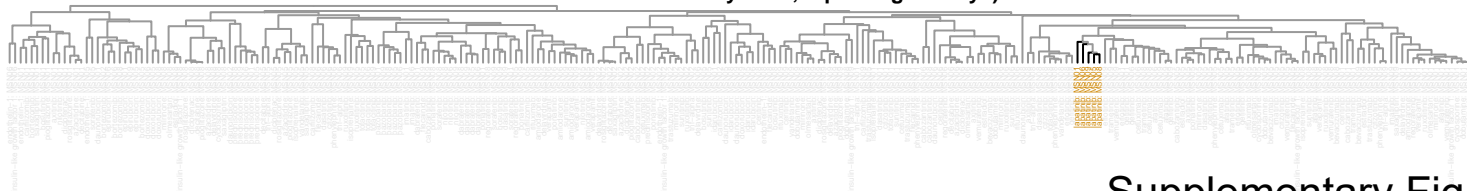
imatinib in decomposed data (F1 score weight: 0.4 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 0.84, top 146 eigenarrays)



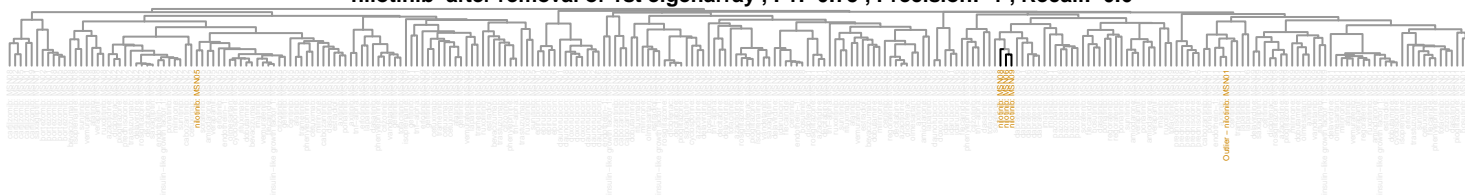
lapatinib after removal of 1st eigenarray , F1: 0.57 , Precision: 1 , Recall: 0.4



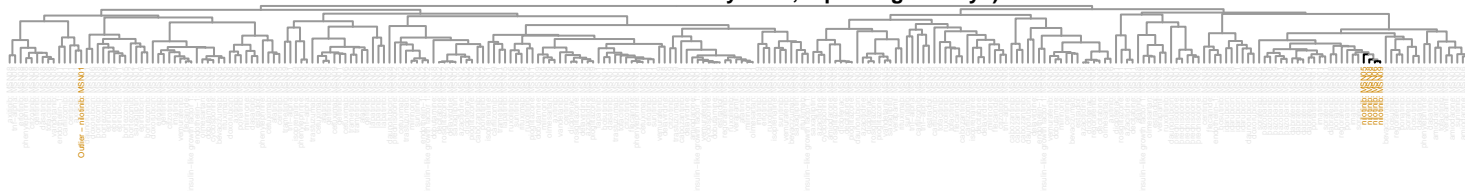
lapatinib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.75, top 37 eigenarrays)



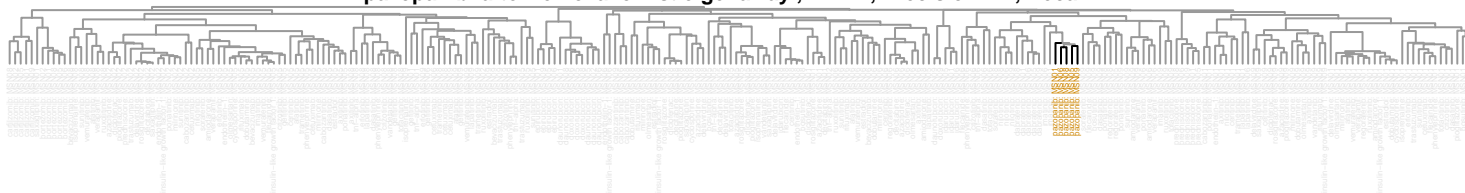
nilotinib after removal of 1st eigenarray , F1: 0.75 , Precision: 1 , Recall: 0.6



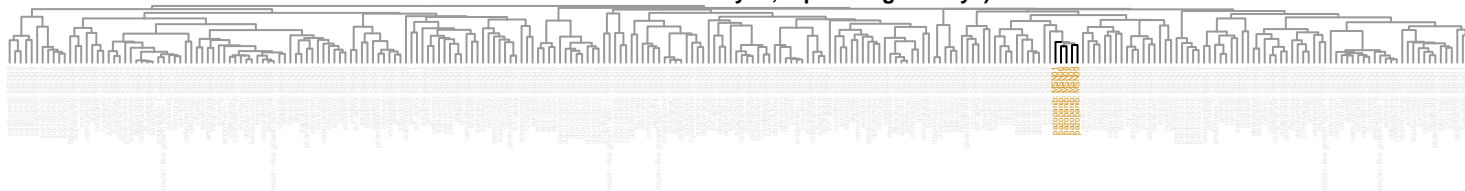
nilotinib in decomposed data (F1 score weight: 0.65 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.77, top 21 eigenarrays)



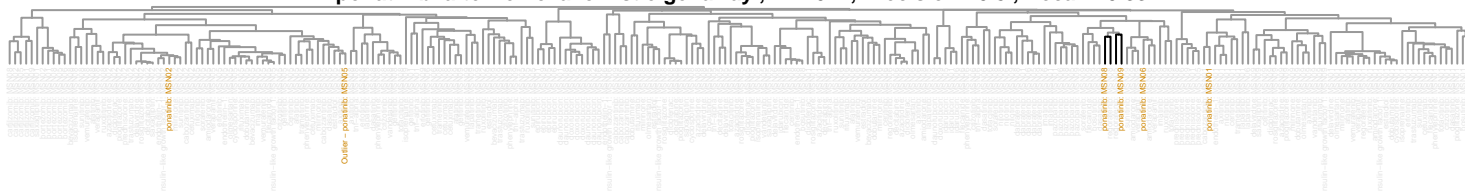
pazopanib after removal of 1st eigenarray , F1: 1 , Precision: 1 , Recall: 1



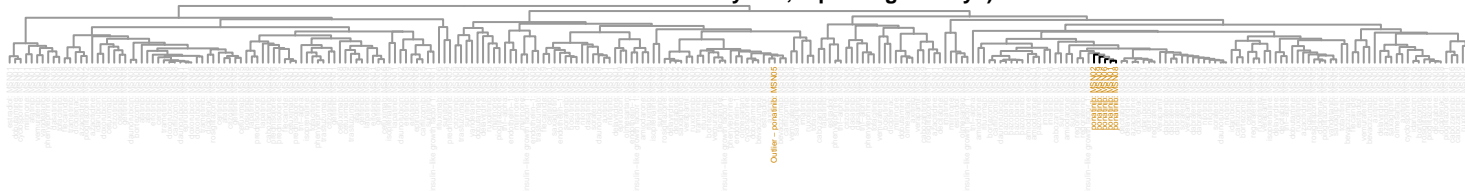
pazopanib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 1, top 266 eigenarrays)



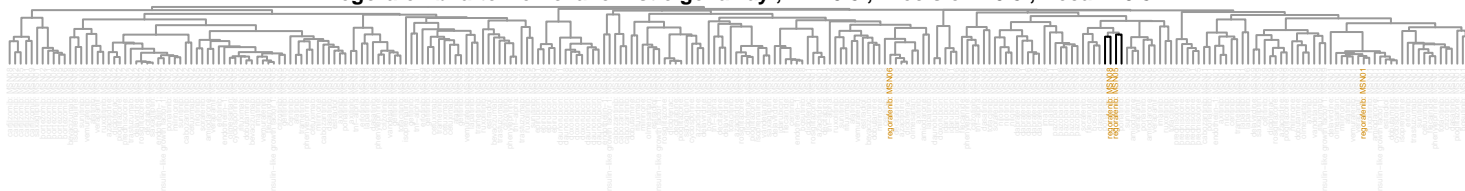
ponatinib after removal of 1st eigenarray , F1: 0.4 , Precision: 0.5 , Recall: 0.33



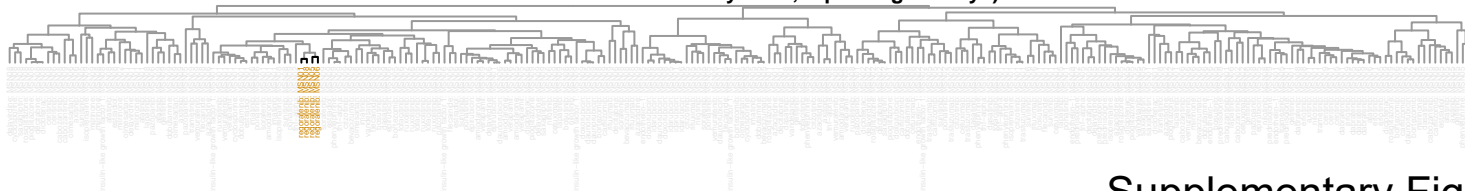
ponatinib in decomposed data (F1 score weight: 0.7 , F1: 0.91, Precision: 1, Recall: 0.83, mediane cosine similarity: 0.4, top 15 eigenarrays)



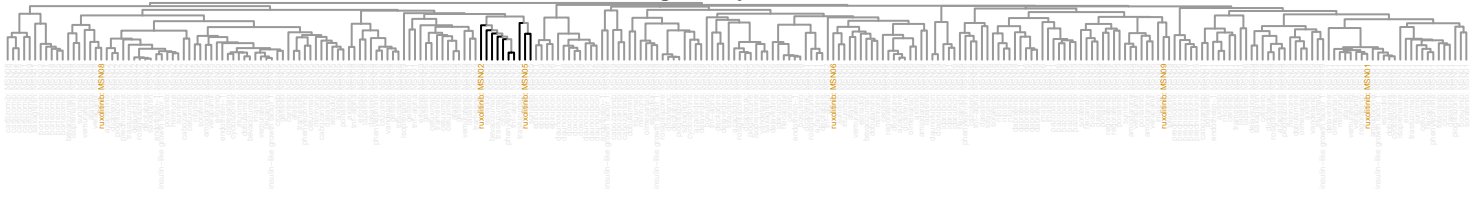
regorafenib after removal of 1st eigenarray , F1: 0.5 , Precision: 0.5 , Recall: 0.5



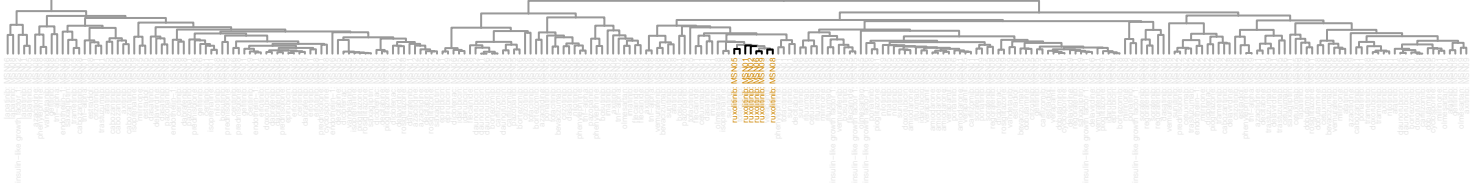
regorafenib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.33, top 16 eigenarrays)



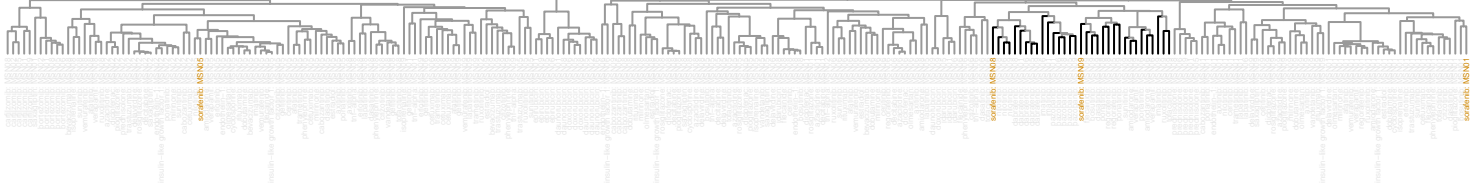
ruxolitinib after removal of 1st eigenarray , F1: 0.25 , Precision: 0.2 , Recall: 0.33



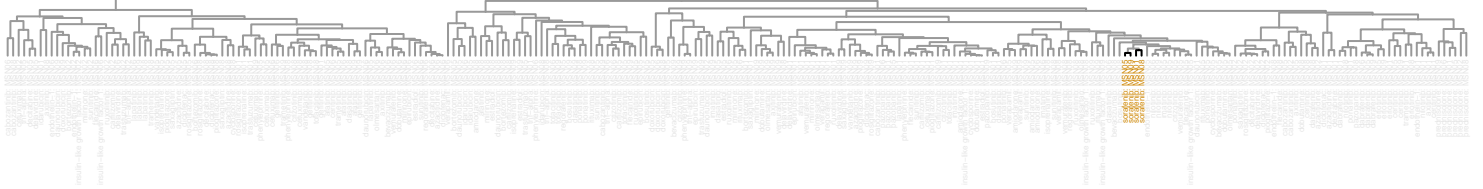
ruxolitinib in decomposed data (F1 score weight: 0.95 , F1: 0.86, Precision: 0.75, Recall: 1, mediane cosine similarity: 0.29, top 12 eigenarrays)



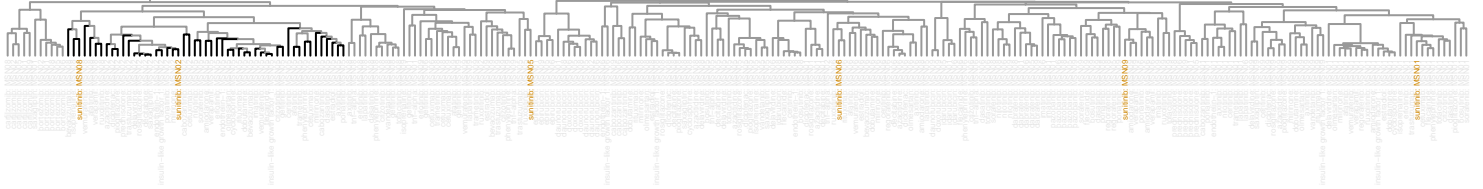
sorafenib after removal of 1st eigenarray , F1: 0.11 , Precision: 0.06 , Recall: 0.5



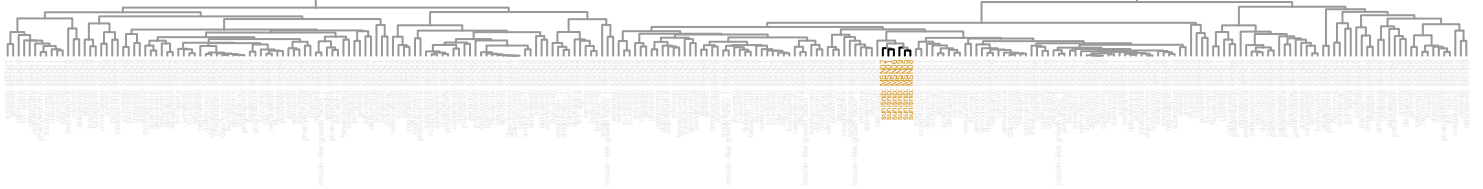
sorafenib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.52, top 19 eigenarrays)



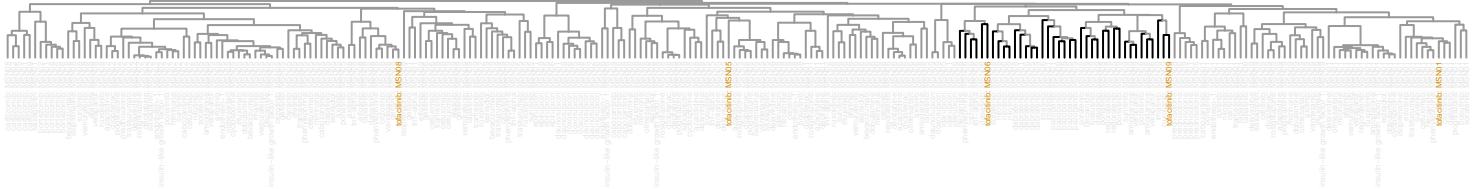
sunitinib after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.33



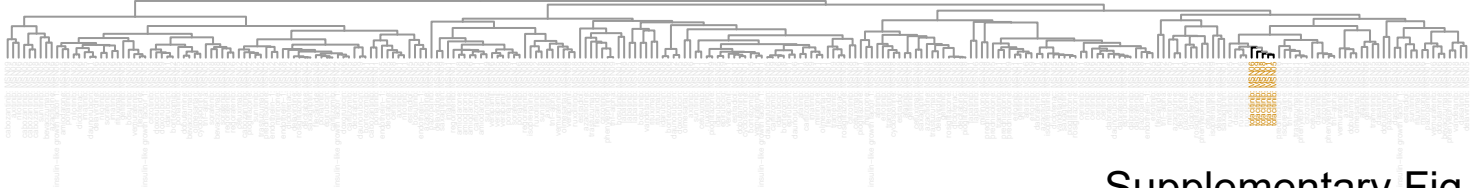
sunitinib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.2, top 14 eigenarrays)



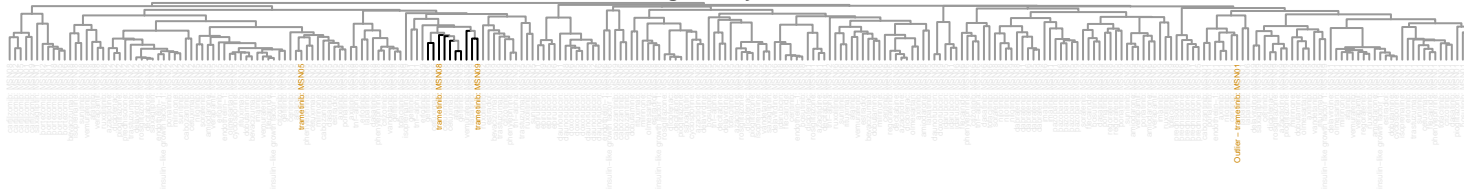
tofacitinib after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



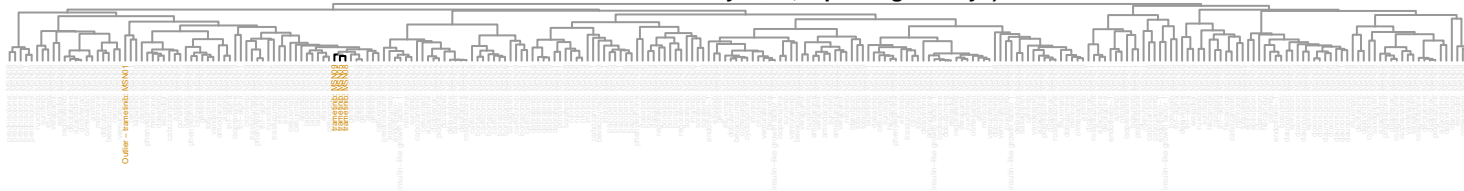
tofacitinib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.37, top 12 eigenarrays)



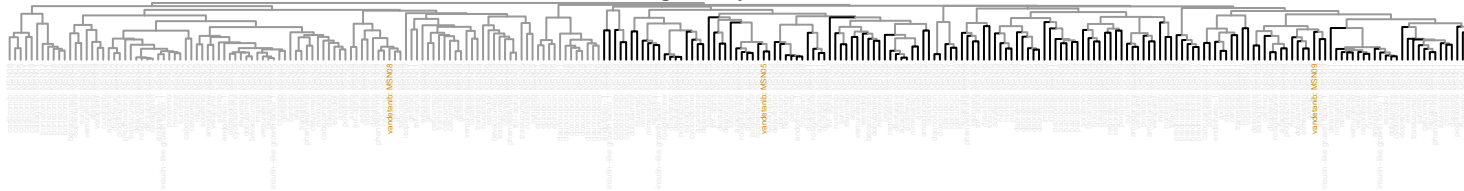
trametinib after removal of 1st eigenarray , F1: 0.29 , Precision: 0.2 , Recall: 0.5



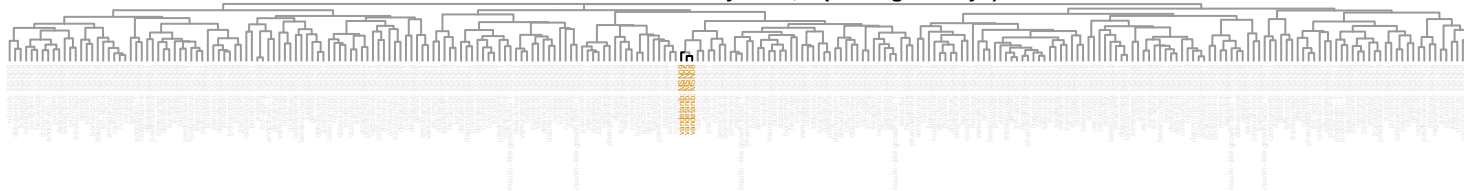
trametinib in decomposed data (F1 score weight: 0.35 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 0.79, top 31 eigenarrays)



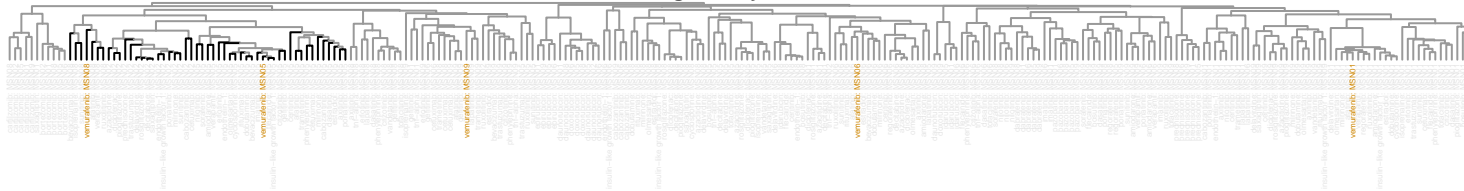
vandetanib after removal of 1st eigenarray , F1: 0.02 , Precision: 0.01 , Recall: 0.67



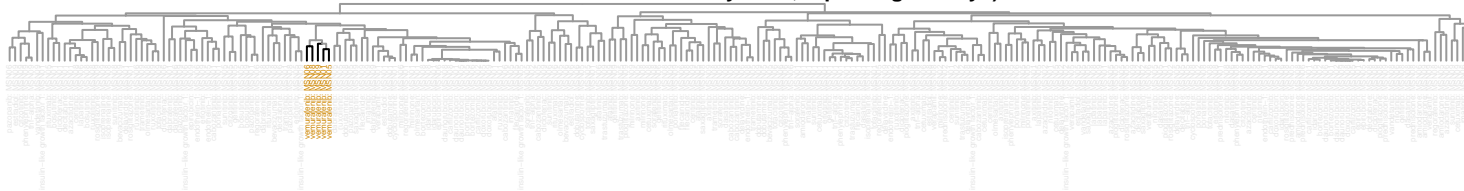
vandetanib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.14, top 16 eigenarrays)



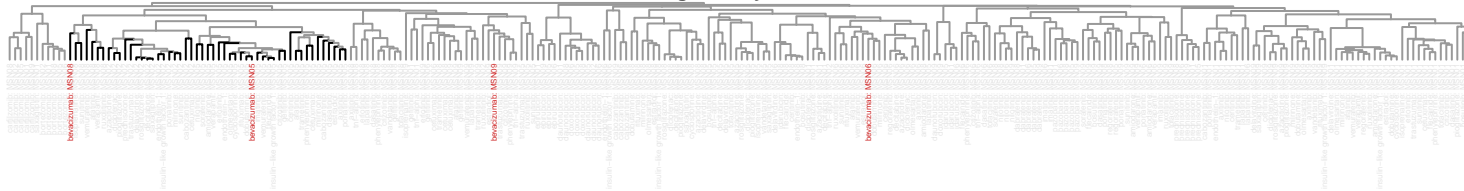
vemurafenib after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.4



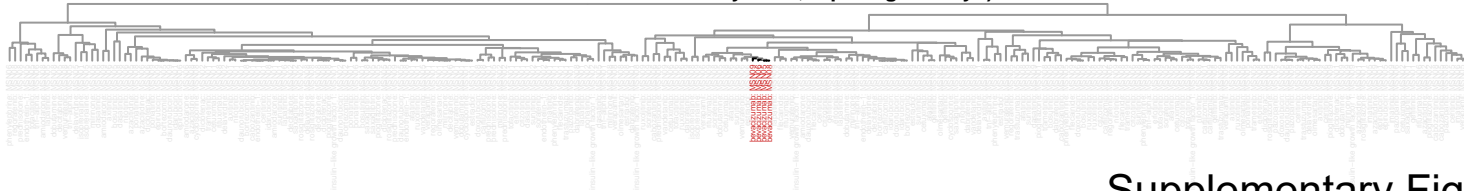
vemurafenib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.21, top 19 eigenarrays)



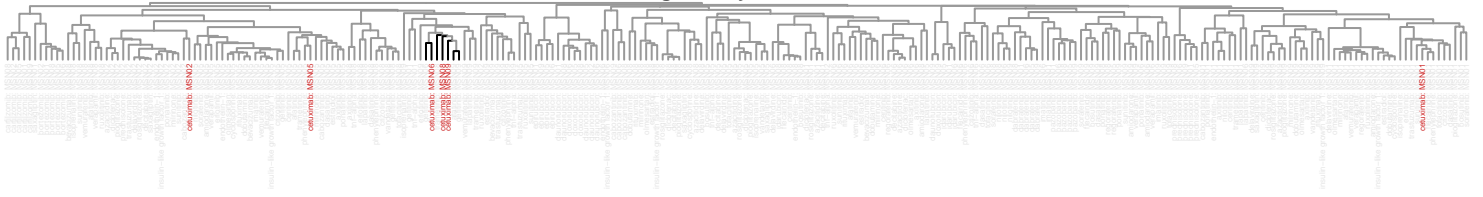
bevacizumab after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.5



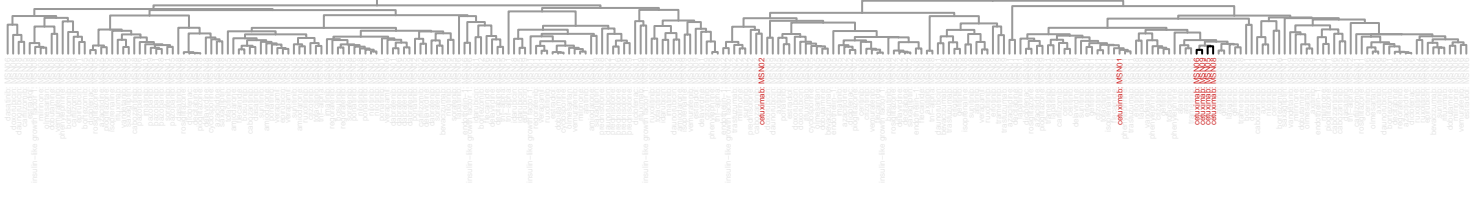
bevacizumab in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.19, top 8 eigenarrays)



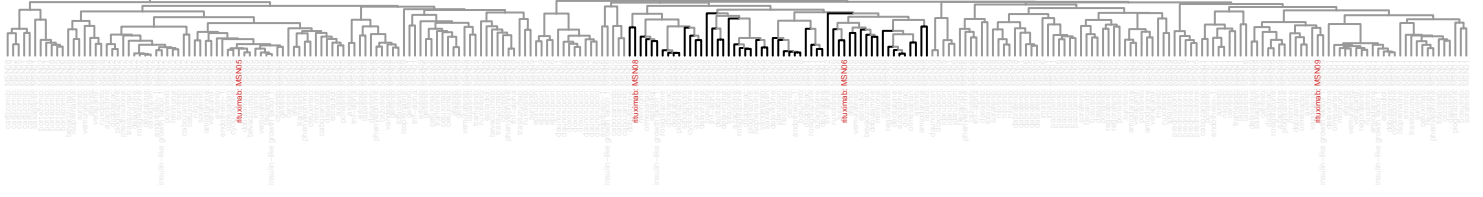
cetuximab after removal of 1st eigenarray , F1: 0.46 , Precision: 0.43 , Recall: 0.5



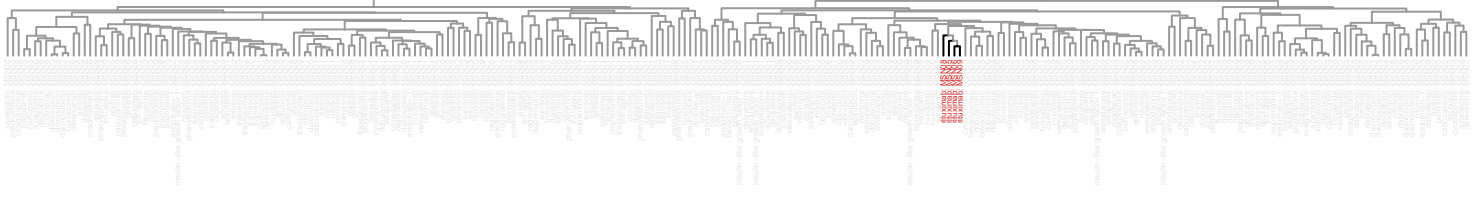
cetuximab in decomposed data (F1 score weight: 0.95 , F1: 0.8, Precision: 1, Recall: 0.67, mediane cosine similarity: 0.43, top 23 eigenarrays)



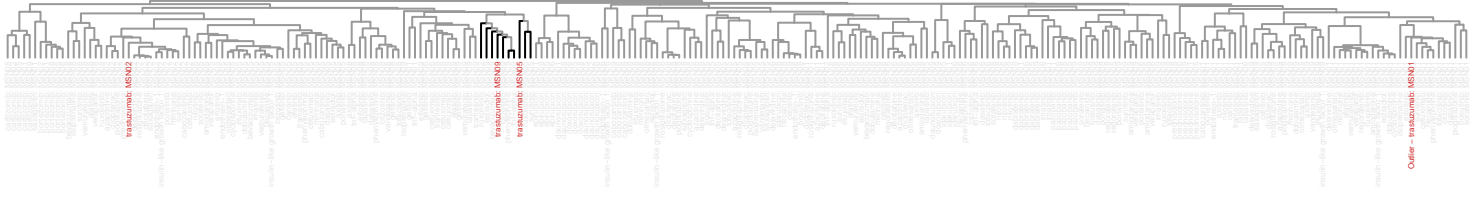
rituximab after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.5



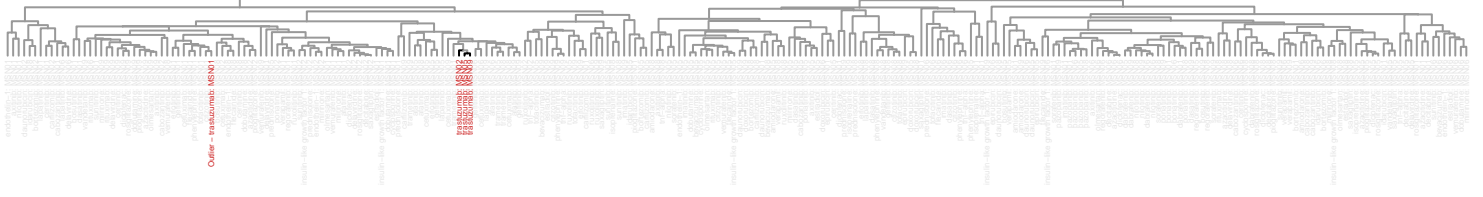
rituximab in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.31, top 44 eigenarrays)



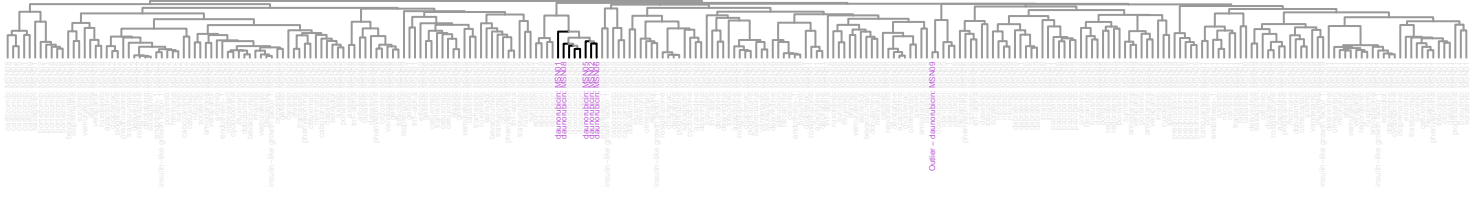
trastuzumab after removal of 1st eigenarray , F1: 0.29 , Precision: 0.2 , Recall: 0.5



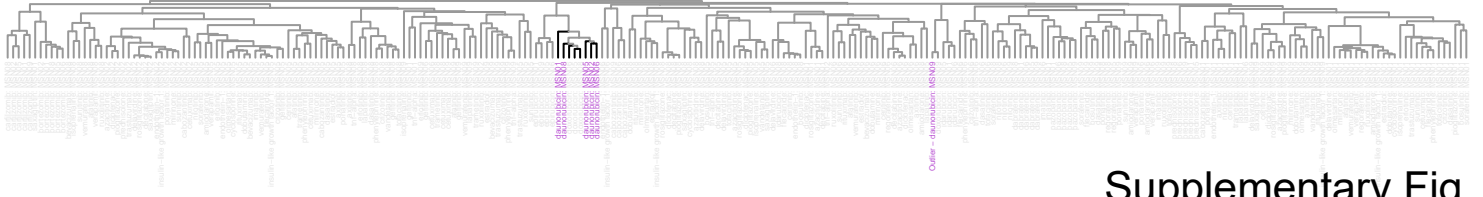
trastuzumab in decomposed data (F1 score weight: 0.65 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 0.41, top 29 eigenarrays)



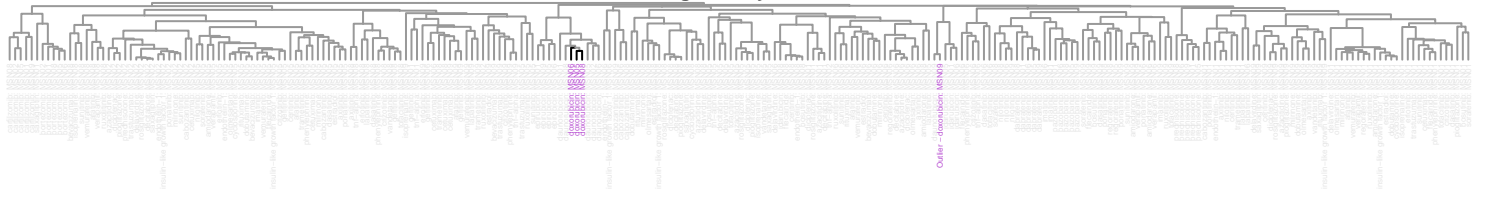
daunorubicin after removal of 1st eigenarray , F1: 0.71 , Precision: 0.62 , Recall: 0.83



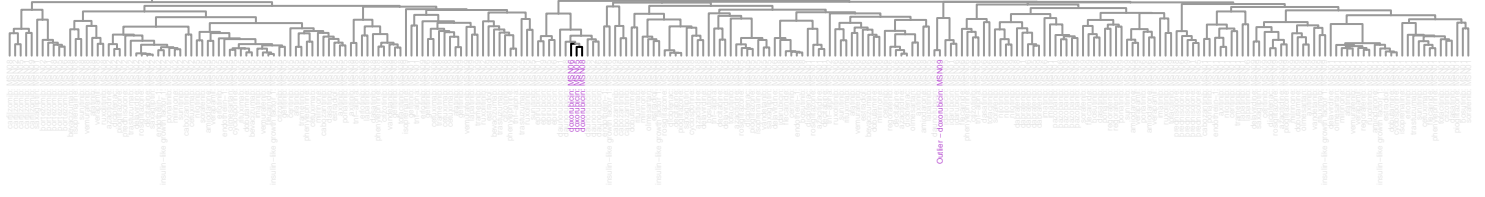
daunorubicin in decomposed data (F1 score weight: 0 , F1: 0.71, Precision: 0.62, Recall: 0.83, mediane cosine similarity: 1, top 266 eigenarrays)



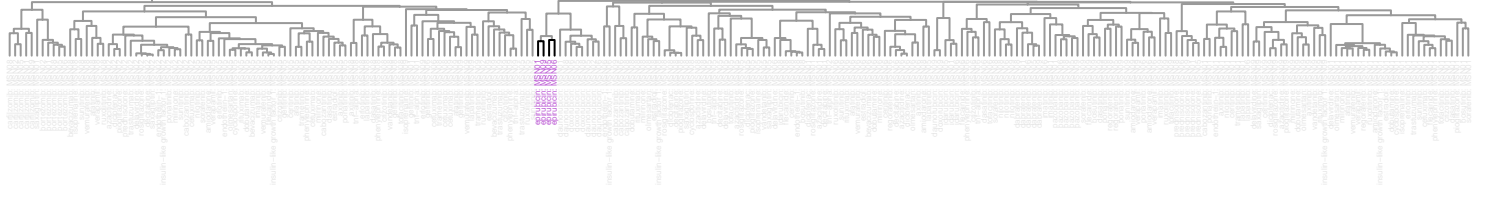
doxorubicin after removal of 1st eigenarray , F1: 0.86 , Precision: 1 , Recall: 0.75



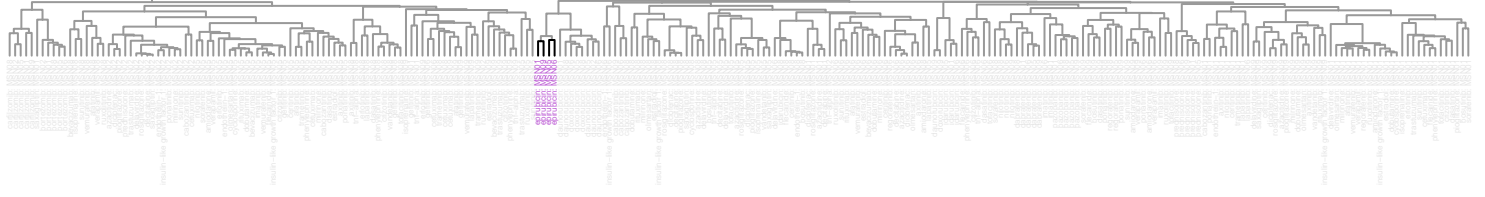
doxorubicin in decomposed data (F1 score weight: 0 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 1, top 266 eigenarrays)



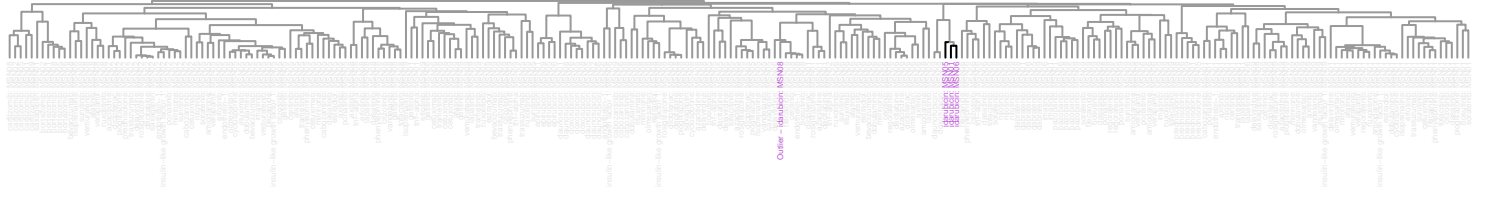
epirubicin after removal of 1st eigenarray , F1: 1 , Precision: 1 , Recall: 1



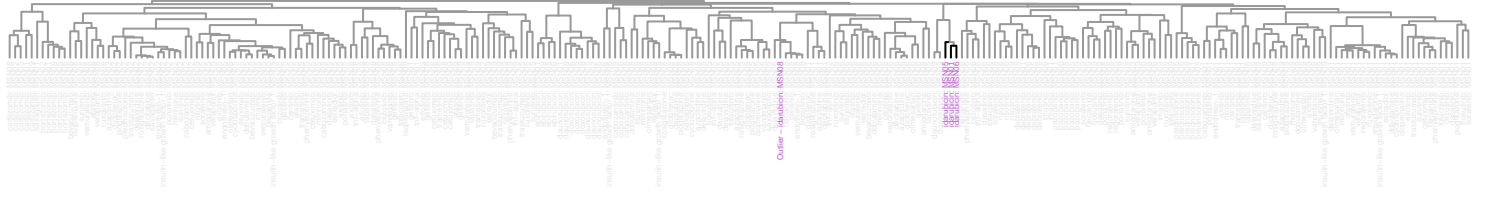
epirubicin in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 1, top 266 eigenarrays)



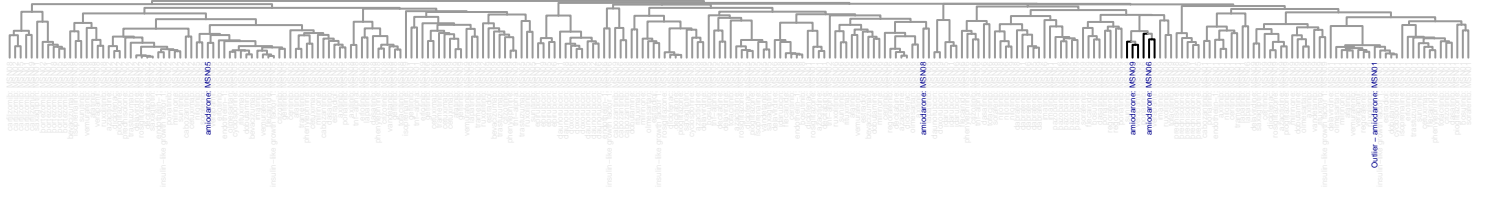
idarubicin after removal of 1st eigenarray , F1: 0.86 , Precision: 1 , Recall: 0.75



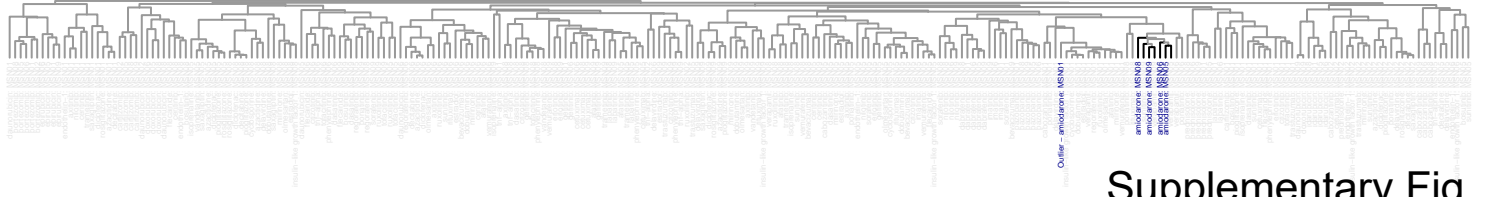
idarubicin in decomposed data (F1 score weight: 0 , F1: 0.86, Precision: 1, Recall: 0.75, mediane cosine similarity: 1, top 266 eigenarrays)



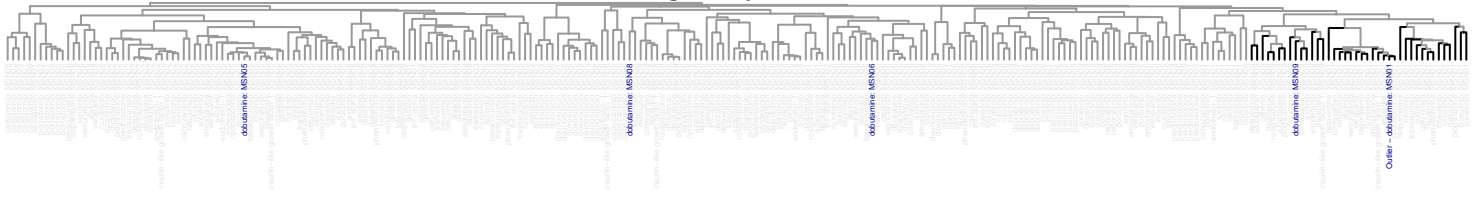
amiodarone after removal of 1st eigenarray , F1: 0.36 , Precision: 0.33 , Recall: 0.4



amiodarone in decomposed data (F1 score weight: 0.5 , F1: 0.67, Precision: 0.57, Recall: 0.8, mediane cosine similarity: 0.87, top 161 eigenarrays)



dobutamine after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



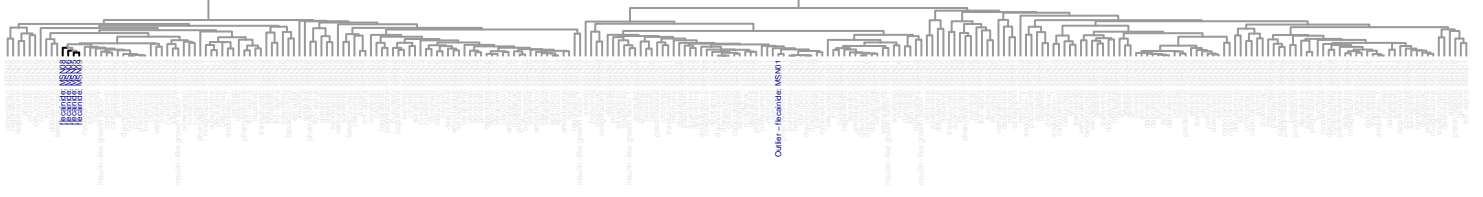
dobutamine in decomposed data (F1 score weight: 0.55 , F1: 0.8, Precision: 0.8, Recall: 0.8, mediane cosine similarity: 0.29, top 31 eigenarrays)



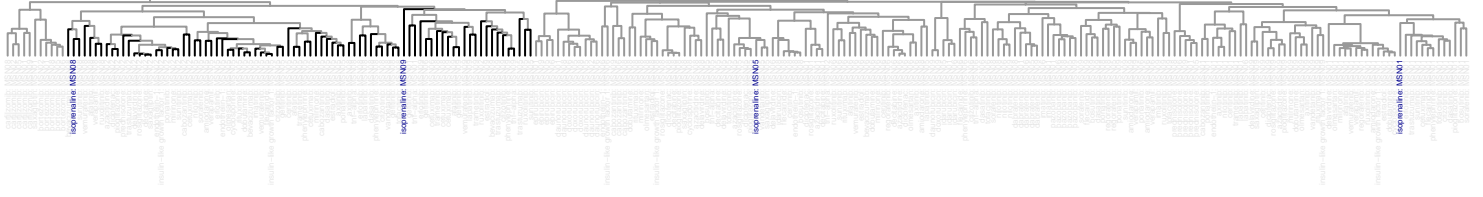
flecainide after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



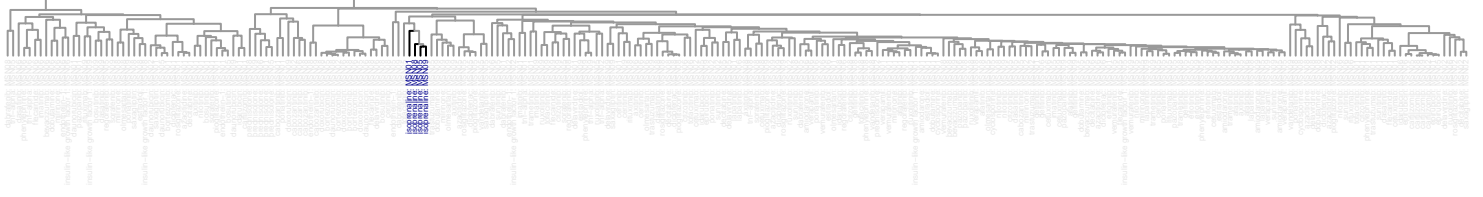
flecainide in decomposed data (F1 score weight: 0.55 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.21, top 24 eigenarrays)



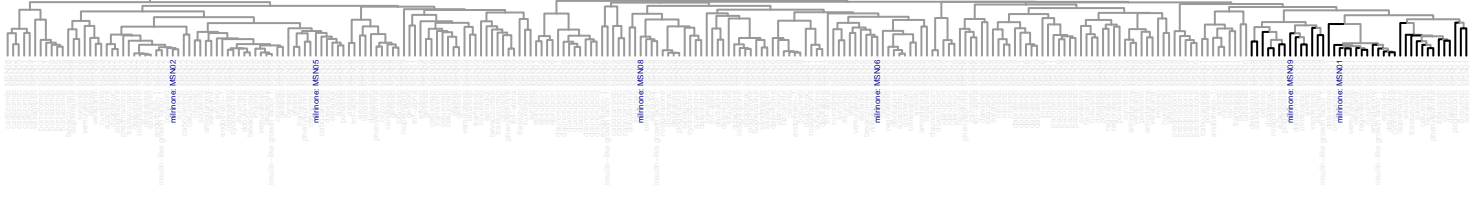
isoprenaline after removal of 1st eigenarray , F1: 0.04 , Precision: 0.02 , Recall: 0.5



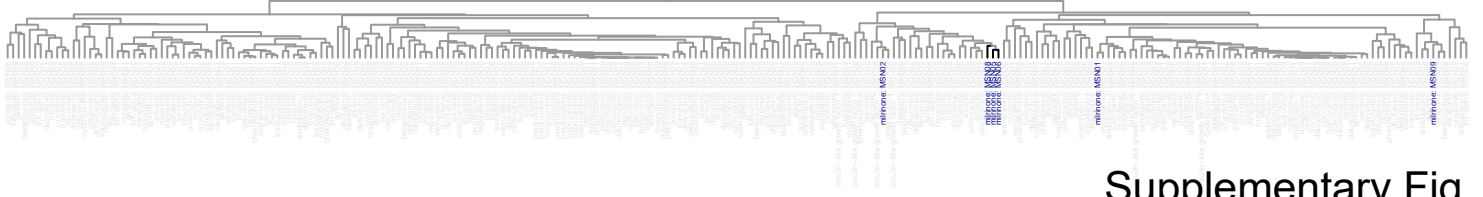
isoprenaline in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.5, top 34 eigenarrays)



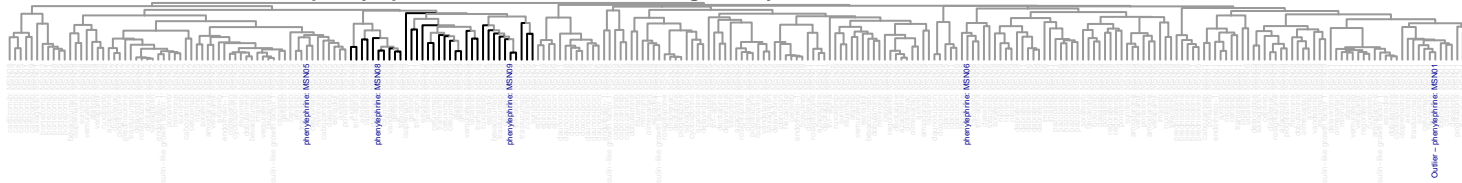
milrinone after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.33



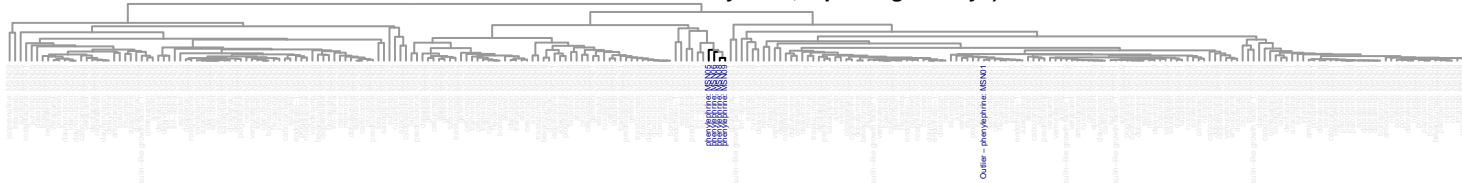
milrinone in decomposed data (F1 score weight: 0.95 , F1: 0.67, Precision: 1, Recall: 0.5, mediane cosine similarity: 0.12, top 14 eigenarrays)



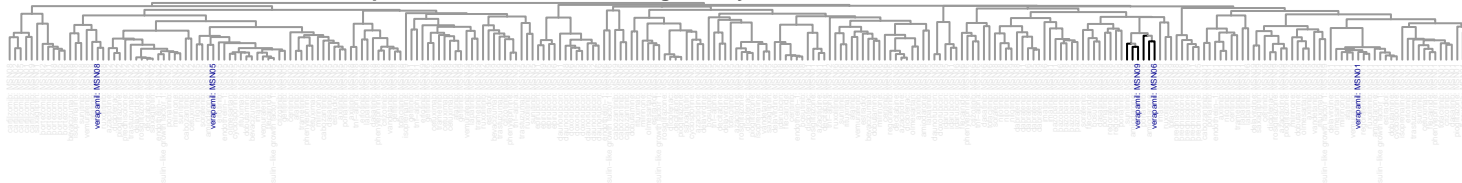
phenylephrine after removal of 1st eigenarray , F1: 0.1 , Precision: 0.06 , Recall: 0.4



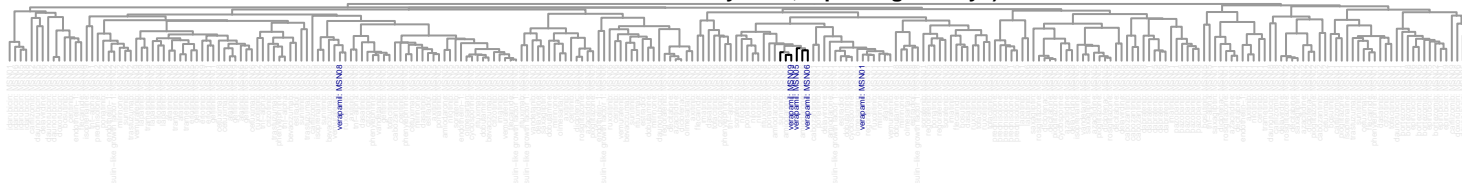
phenylephrine in decomposed data (F1 score weight: 0.55 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.14, top 13 eigenarrays)



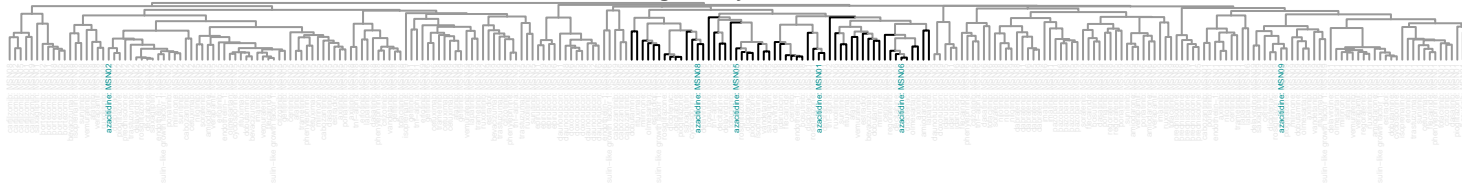
verapamil after removal of 1st eigenarray , F1: 0.36 , Precision: 0.33 , Recall: 0.4



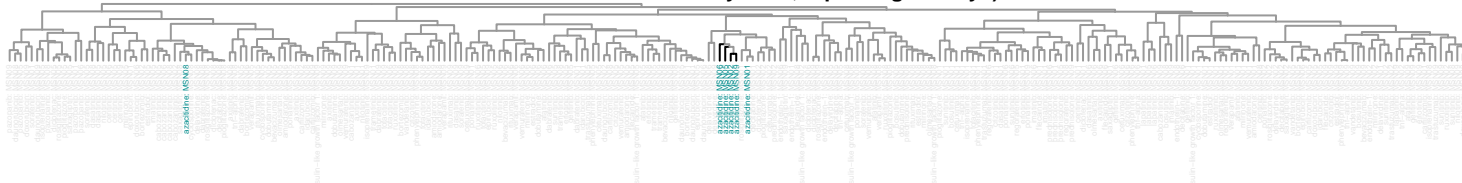
verapamil in decomposed data (F1 score weight: 0.95 , F1: 0.55, Precision: 0.5, Recall: 0.6, mediane cosine similarity: 0.83, top 91 eigenarrays)



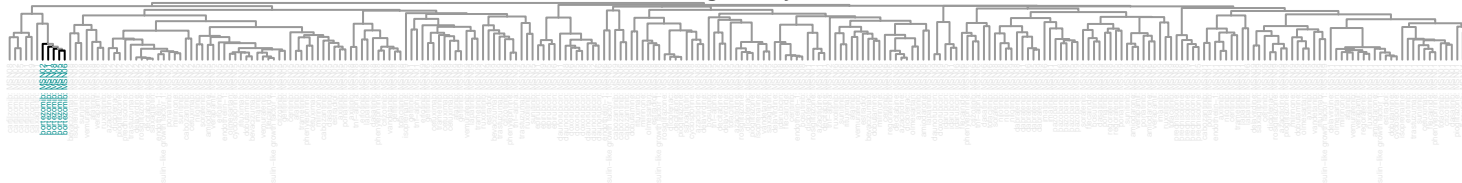
azacitidine after removal of 1st eigenarray , F1: 0.13 , Precision: 0.07 , Recall: 0.67



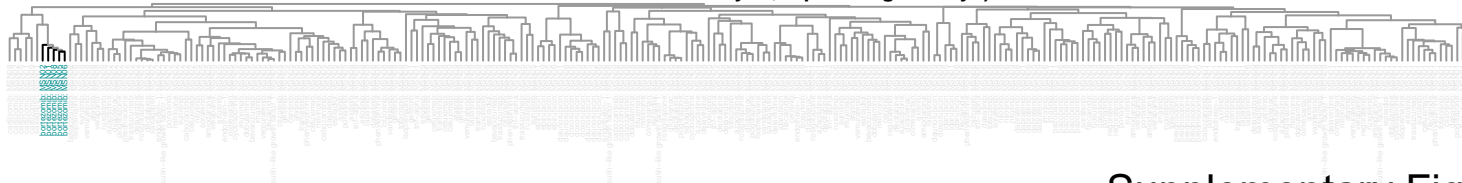
azacitidine in decomposed data (F1 score weight: 0.95 , F1: 0.8, Precision: 1, Recall: 0.67, mediane cosine similarity: 0.29, top 15 eigenarrays)



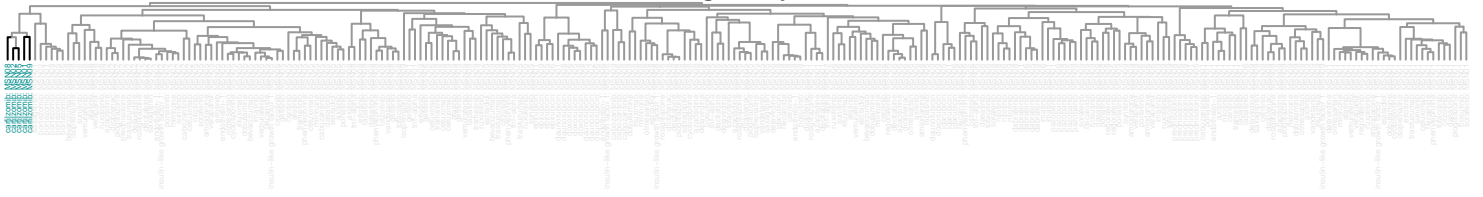
bortezomib after removal of 1st eigenarray , F1: 1 , Precision: 1 , Recall: 1



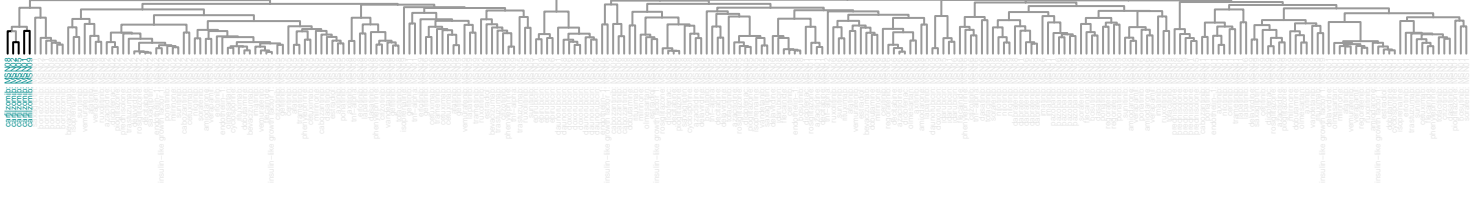
bortezomib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 1, top 266 eigenarrays)



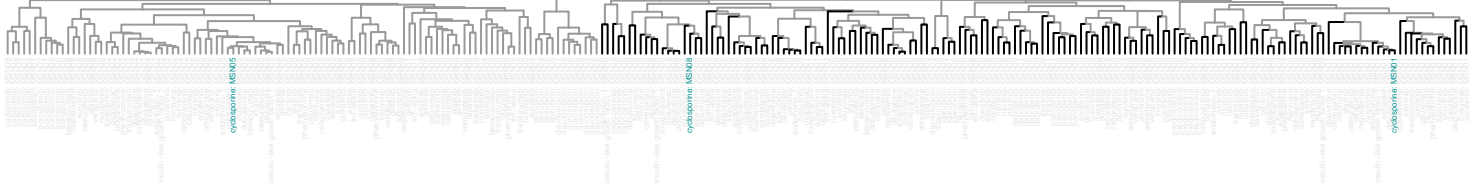
carfilzomib after removal of 1st eigenarray , F1: 1 , Precision: 1 , Recall: 1



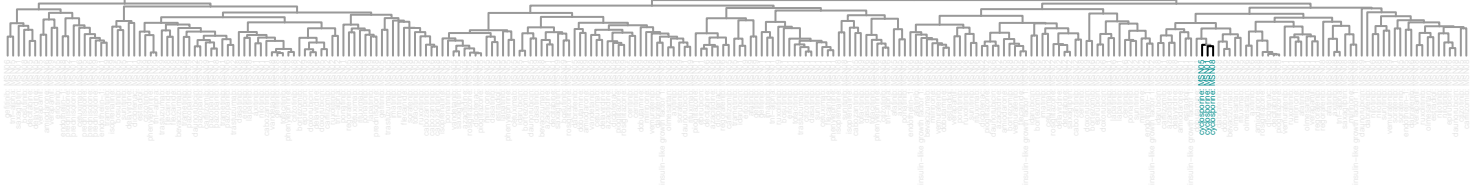
carfilzomib in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 1, top 266 eigenarrays)



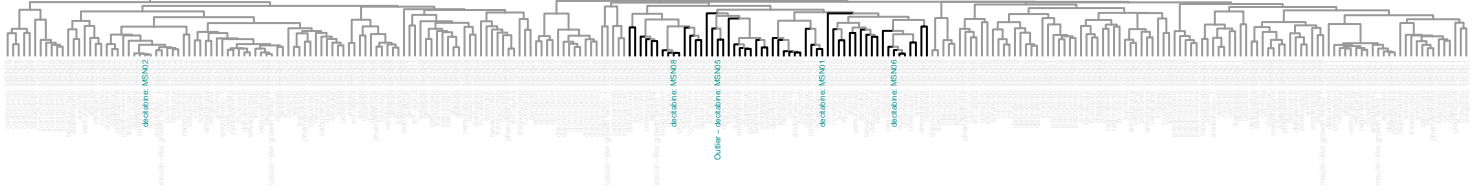
cyclosporine after removal of 1st eigenarray , F1: 0.02 , Precision: 0.01 , Recall: 0.67



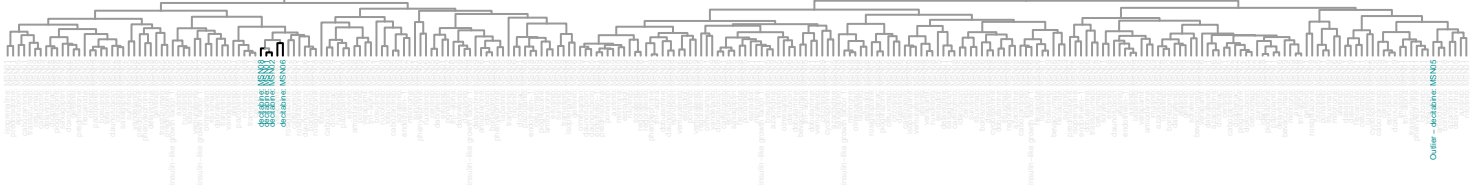
cyclosporine in decomposed data (F1 score weight: 0.95 , F1: 1, Precision: 1, Recall: 1, mediane cosine similarity: 0.22, top 34 eigenarrays)



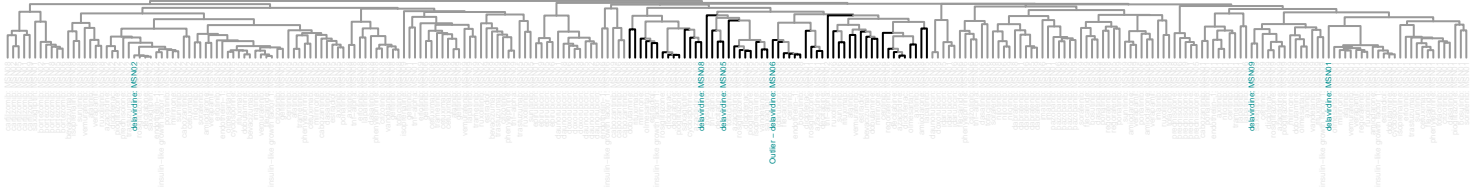
decitabine after removal of 1st eigenarray , F1: 0.13 , Precision: 0.07 , Recall: 0.8



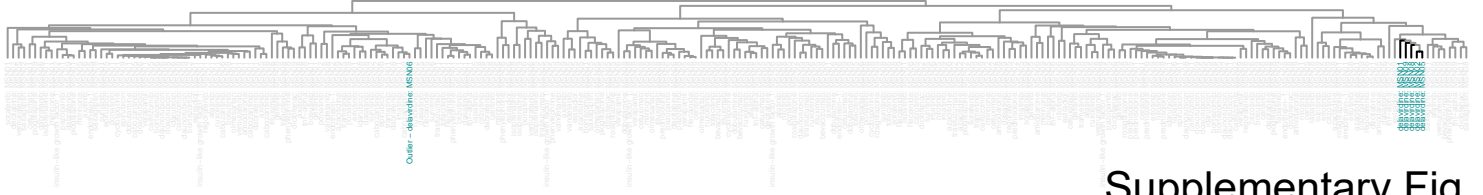
decitabine in decomposed data (F1 score weight: 0.65 , F1: 0.8, Precision: 0.8, Recall: 0.8, mediane cosine similarity: 0.09, top 12 eigenarrays)



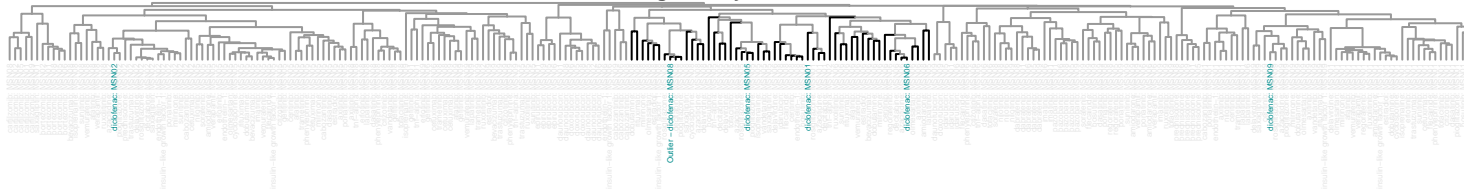
delavirdine after removal of 1st eigenarray , F1: 0.1 , Precision: 0.05 , Recall: 0.5



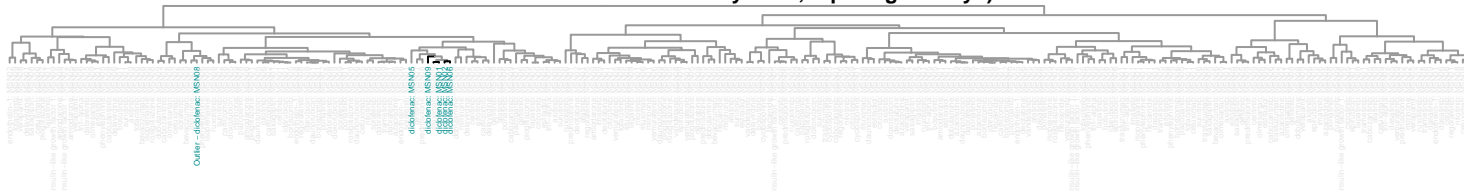
delavirdine in decomposed data (F1 score weight: 0.55 , F1: 0.91, Precision: 1, Recall: 0.83, mediane cosine similarity: 0.13, top 14 eigenarrays)



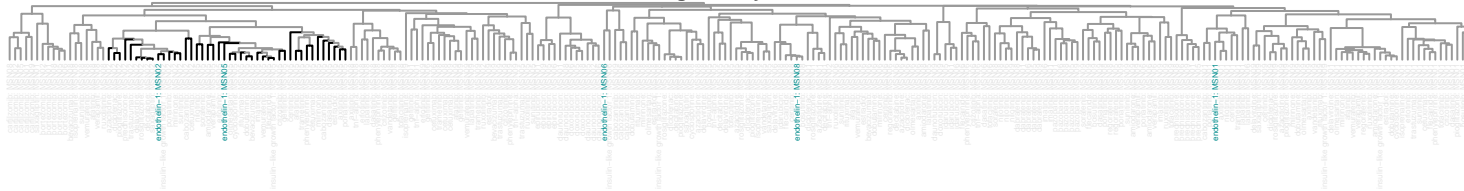
diclofenac after removal of 1st eigenarray , F1: 0.13 , Precision: 0.07 , Recall: 0.67



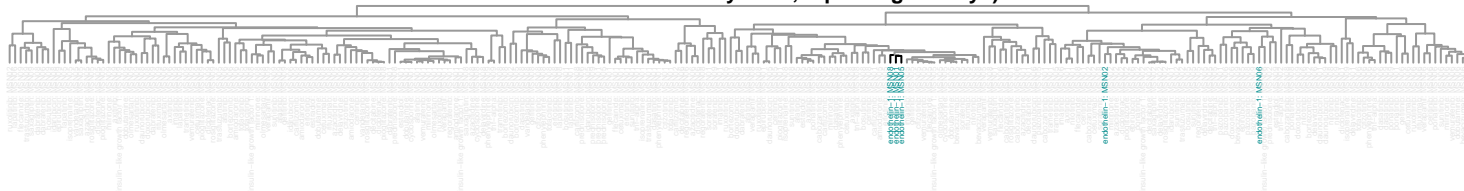
diclofenac in decomposed data (F1 score weight: 0.65 , F1: 0.73, Precision: 0.8, Recall: 0.67, mediane cosine similarity: 0.04, top 6 eigenarrays)



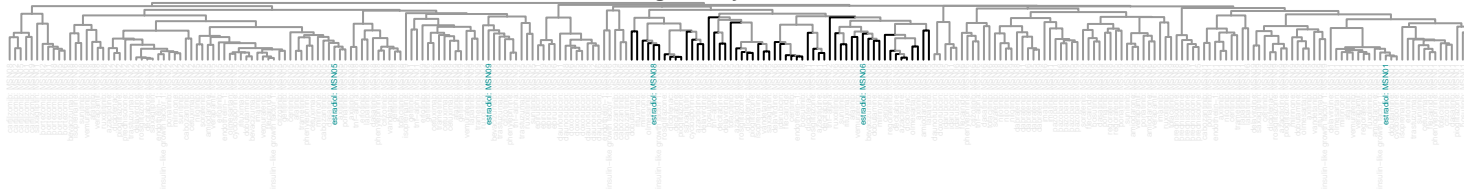
endothelin-1 after removal of 1st eigenarray , F1: 0.08 , Precision: 0.05 , Recall: 0.4



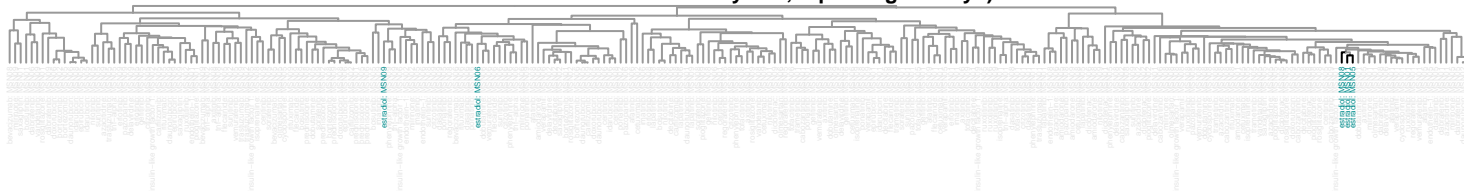
endothelin-1 in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, mediane cosine similarity: 0.29, top 21 eigenarrays)



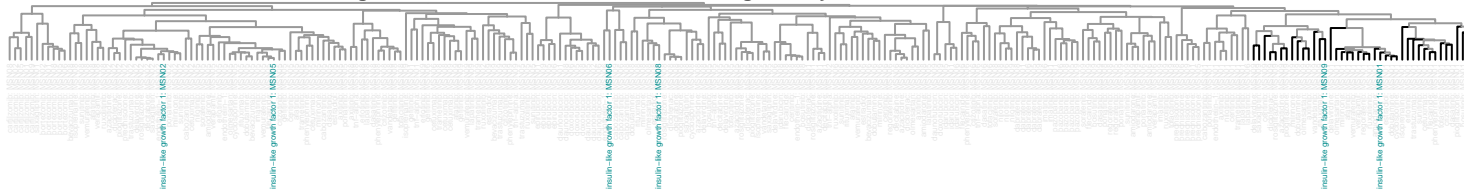
estradiol after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.4



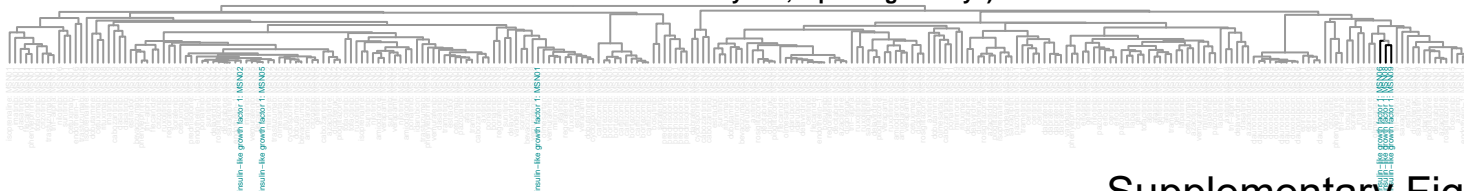
estradiol in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, mediane cosine similarity: 0.3, top 34 eigenarrays)



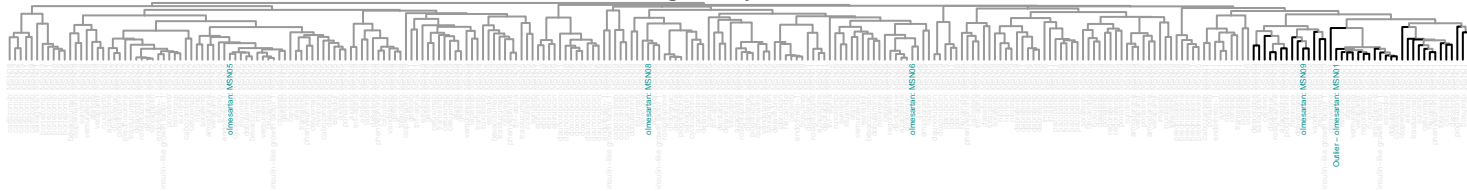
insulin-like growth factor 1 after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.33



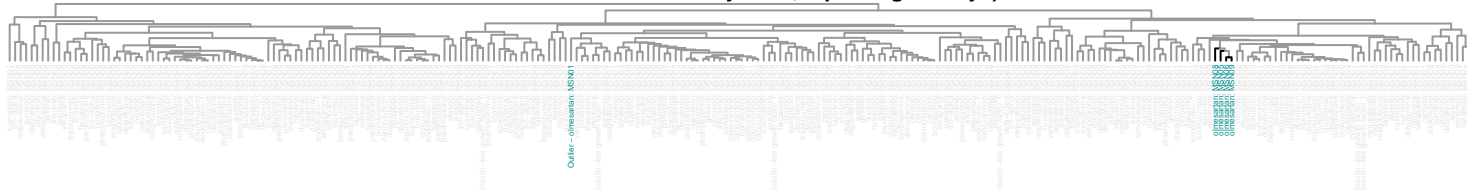
insulin-like growth factor 1 in decomposed data (F1 score weight: 0.95 , F1: 0.67, Precision: 1, Recall: 0.5, mediane cosine similarity: 0.5, top 63 eigenarrays)



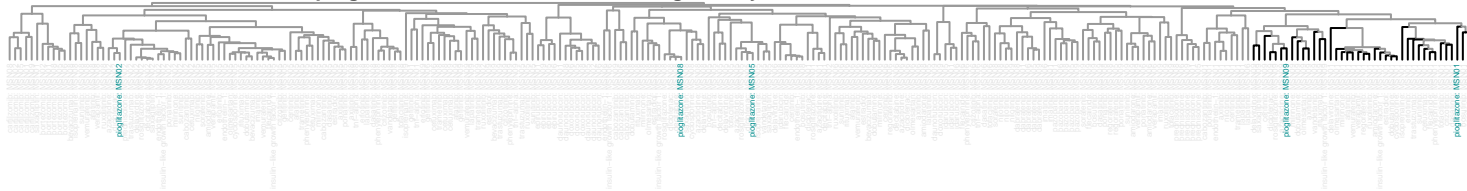
olmesartan after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



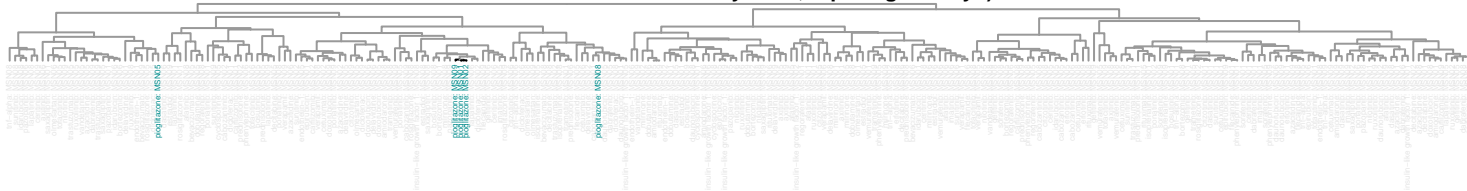
olmesartan in decomposed data (F1 score weight: 0.55 , F1: 0.89, Precision: 1, Recall: 0.8, mediane cosine similarity: 0.15, top 17 eigenarrays)



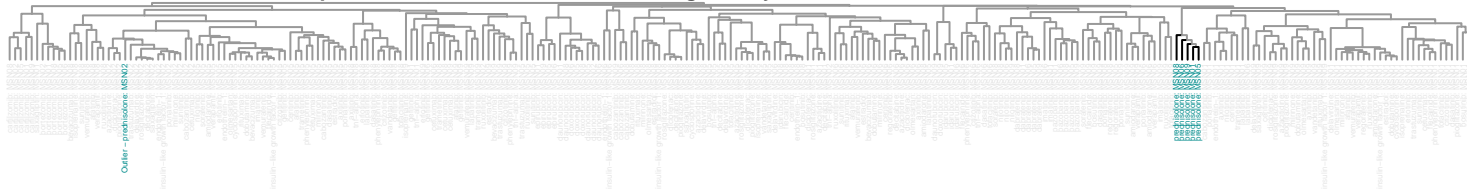
pioglitazone after removal of 1st eigenarray , F1: 0.09 , Precision: 0.05 , Recall: 0.4



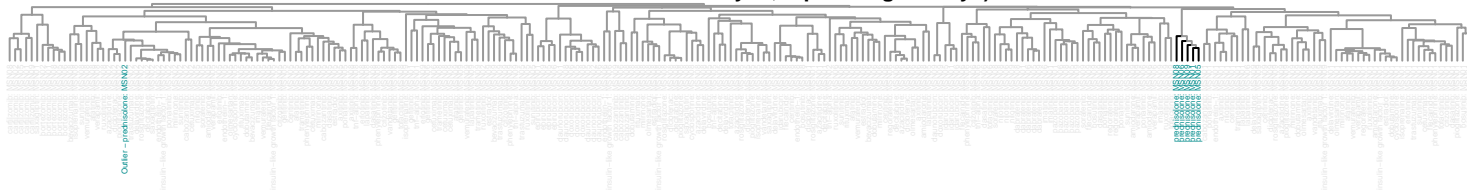
pioglitazone in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, mediane cosine similarity: 0.06, top 8 eigenarrays)



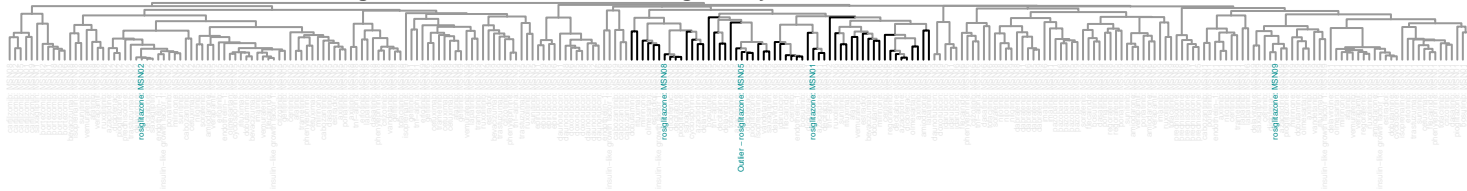
prednisolone after removal of 1st eigenarray , F1: 0.91 , Precision: 1 , Recall: 0.83



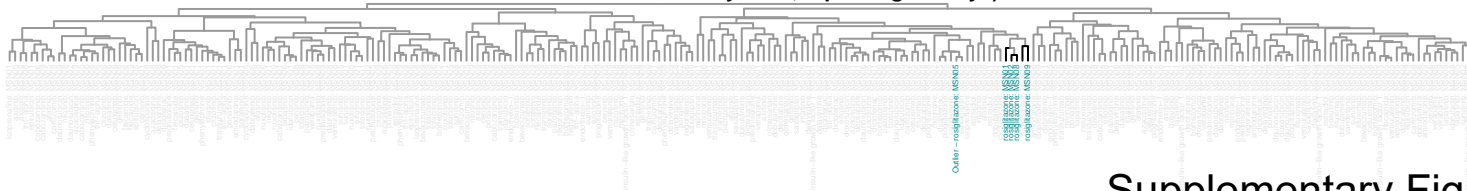
prednisolone in decomposed data (F1 score weight: 0 , F1: 0.91, Precision: 1, Recall: 0.83, mediane cosine similarity: 1, top 266 eigenarrays)



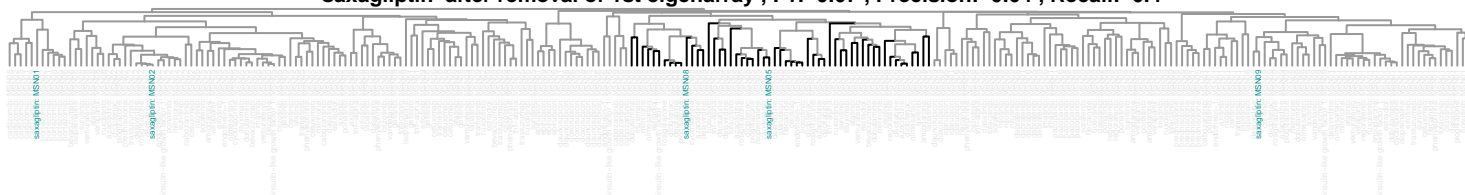
rosiglitazone after removal of 1st eigenarray , F1: 0.1 , Precision: 0.05 , Recall: 0.6



rosiglitazone in decomposed data (F1 score weight: 0.6 , F1: 0.8, Precision: 0.8, Recall: 0.8, mediane cosine similarity: 0.16, top 17 eigenarrays)



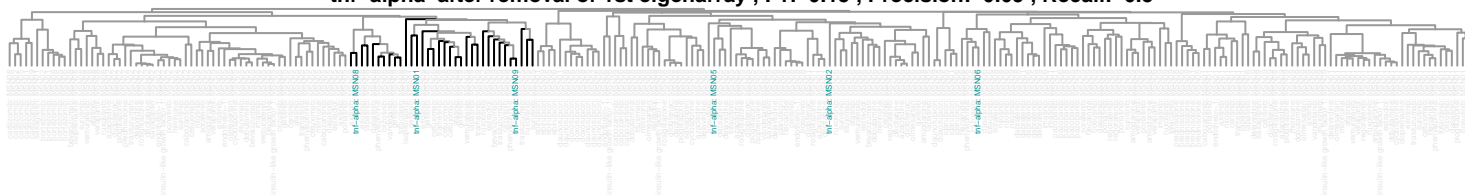
saxagliptin after removal of 1st eigenarray , F1: 0.07 , Precision: 0.04 , Recall: 0.4



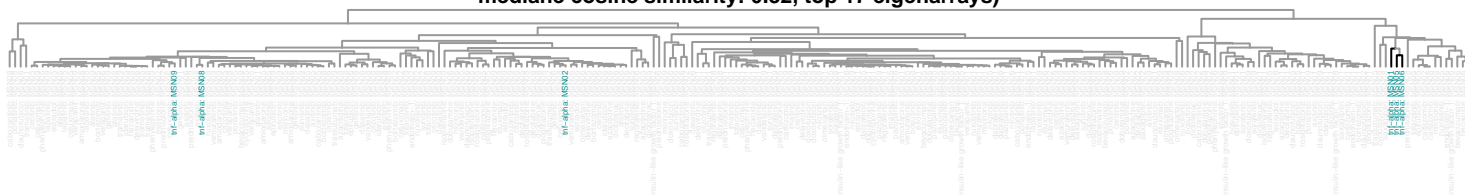
saxagliptin in decomposed data (F1 score weight: 0.95 , F1: 0.75, Precision: 1, Recall: 0.6, median cosine similarity: 0.07, top 5 eigenarrays)



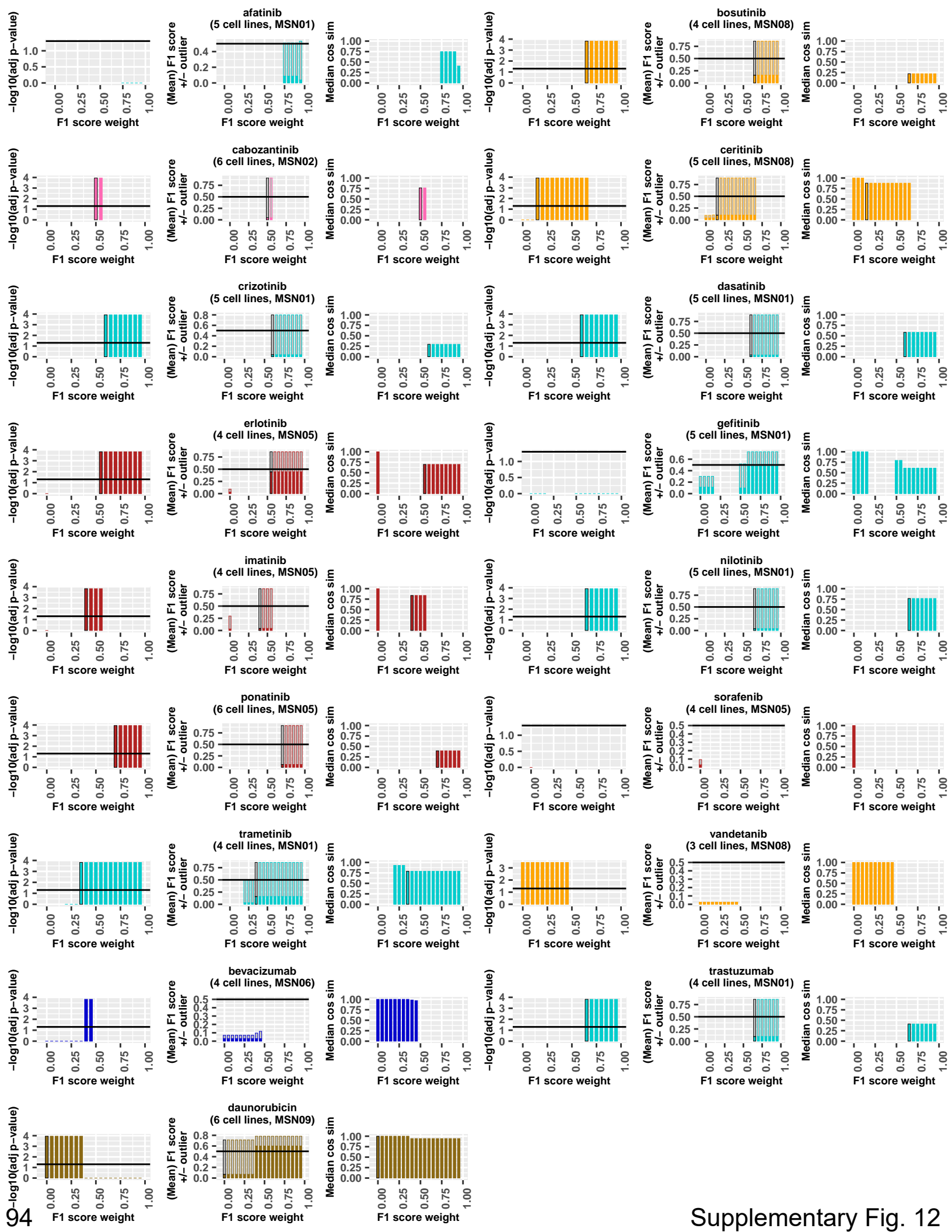
tnf-alpha after removal of 1st eigenarray , F1: 0.15 , Precision: 0.09 , Recall: 0.5

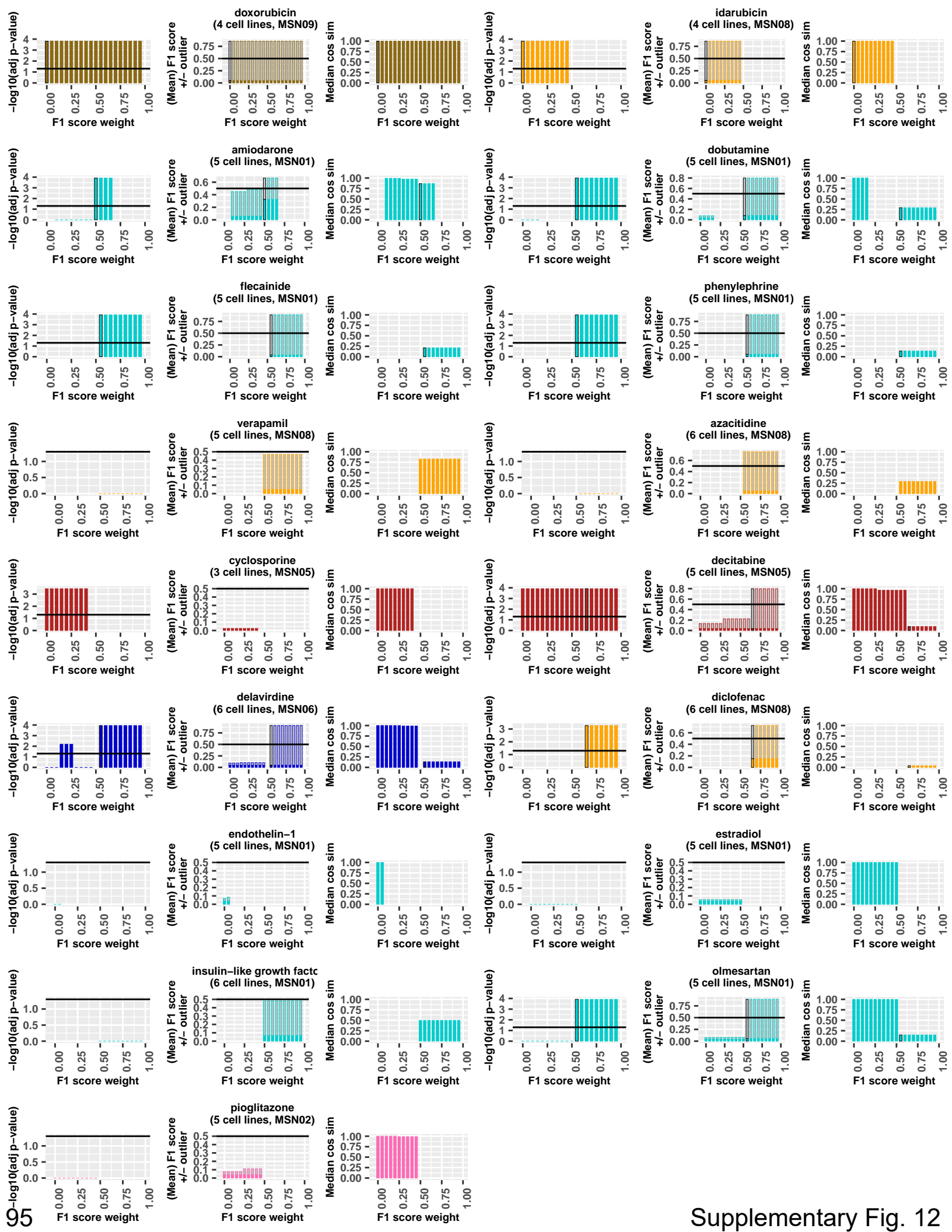


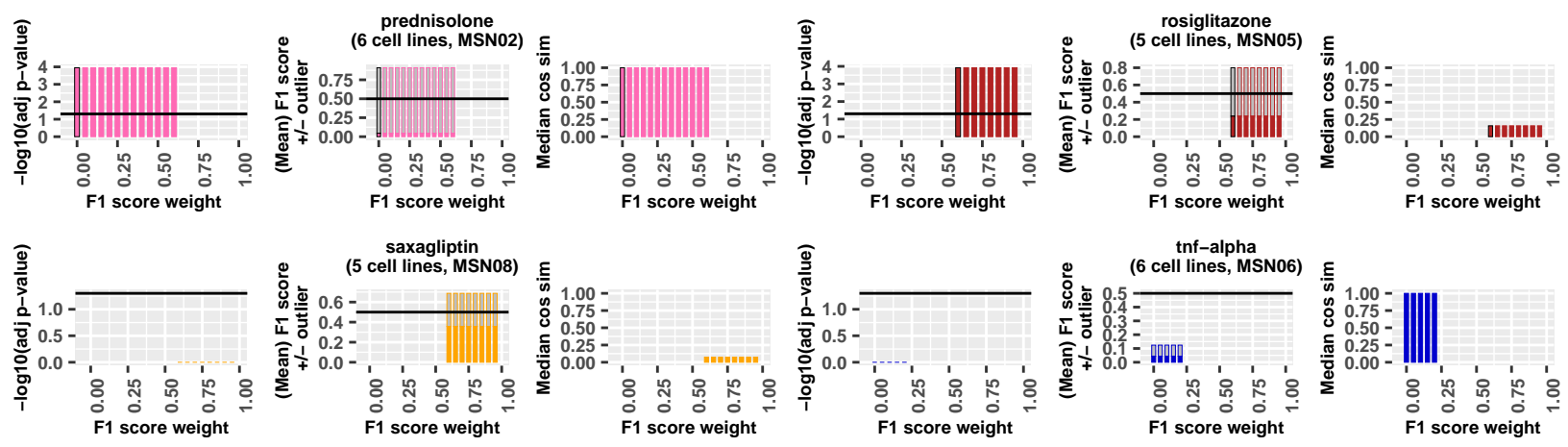
tnf-alpha in decomposed data (F1 score weight: 0.95 , F1: 0.67, Precision: 1, Recall: 0.5, median cosine similarity: 0.32, top 17 eigenarrays)



Supplementary Figure 11. Clustering results for each drug after removal of the first eigenarray and in the final drug-selective subspaces. Clusters with the highest F1 scores are labeled black. Small molecule kinase inhibitors, monoclonal antibodies, anthracyclines, cardiac acting and non-cardiac acting drugs are labeled orange, red, purple, blue and gray-blue. The cluster dendrogram shown in Suppl. Figure 10D is part of this figure set as well.



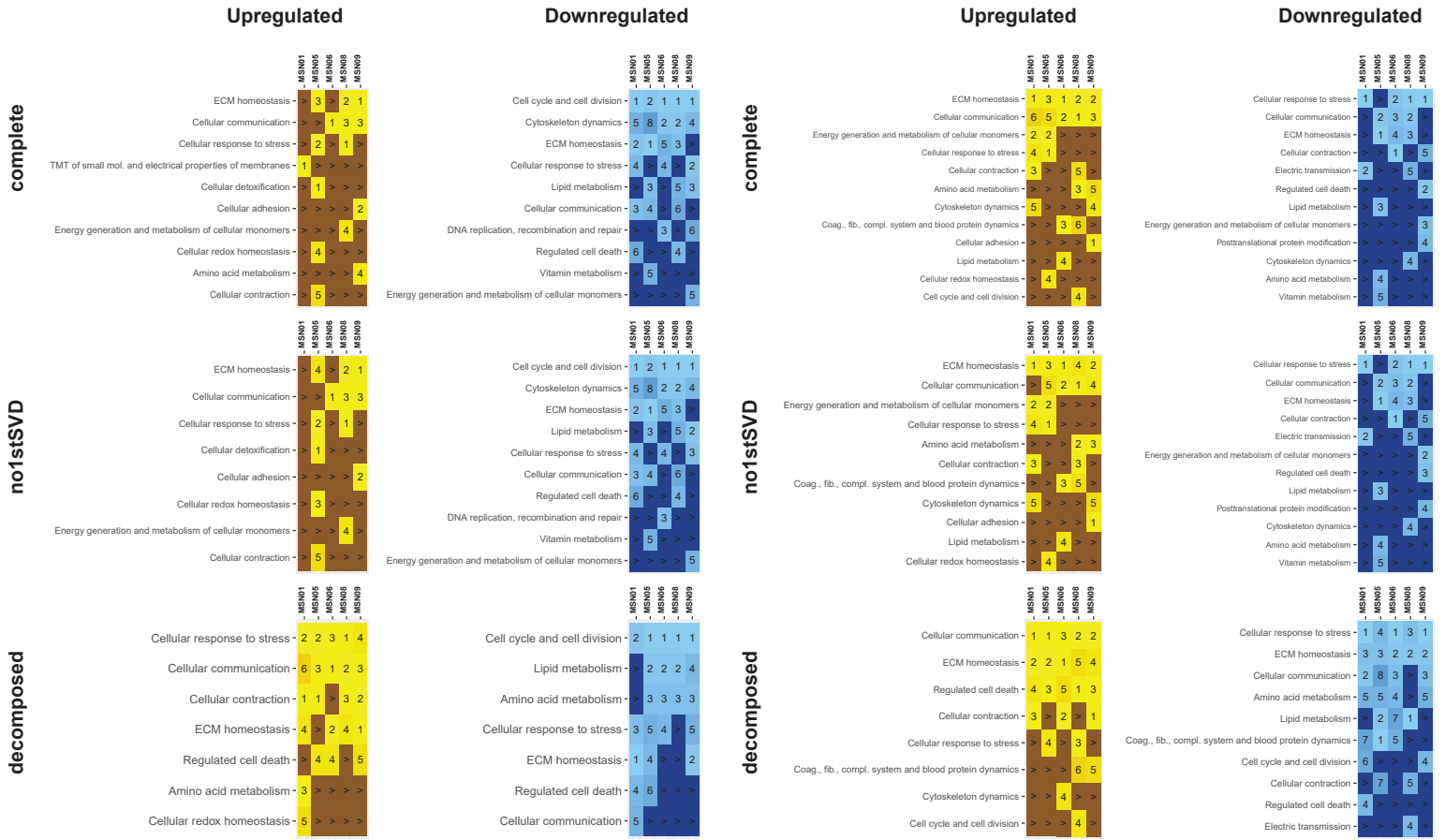




Supplementary Figure 12. Identification of outlier responses. For each drug, we screened all 20 potential drug-selective subspaces (that are defined by different F1 score weights) for subspaces where one cell line/drug combination shows a different transcriptomic response to the drug of interest than all other cell line/drug combinations. As shown for an example in Suppl. Figure 10D, we calculated cell line/drug combination-specific F1 scores, using the same approach described above, except that the cell line/drug combination of interest has to be part of the corresponding cluster. Dixon's Q test of cell line/drug combination-specific F1 scores was used to identify outliers (adj. p-value = 0.05). Identified outliers were only accepted, if the mean F1 score of all non-outlier cell line/drug combinations was larger than 0.5 (empty bars in middle figure). We selected that subspace with the most significant adjusted p-value as the final drug-selective subspace (black frame). Mean F1 scores of all non-outlier cell line/drug combinations and decreasing F1 score weight were used as first and second tiebreakers, respectively. If no outlier was identified, we selected that subspace with the highest selection score based on an F1 score weight of 0.95.

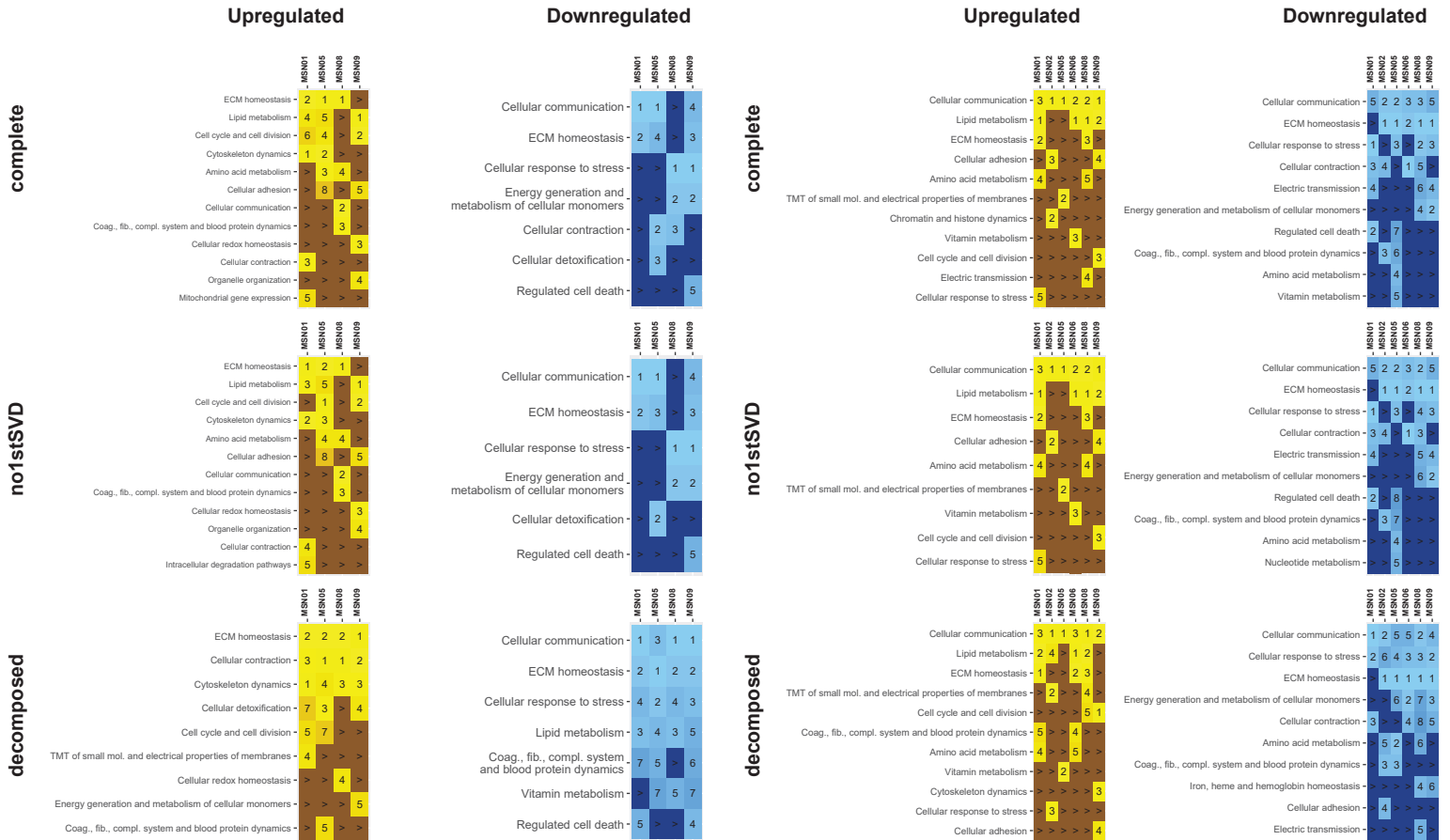
**MBCOL1
afatinib**
(is c.toxic: no)

**MBCOL1
axitinib**
(is c.toxic: no)



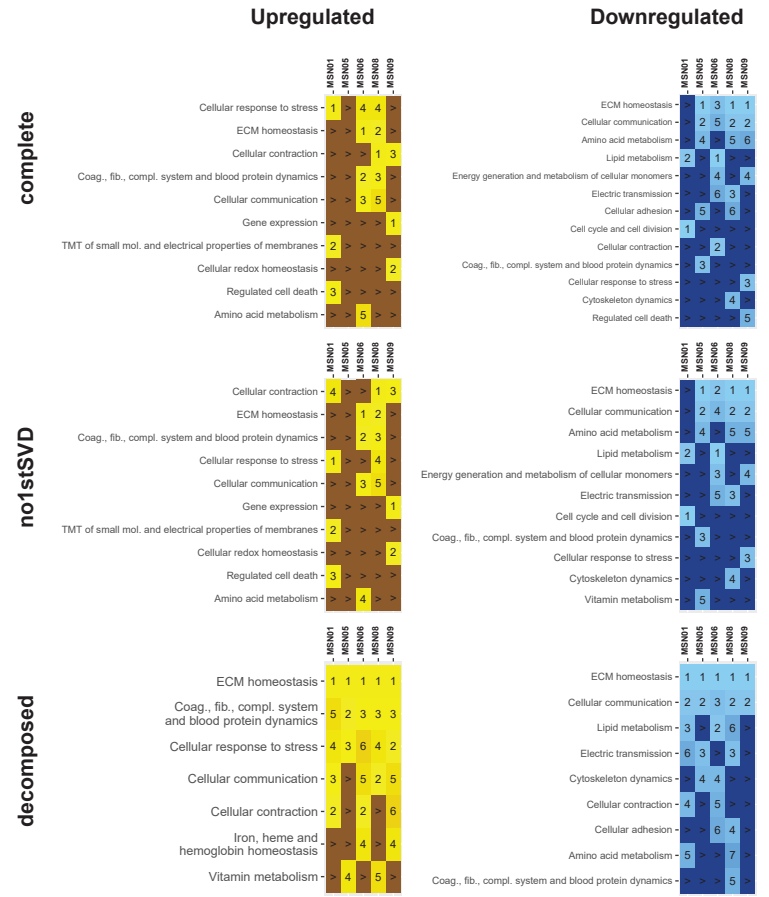
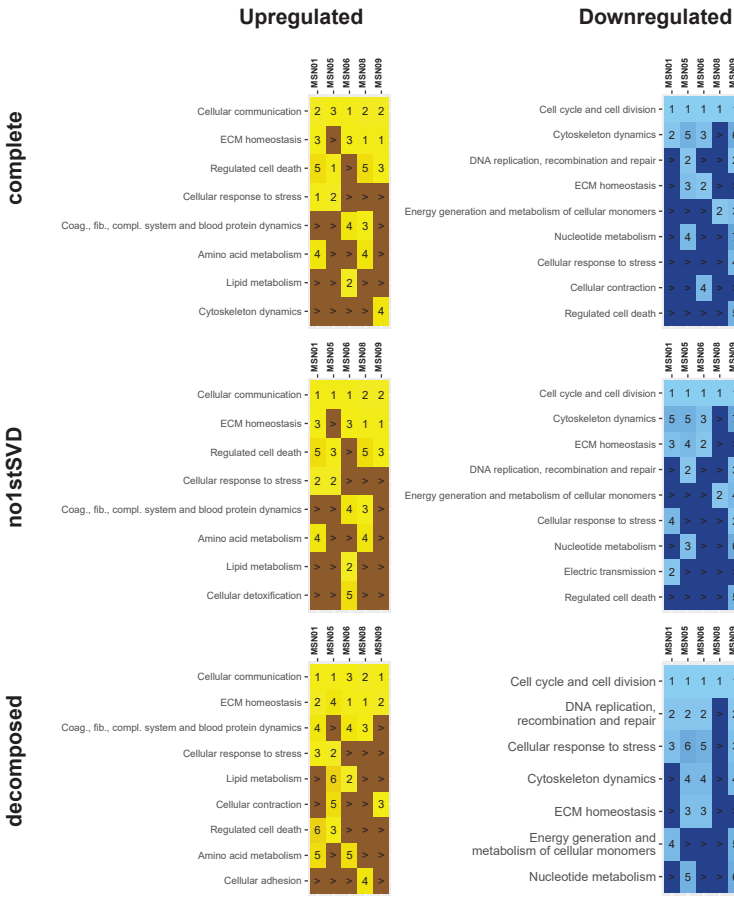
**MBCOL1
bosutinib**
(is c.toxic: no)

**MBCOL1
cabozantinib**
(is c.toxic: no)



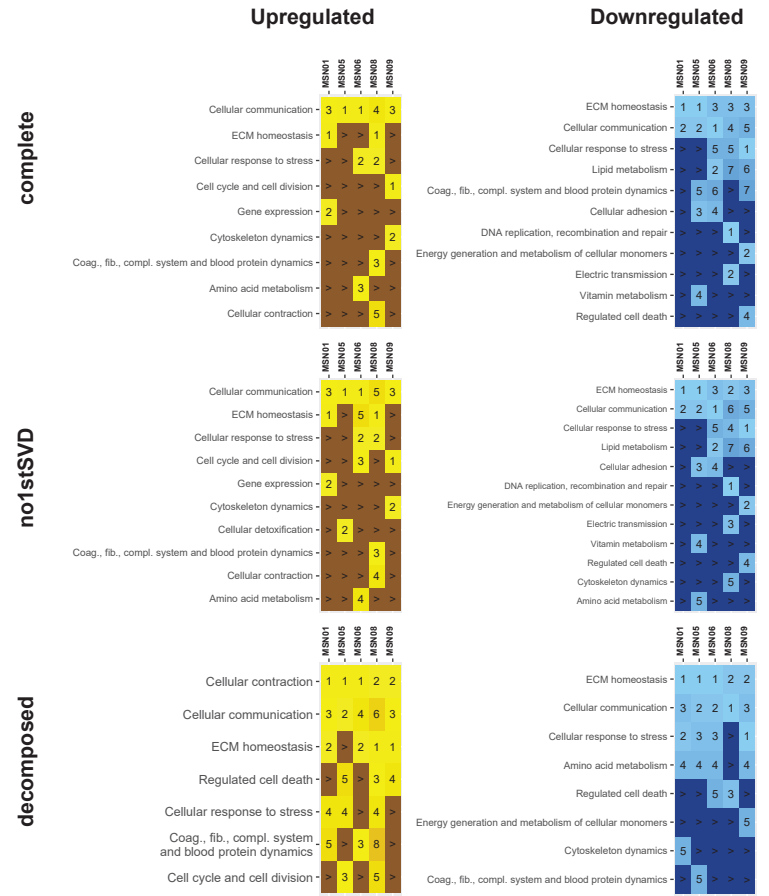
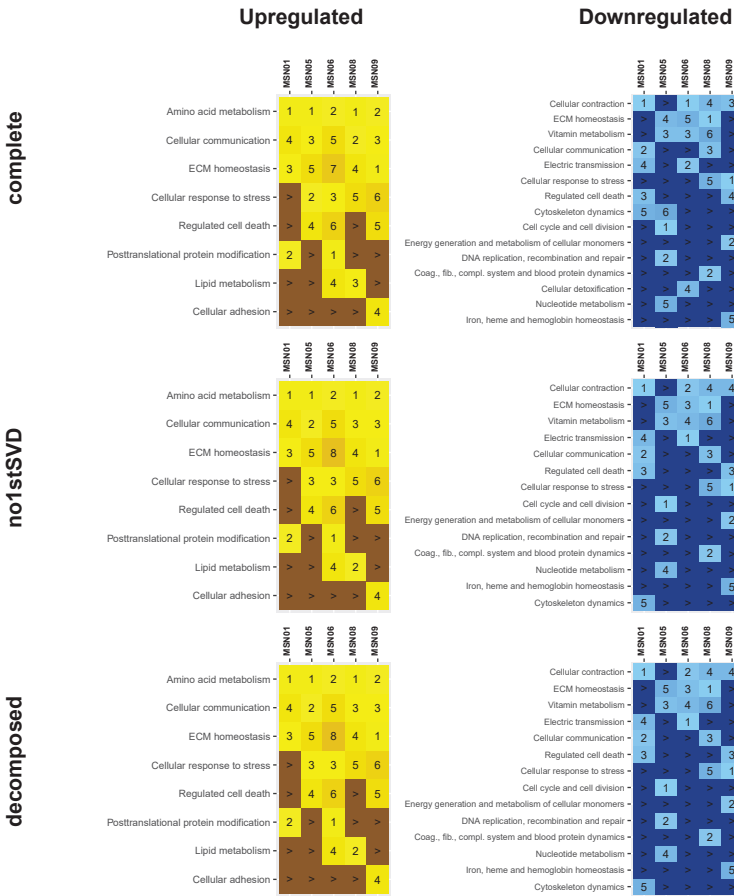
**MBCOL1
ceritinib
(is c.toxic: no)**

**MBCOL1
crizotinib
(is c.toxic: no)**



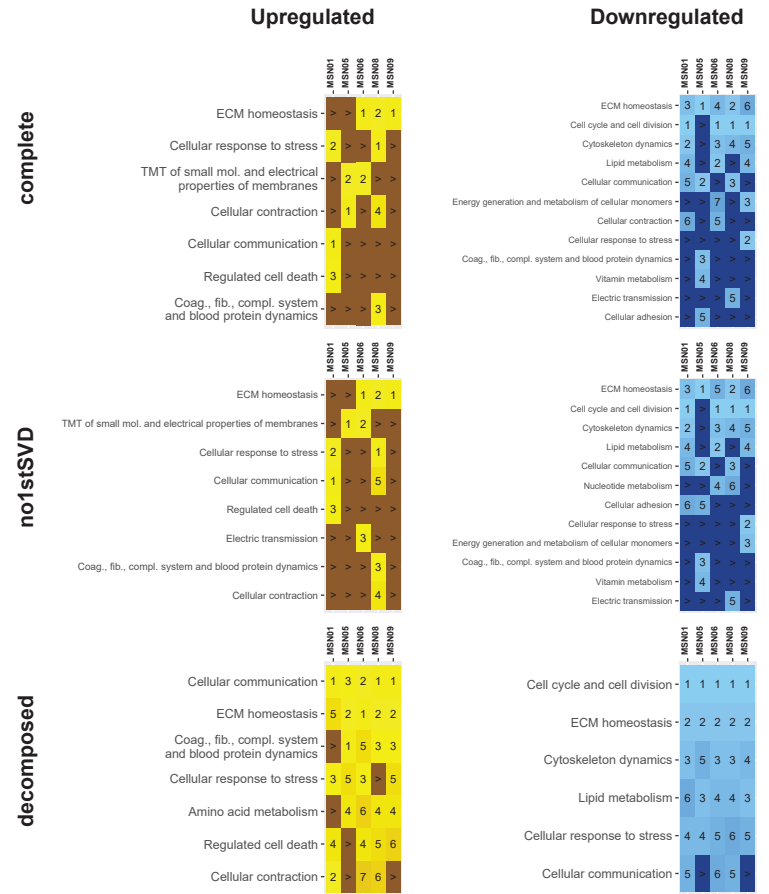
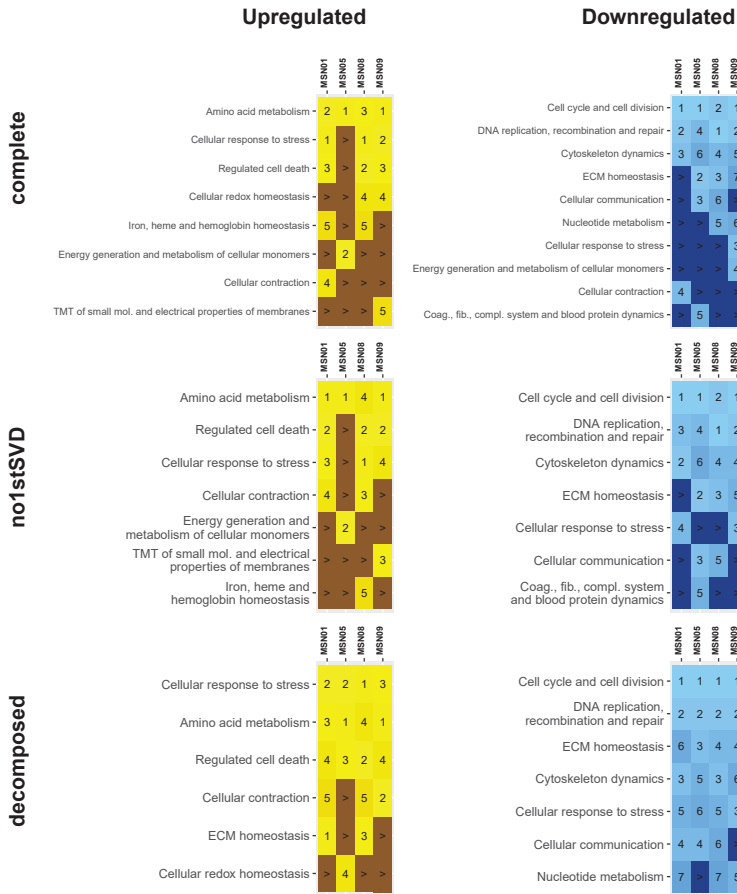
**MBCOL1
dabrafenib
(is c.toxic: yes)**

**MBCOL1
dasatinib
(is c.toxic: no)**



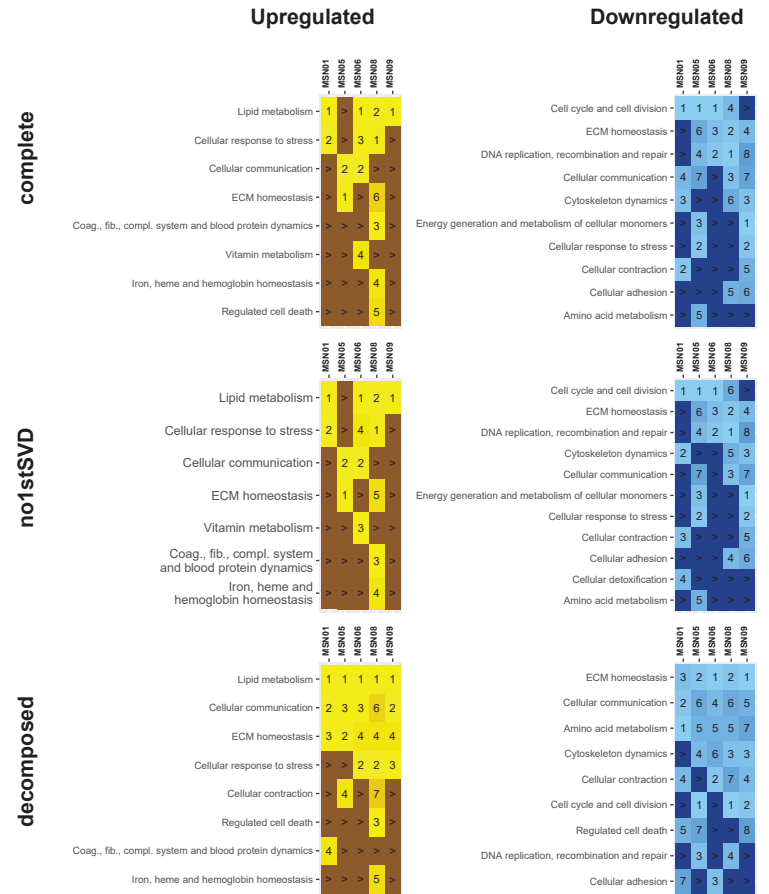
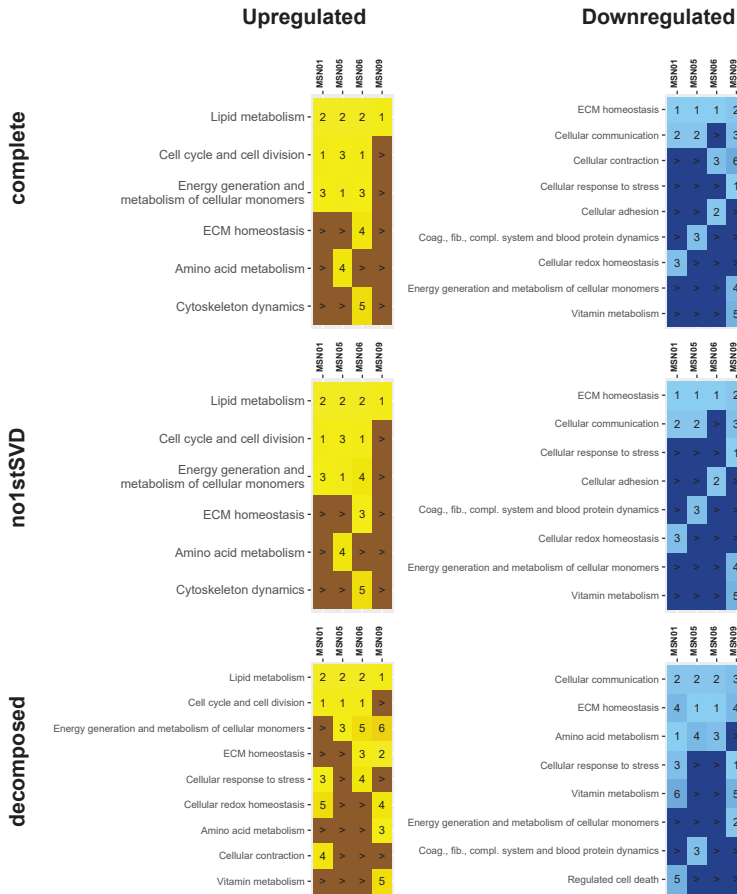
**MBCOL1
erlotinib
(is c.toxic: no)**

**MBCOL1
gefitinib
(is c.toxic: no)**



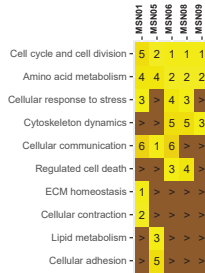
**MBCOL1
imatinib
(is c.toxic: no)**

**MBCOL1
lapatinib
(is c.toxic: yes)**

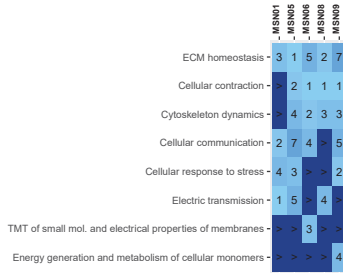


MBCOL1
nilotinib
(is c.toxic: no)

Upregulated

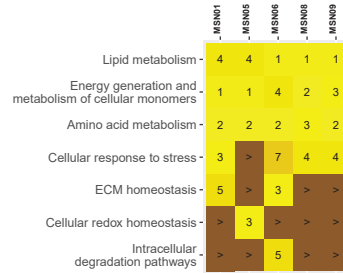


Downregulated

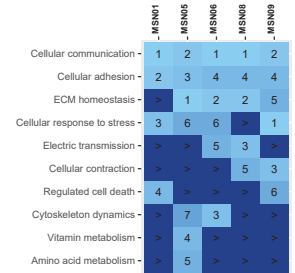


MBCOL1
pazopanib
(is c.toxic: yes)

Upregulated



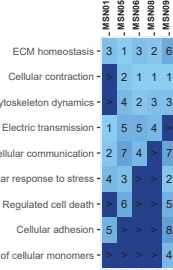
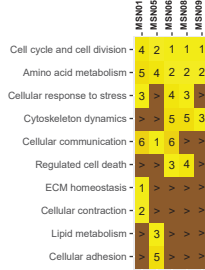
Downregulated



complete

no1stSVD

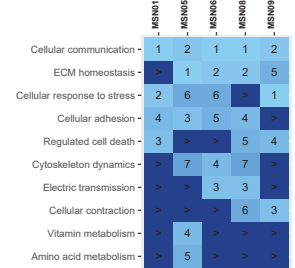
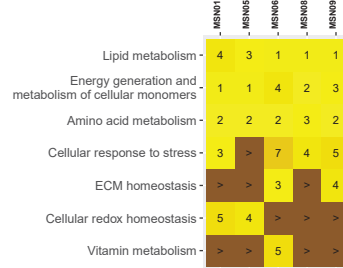
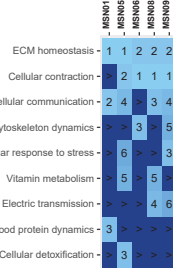
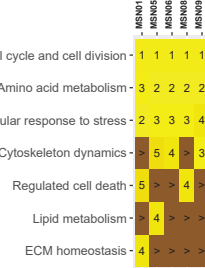
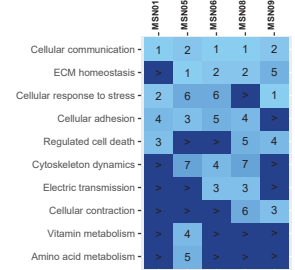
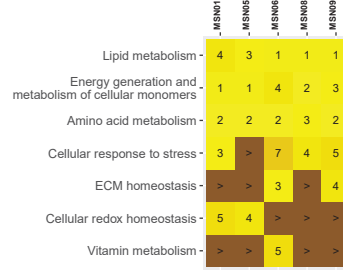
decomposed



complete

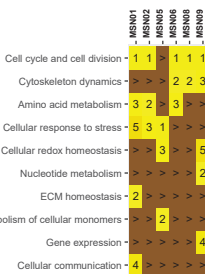
no1stSVD

decomposed

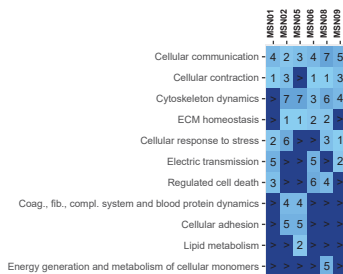


MBCOL1
ponatinib
(is c.toxic: yes)

Upregulated

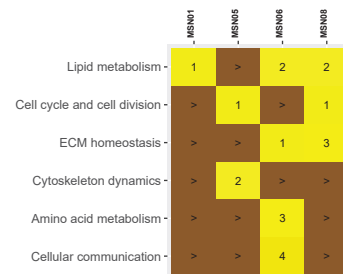


Downregulated

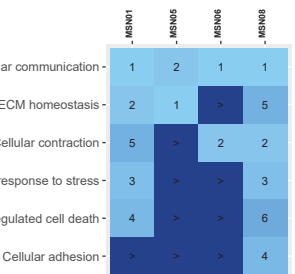


MBCOL1
regorafenib
(is c.toxic: no)

Upregulated



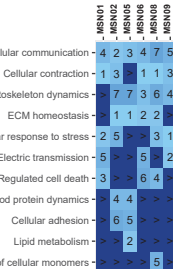
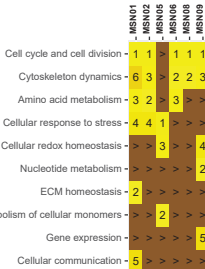
Downregulated



complete

no1stSVD

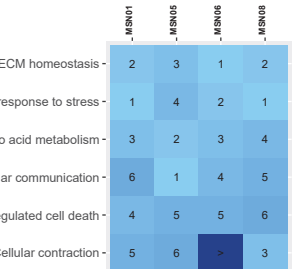
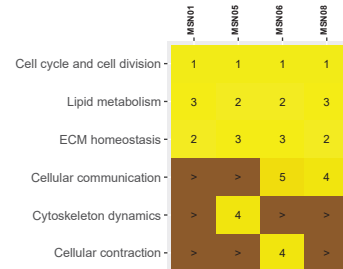
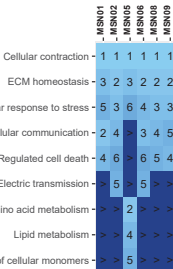
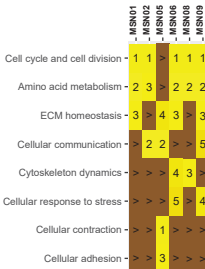
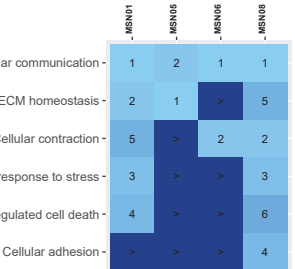
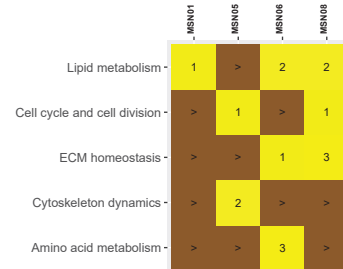
decomposed



complete

no1stSVD

decomposed



**MBCOL1
ruxolitinib
(is c.toxic: no)**

**MBCOL1
sorafenib
(is c.toxic: yes)**

complete

Upregulated

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
ECM homeostasis	>>>	1	1	1	>	
Cellular communication	>>>	2	4	3	>	
Cellular adhesion	>>>	>	>	2	2	
Gene expression	>	1	>	>	>	
Cellular redox homeostasis	1	>	>	>	>	
Cell cycle and cell division	>>	1	>	>	>	
DNA replication, recombination and repair	>>	2	>	>	>	
Lipid metabolism	>>	>	3	>	>	
Electric transmission	>>	>	3	>	>	

Downregulated

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
Cellular communication	1	2	5	1	3	3
ECM homeostasis	3	1	1	2	1	>
Cellular response to stress	2	4	4	2	1	
Regulated cell death	5	2	3	4	>	
Cellular contraction	6	7	3	4	>	
Energy generation and metabolism of cellular monomers	>	>	6	6	2	
Cytoskeleton dynamics	4	>	>	7	>	
Coag., fib., compl. system and blood protein dynamics	6	6	5	>	>	
Cellular adhesion	3	>	>	>	>	
Lipid metabolism	>	>	>	>	4	
Cell cycle and cell division	4	>	>	>	>	
Electric transmission	>	>	5	>	>	
Cellular protrusion dynamics	5	>	>	>	>	

complete

Upregulated

	_MSN01	_MSN05	_MSN08	_MSN09
Cell cycle and cell division	1	1	1	1
Lipid metabolism	2	2	>	2
Amino acid metabolism	>	>	2	>
Cytoskeleton dynamics	>	>	>	3
Cellular communication	>	>	>	4
Cellular adhesion	>	>	>	5

Downregulated

	_MSN01	_MSN05	_MSN08	_MSN09
Cellular communication	1	2	2	2
ECM homeostasis	4	1	1	5
Cellular response to stress	3	3	4	1
Cellular contraction	2	>	3	3
Vitamin metabolism	5	4	>	>
Regulated cell death	6	>	4	>
Electric transmission	5	>	>	>

no1stSVD

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
ECM homeostasis	>>>	>	1	1	1	
Cellular communication	>>>	>	2	4	3	
Cellular adhesion	>>>	>	>	3	2	
Gene expression	>	1	>	>	>	
Cellular contraction	1	>	>	>	>	
Cell cycle and cell division	>>	1	>	>	>	
Electric transmission	>>	2	>	2	>	
DNA replication, recombination and repair	>>	2	>	>	>	
Cellular redox homeostasis	2	>	>	>	>	
Lipid metabolism	>	>	3	>	>	

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
Cellular communication	1	2	5	1	5	3
ECM homeostasis	3	1	1	5	1	>
Cellular response to stress	2	4	4	2	1	
Regulated cell death	5	2	3	3	>	
Cellular contraction	6	7	3	4	6	2
Energy generation and metabolism of cellular monomers	>	>	6	6	2	
Cytoskeleton dynamics	4	>	>	7	>	
Coag., fib., compl. system and blood protein dynamics	6	6	5	>	>	
Cellular adhesion	3	>	>	>	>	
Lipid metabolism	>	>	>	>	4	
Cell cycle and cell division	4	>	>	>	>	
Electric transmission	>	>	5	>	>	
Cellular protrusion dynamics	5	>	>	>	>	

no1stSVD

	_MSN01	_MSN05	_MSN08	_MSN09
Cell cycle and cell division	1	1	1	1
Lipid metabolism	2	2	>	2
Amino acid metabolism	>	>	2	>
Cytoskeleton dynamics	>	>	>	3
Cellular communication	>	>	>	4
Cellular adhesion	>	>	>	5

	_MSN01	_MSN05	_MSN08	_MSN09
Cellular communication	1	2	3	2
Cellular response to stress	3	3	2	1
ECM homeostasis	4	1	1	>
Cellular contraction	2	>	4	3
Regulated cell death	6	6	5	4
Vitamin metabolism	5	4	>	>
Electric transmission	5	>	>	>

decomposed

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
ECM homeostasis	2	2	1	1	1	1
Coag., fib., compl. system and blood protein dynamics	>	3	4	3	2	3
Cellular communication	3	>	2	5	3	5
Cell cycle and cell division	1	1	>	4	>	2
Lipid metabolism	>	>	3	2	4	4
Cellular response to stress	>	5	5	>	>	>
DNA replication, recombination and repair	>	4	>	>	>	>
Iron, heme and hemoglobin homeostasis	>	>	>	>	5	>

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
Cellular contraction	2	1	2	1	1	3
Amino acid metabolism	1	2	1	2	2	2
ECM homeostasis	5	3	3	3	1	1
Cellular communication	4	6	5	4	6	5
Regulated cell death	7	4	6	7	5	4
Cytoskeleton dynamics	6	5	>	7	7	
Coag., fib., compl. system and blood protein dynamics	>	4	>	4	>	
Cellular response to stress	3	>	>	>	>	
Electric transmission	>	>	5	>	>	

decomposed

	_MSN01	_MSN05	_MSN08	_MSN09
Cell cycle and cell division	1	1	1	1
Cytoskeleton dynamics	4	3	5	3
Lipid metabolism	2	2	4	>
Cellular response to stress	5	5	3	>
Regulated cell death	>	4	>	4
Coag., fib., compl. system and blood protein dynamics	>	7	>	5
ECM homeostasis	>	>	>	2
Amino acid metabolism	>	>	2	>
Mitochondrial gene expression	3	>	>	>

	_MSN01	_MSN05	_MSN08	_MSN09
Cellular communication	3	1	2	1
Cellular response to stress	1	2	3	2
ECM homeostasis	2	3	1	3
Cellular contraction	4	4	>	4
Amino acid metabolism	5	6	>	>
Vitamin metabolism	>	>	>	5
Coag., fib., compl. system and blood protein dynamics	5	5	>	>

**MBCOL1
sunitinib
(is c.toxic: yes)**

**MBCOL1
tofacitinib
(is c.toxic: no)**

complete

Upregulated

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
Amino acid metabolism	>>	1	5	1	2	
ECM homeostasis	>	3	2	1	>	
Cellular communication	>>	3	4	4	1	
Energy generation and metabolism of cellular monomers	1	2	>	>	>	
Cellular response to stress	2	1	>	4	>	
Coag., fib., compl. system and blood protein dynamics	>	4	>	>	3	
Organelle organization	3	>	>	>	>	
Lipid metabolism	>	3	>	>	>	
Mitochondrial gene expression	4	>	>	>	>	
Electric transmission	>	>	>	>	4	
Iron, heme and hemoglobin homeostasis	>	>	>	>	5	

Downregulated

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
ECM homeostasis	4	1	1	1	1	1
Cellular contraction	4	>	2	3	3	3
Cellular communication	2	3	4	5	7	
Coag., fib., compl. system and blood protein dynamics	3	4	>	4	8	
Regulated cell death	2	>	>	6	5	
Cytoskeleton dynamics	3	4	>	6	6	
Cellular response to stress	>	>	>	2	4	
Cell cycle and cell division	1	>	>	>	>	
Energy generation and metabolism of cellular monomers	>	>	>	>	2	
Electric transmission	>	>	3	>	>	
Cellular adhesion	5	>	>	>	>	

complete

Upregulated

	_MSN01	_MSN05	_MSN08	_MSN09
ECM homeostasis	>	1	1	2
Cellular communication	>	4	>	3
Cellular response to stress	2	>	>	1
Vitamin metabolism	>	3	>	4
Cellular contraction	1	>	>	>
Cellular adhesion	>	>	>	2
Amino acid metabolism	>	2	>	>
Regulated cell death	3	>	>	>

Downregulated

	_MSN01	_MSN05	_MSN08	_MSN09
Cellular communication	2	2	4	1
ECM homeostasis	4	1	2	7
Lipid metabolism	3	2	4	4
Coag., fib., compl. system and blood protein dynamics	6	3	>	5
Energy generation and metabolism of cellular monomers	1	>	>	1
Electric transmission	5	3	>	3
Cellular response to stress	8	>	>	2
Cellular adhesion	7	>	>	5
Cell cycle and cell division	1	>	>	>
TMT of small mol. and electrical properties of membranes	3	>	>	>
Cytoskeleton dynamics	>	>	>	4

no1stSVD

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
Amino acid metabolism	>	2	6	1	2	
ECM homeostasis	>	3	1	1	>	
Cellular communication	>	3	5	>	1	
Energy generation and metabolism of cellular monomers	1	2	>	>	>	
Cellular response to stress	2	1	>	>	>	
Cellular adhesion	>	4	>	>	3	
Coag., fib., compl. system and blood protein dynamics	>	2	>	>	2	
Organelle organization	3	>	>	>	>	
Lipid metabolism	>	3	>	>	>	
Vitamin metabolism	>	4	>	>	>	
Mitochondrial gene expression	4	>	>	>	>	
Electric transmission	>	>	>	>	4	
Iron, heme and hemoglobin homeostasis	>	>	>	>	5	

	_MSN01	_MSN02	_MSN05	_MSN06	_MSN08	_MSN09
ECM homeostasis	4	1	1	1	1	1
Cellular contraction	4	>	2	3	3	3
Cellular communication	2	3	2	5	7	
Cytoskeleton dynamics	3	4	>	7	6	
Regulated cell death	2	>	>	6	5	
Coag., fib., compl. system and blood protein dynamics	>	3	>	4	8	
Cellular response to stress	>	3	>	2	4	
Cell cycle and cell division	1	>	>	>	>	
Energy generation and metabolism of cellular monomers	>	>	>	>	2	
Electric transmission	>	>	3	>	>	
Cellular adhesion	5	>	>	>	>	

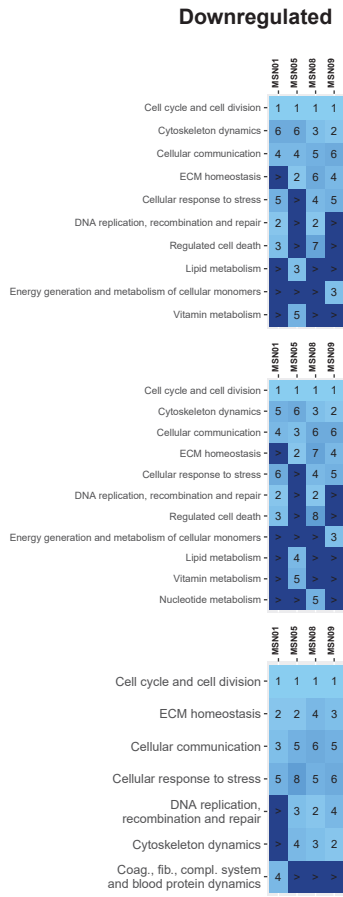
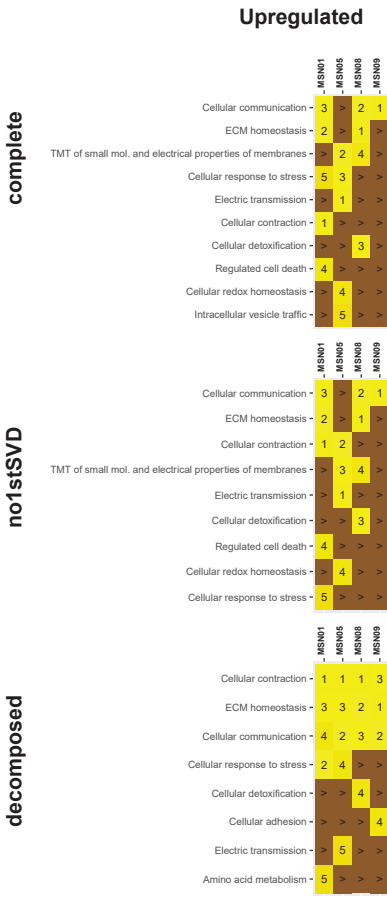
no1stSVD

Upregulated

	_MSN01	_MSN05	_MSN08	_MSN09
ECM homeostasis	>			

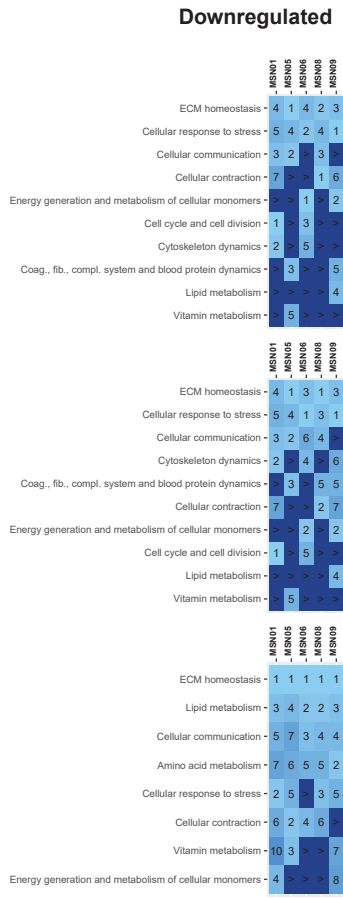
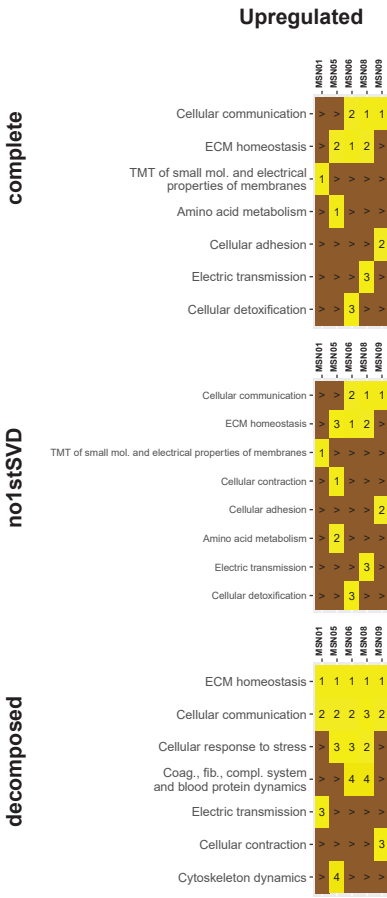
**MBCOL1
trametinib
(is c.toxic: yes)**

**MBCOL1
vandetanib
(is c.toxic: yes)**



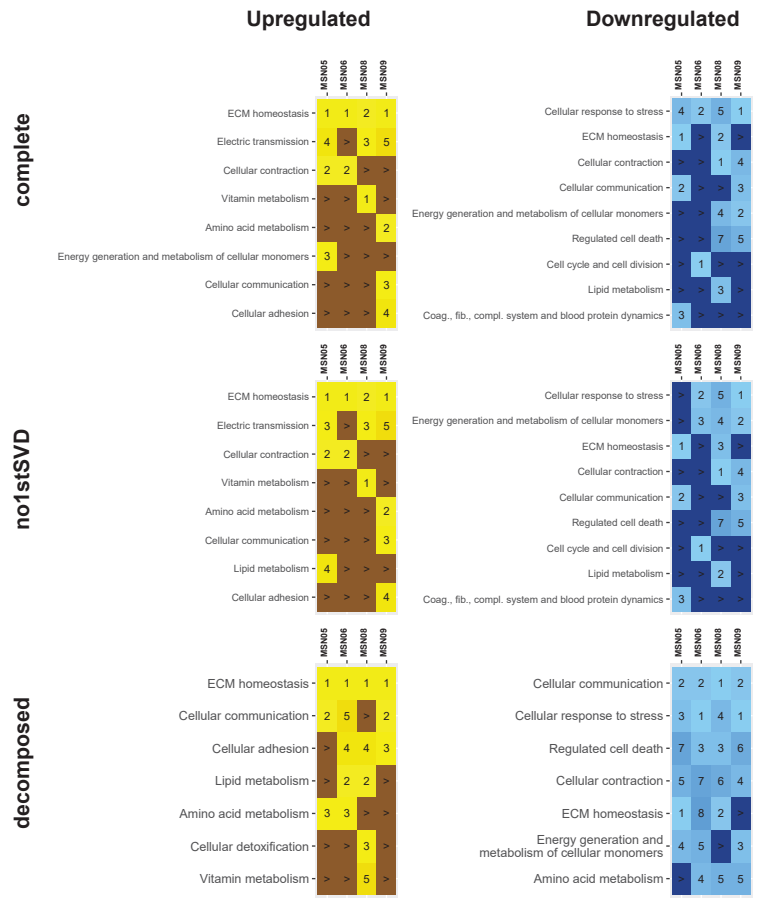
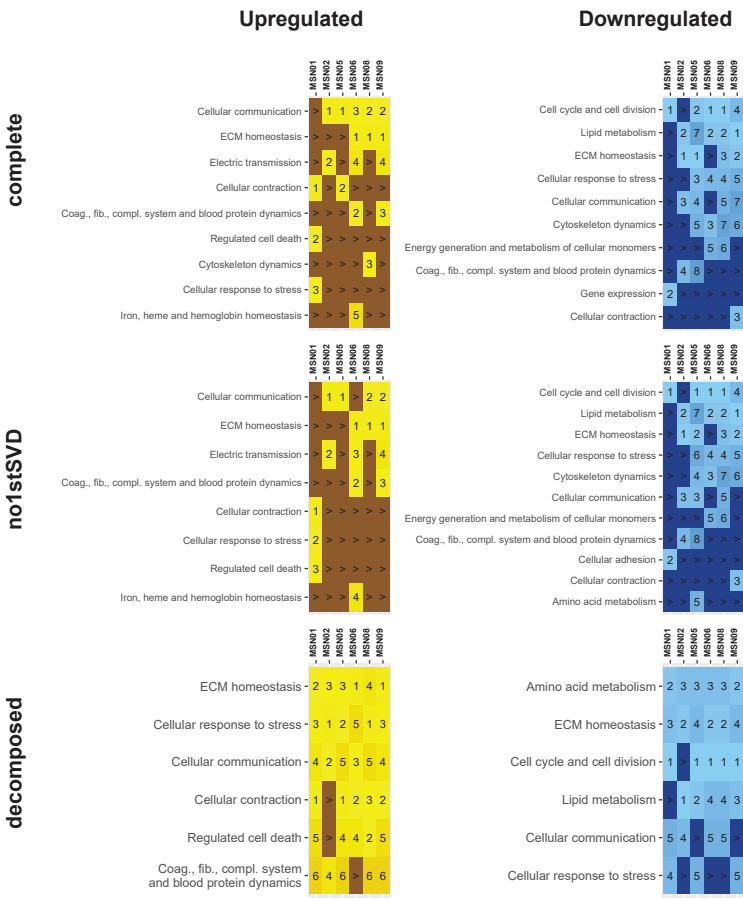
**MBCOL1
vemurafenib
(is c.toxic: no)**

**MBCOL1
bevacizumab
(is c.toxic: yes)**



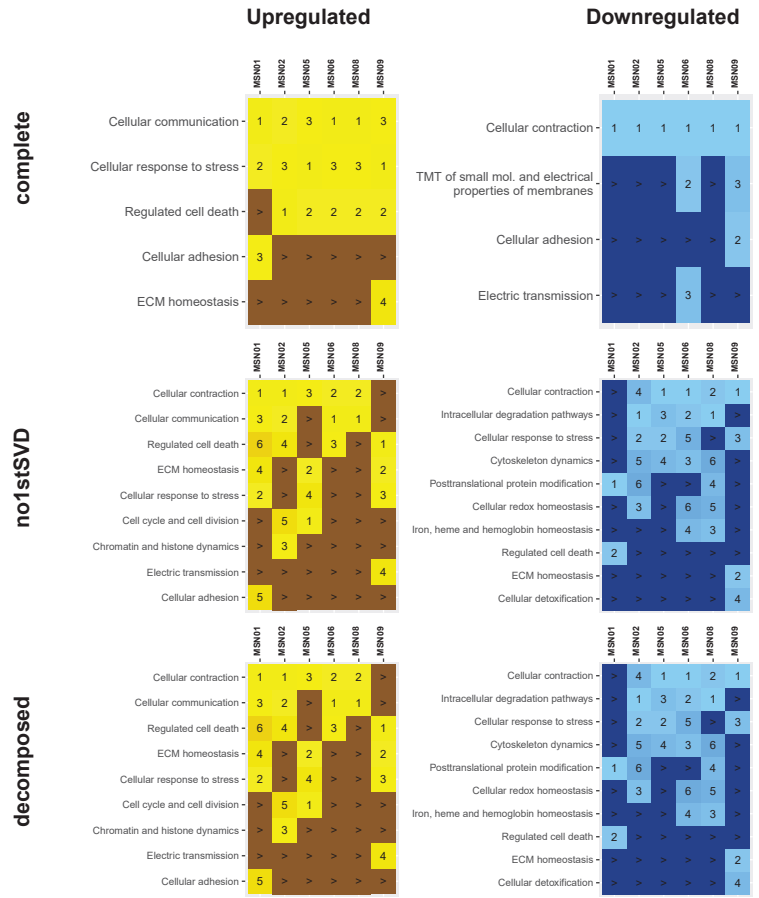
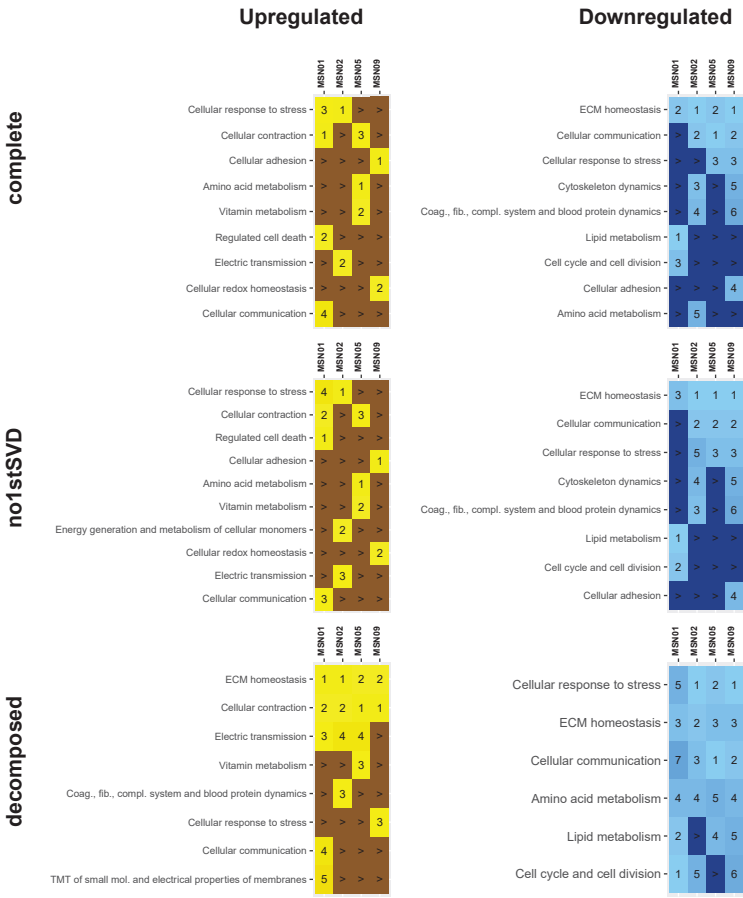
**MBCOL1
cetuximab
(is c.toxic: no)**

**MBCOL1
rituximab
(is c.toxic: no)**



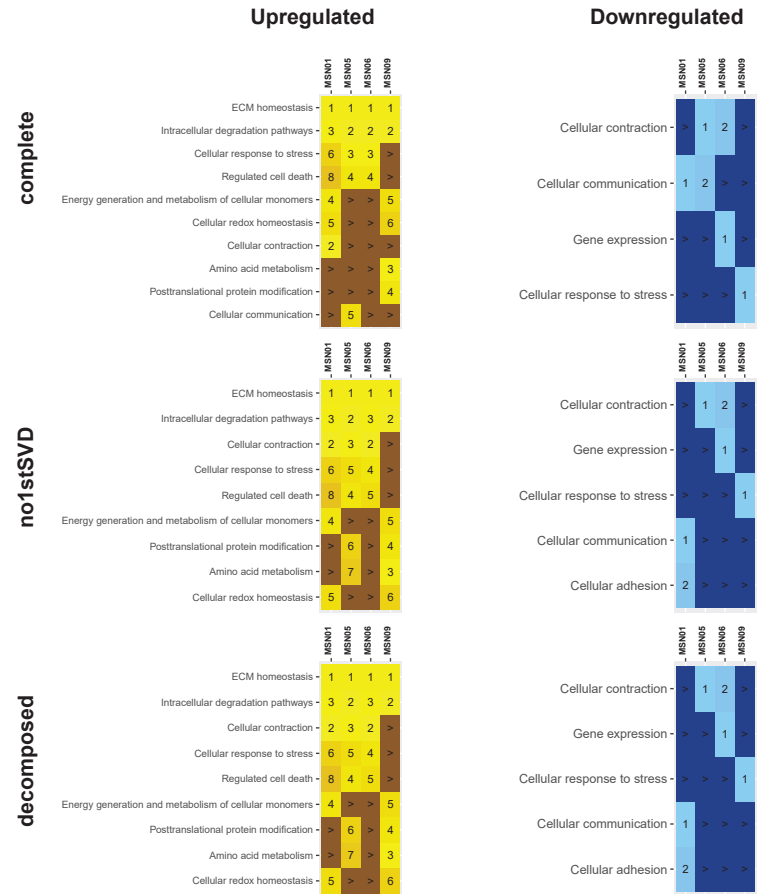
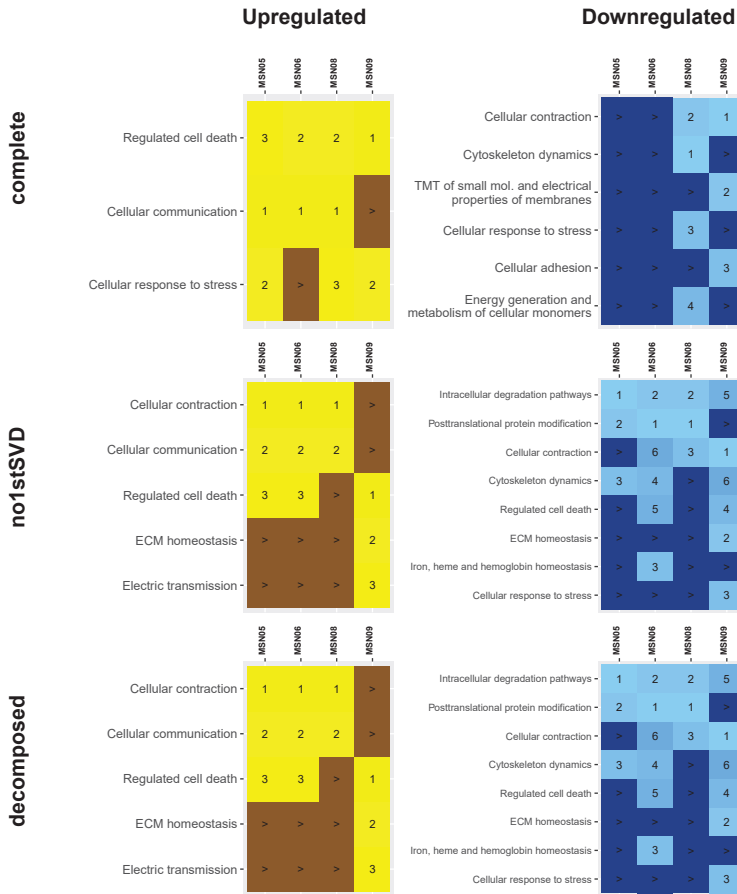
**MBCOL1
trastuzumab
(is c.toxic: yes)**

**MBCOL1
daunorubicin
(is c.toxic: yes)**



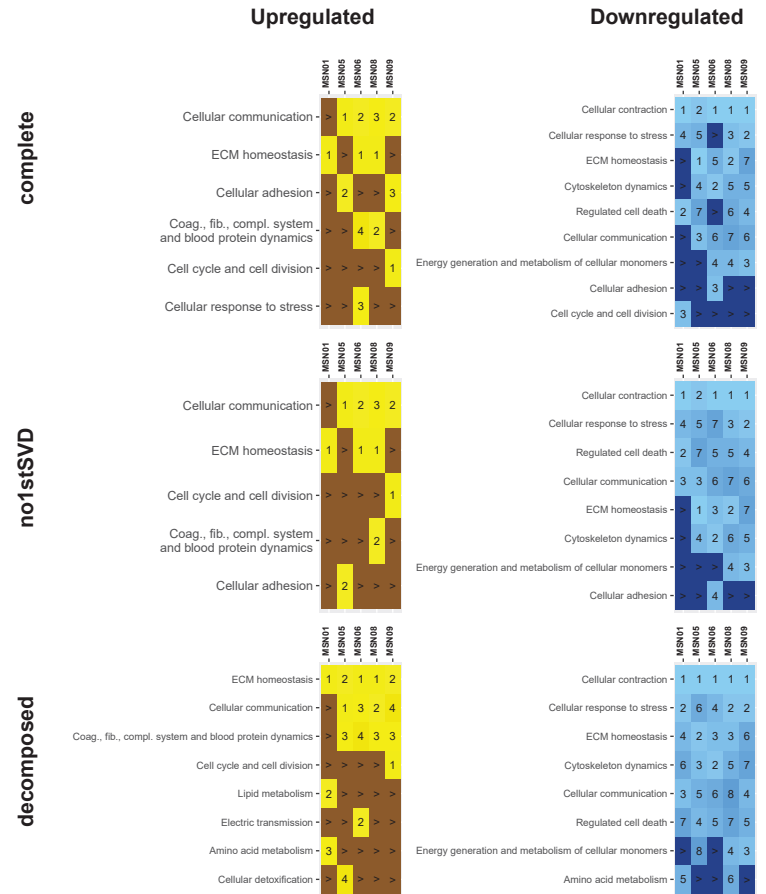
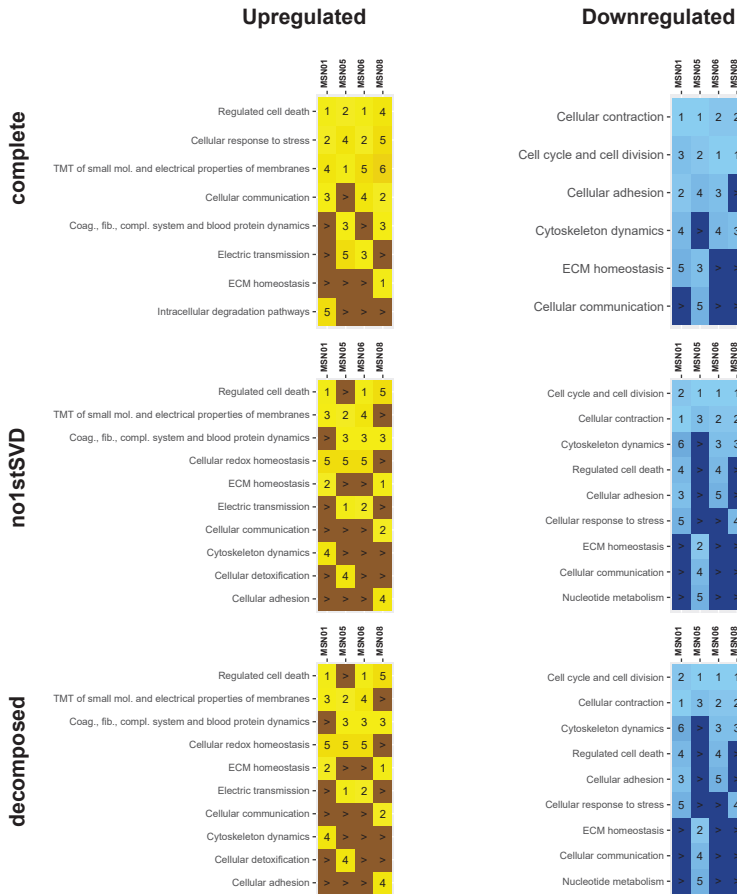
**MBCOL1
doxorubicin**
(is c.toxic: yes)

**MBCOL1
epirubicin**
(is c.toxic: yes)



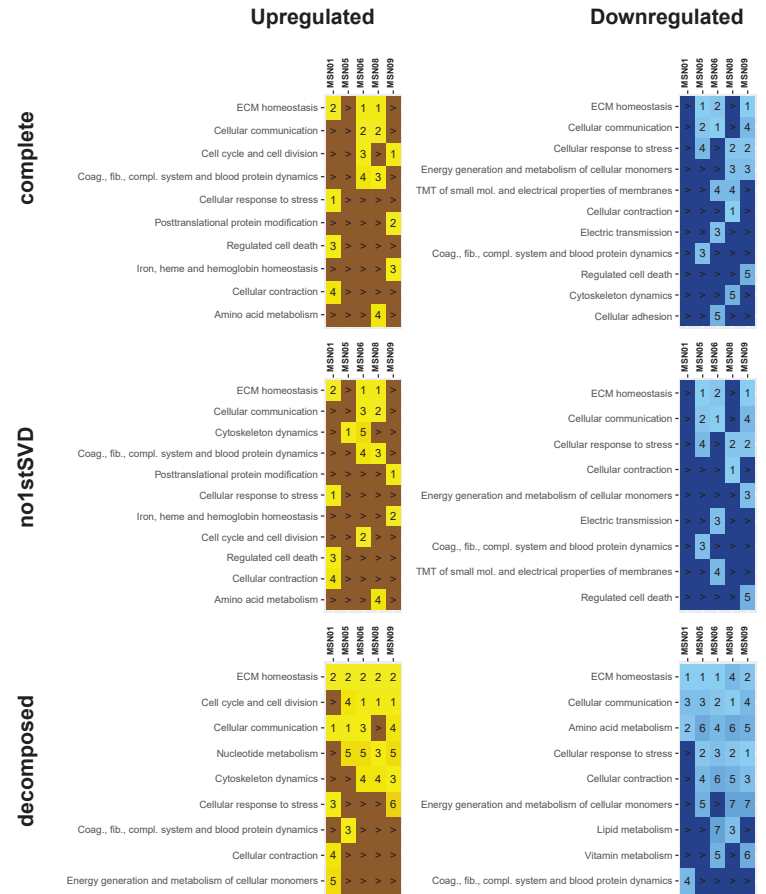
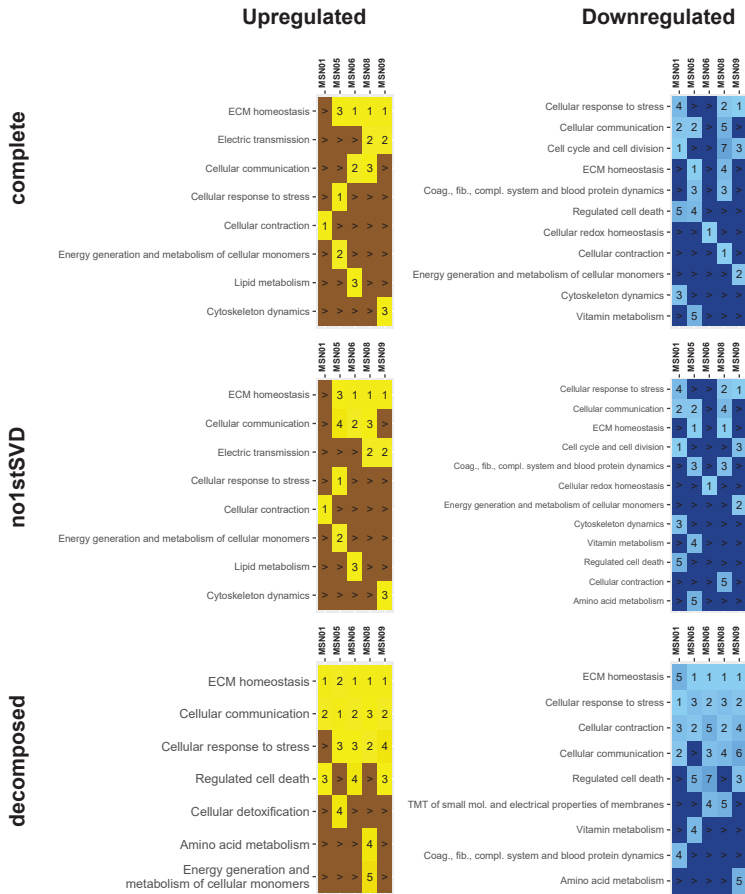
**MBCOL1
idarubicin**
(is c.toxic: yes)

**MBCOL1
amiodarone**
(is c.toxic: nd)



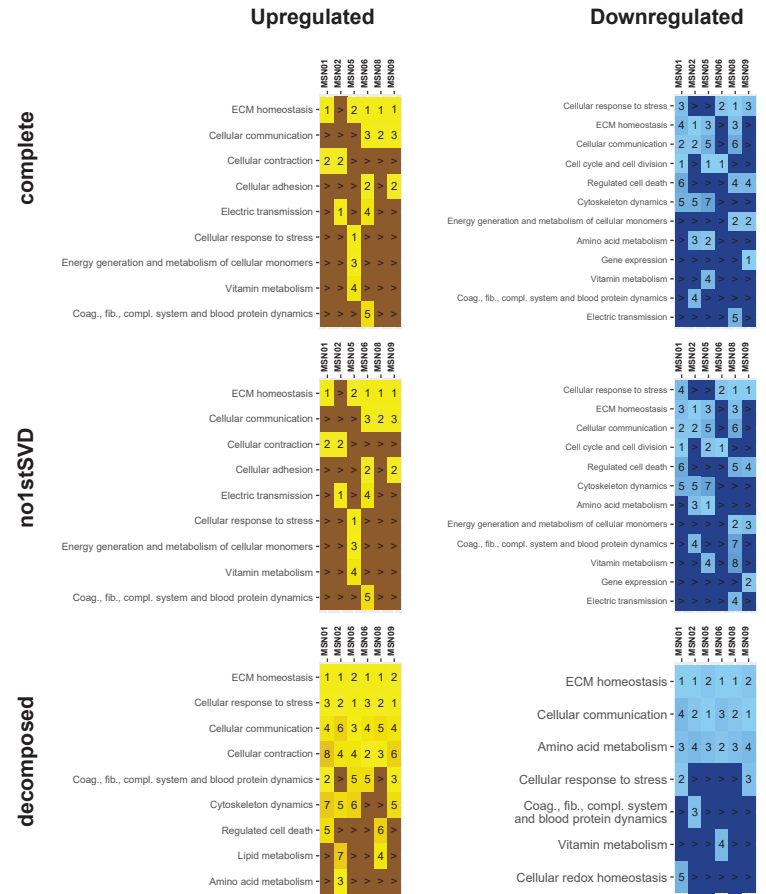
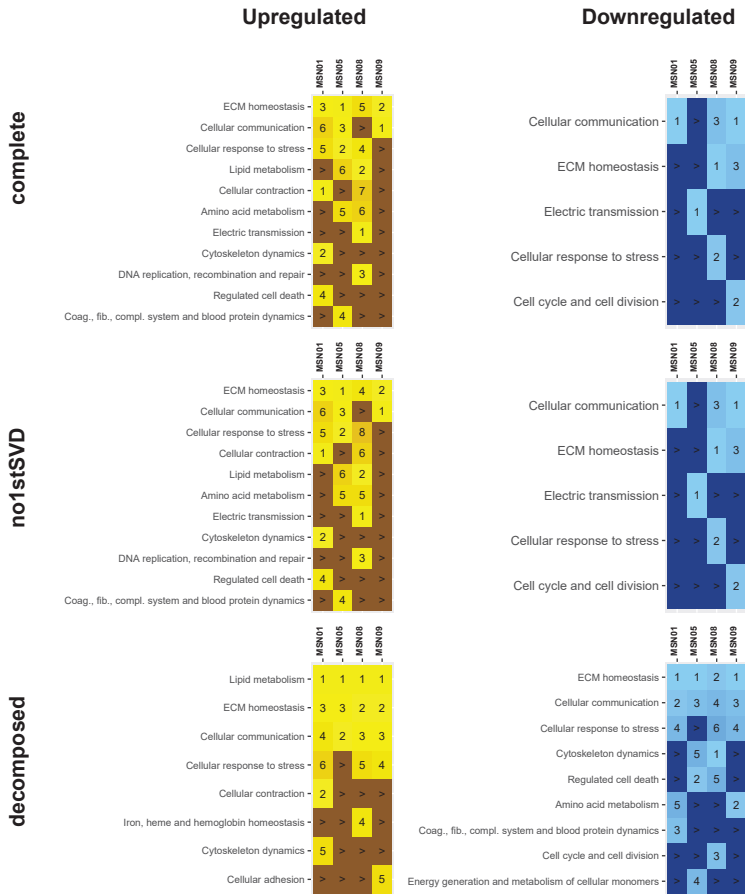
**MBCOL1
dobutamine
(is c.toxic: nd)**

**MBCOL1
flecainide
(is c.toxic: nd)**



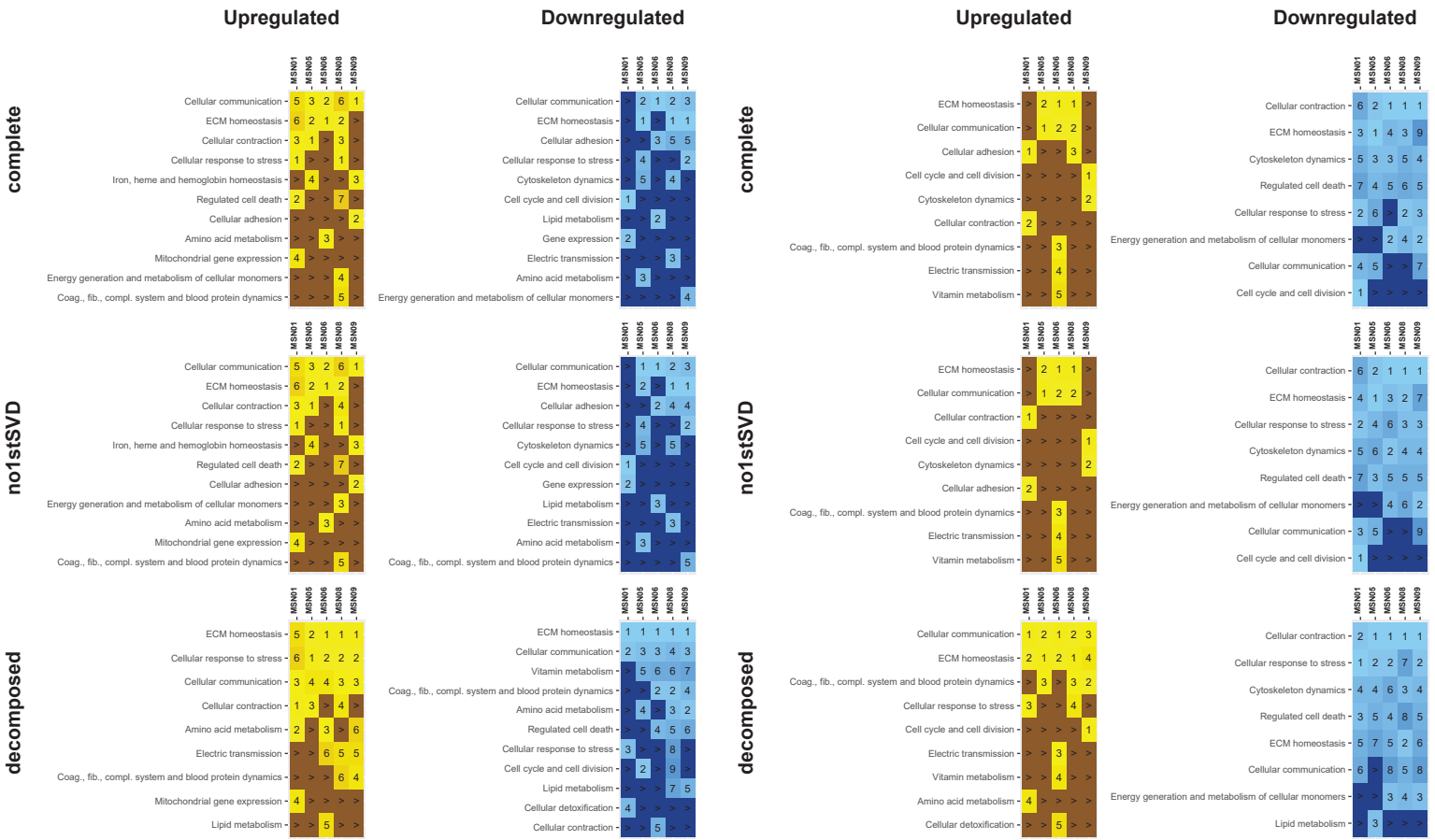
**MBCOL1
isoprenaline
(is c.toxic: nd)**

**MBCOL1
milrinone
(is c.toxic: nd)**



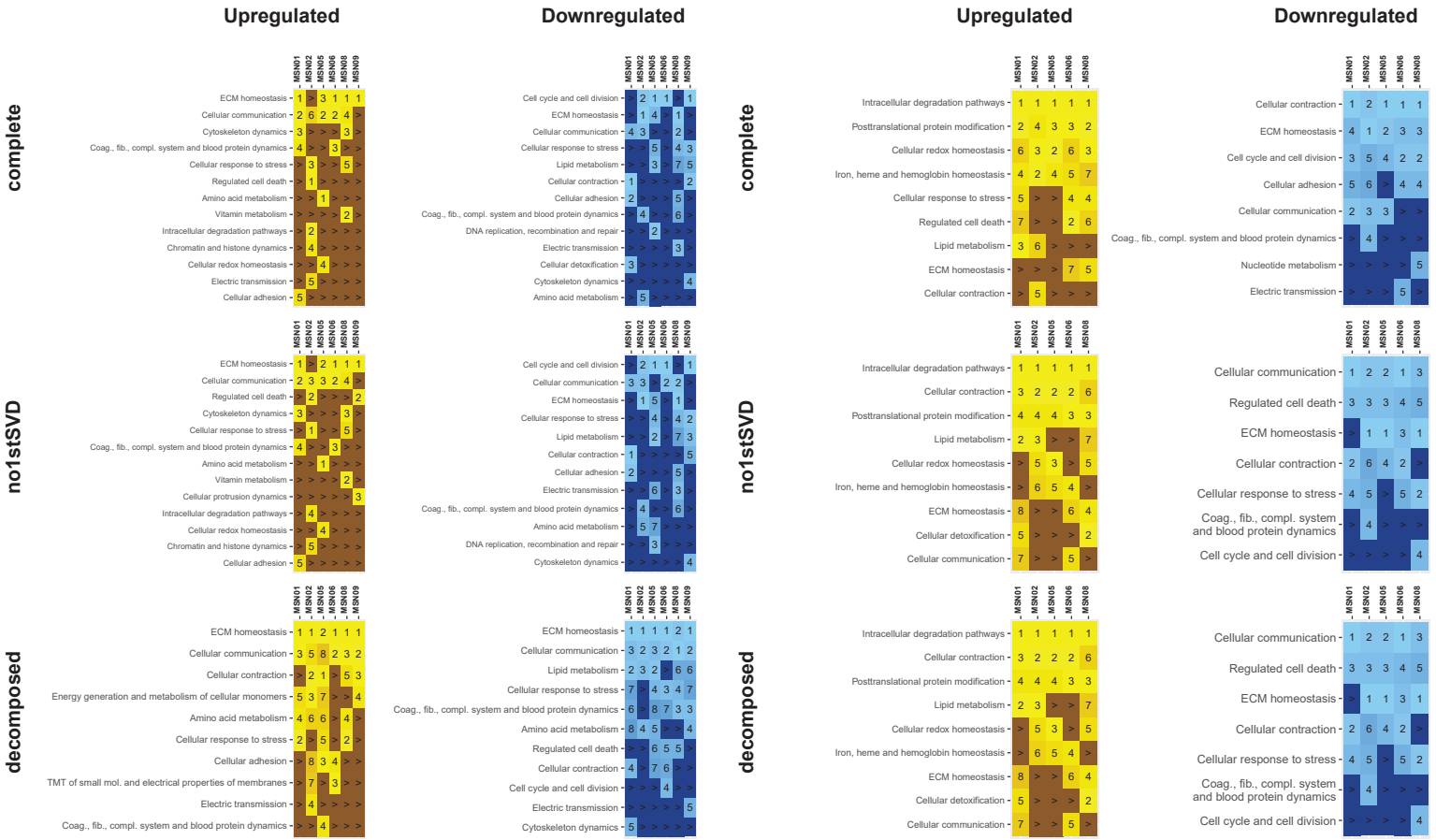
**MBCOL1
phenylephrine
(is c.toxic: nd)**

**MBCOL1
verapamil
(is c.toxic: nd)**



**MBCOL1
azacitidine
(is c.toxic: nd)**

**MBCOL1
bortezomib
(is c.toxic: yes)**



**MBCOL1
carfilzomib
(is c.toxic: yes)**

**MBCOL1
cyclosporine
(is c.toxic: nd)**

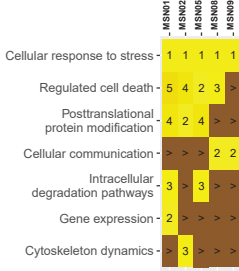
Upregulated

Downregulated

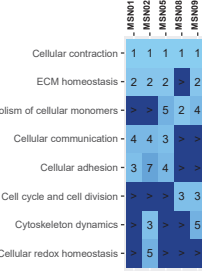
Upregulated

Downregulated

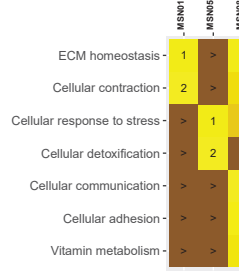
complete



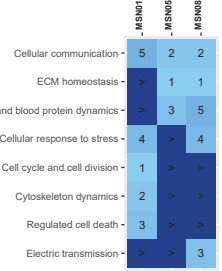
Energy generation and metabolism of cellular monomers



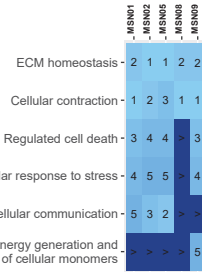
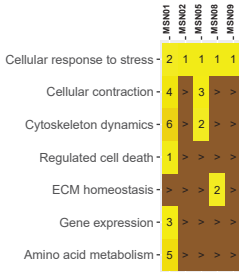
complete



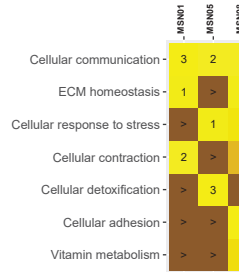
Coag., fib., compl. system and blood protein dynamics



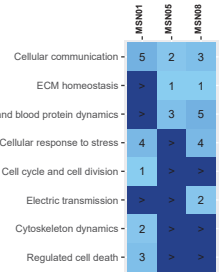
no1stSVD



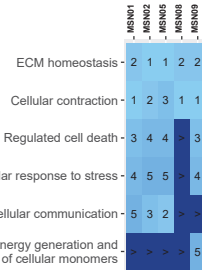
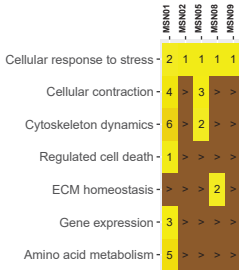
no1stSVD



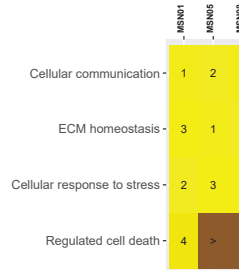
Coag., fib., compl. system and blood protein dynamics



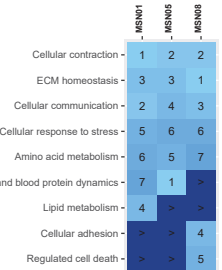
decomposed



decomposed



Coag., fib., compl. system and blood protein dynamics



**MBCOL1
decitabine
(is c.toxic: nd)**

**MBCOL1
delavirdine
(is c.toxic: nd)**

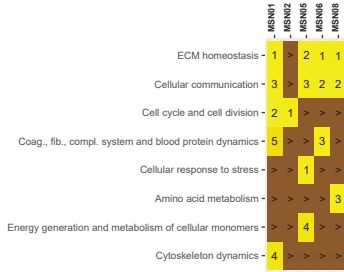
Upregulated

Downregulated

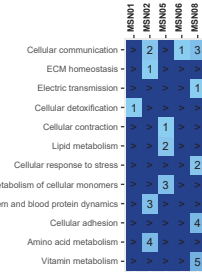
Upregulated

Downregulated

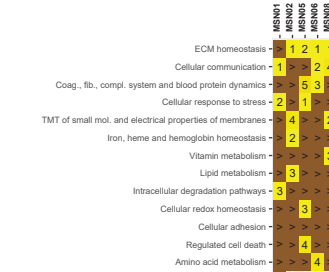
complete



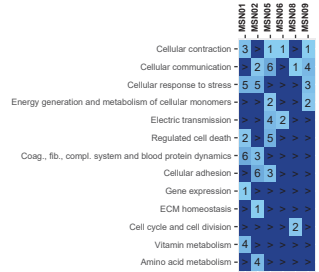
Energy generation and metabolism of cellular monomers



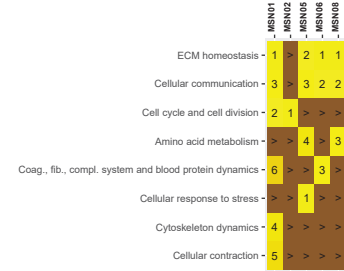
complete



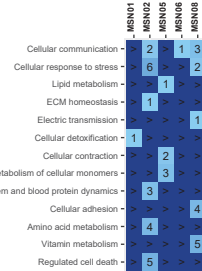
Coag., fib., compl. system and blood protein dynamics



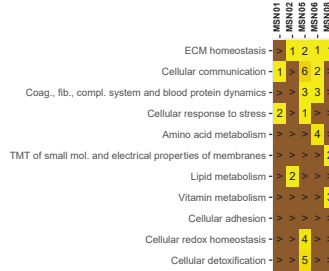
no1stSVD



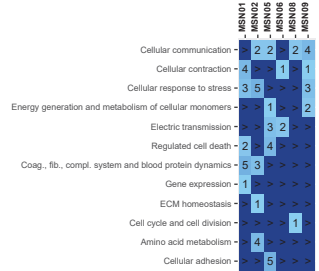
Energy generation and metabolism of cellular monomers



no1stSVD

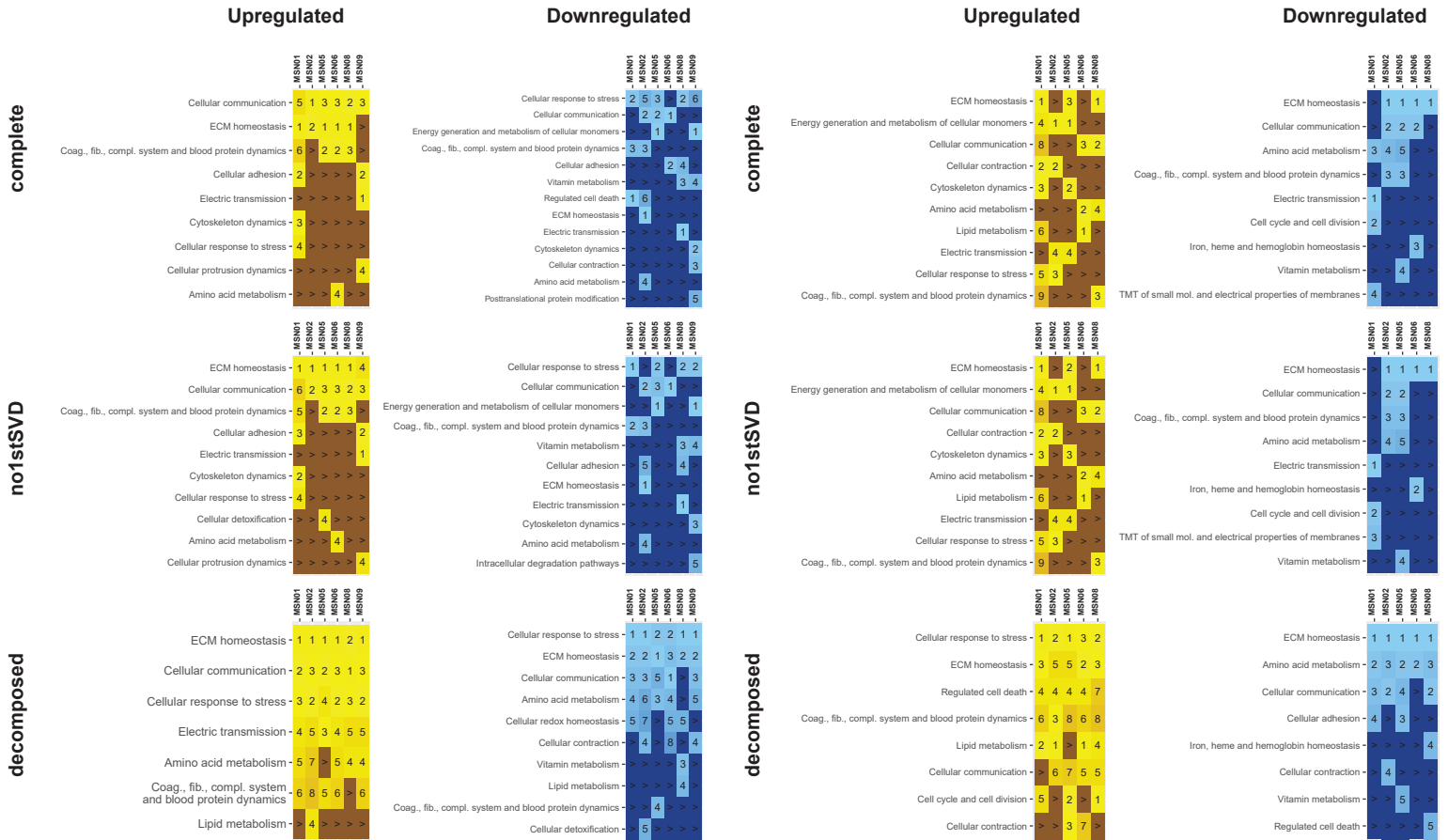


Coag., fib., compl. system and blood protein dynamics



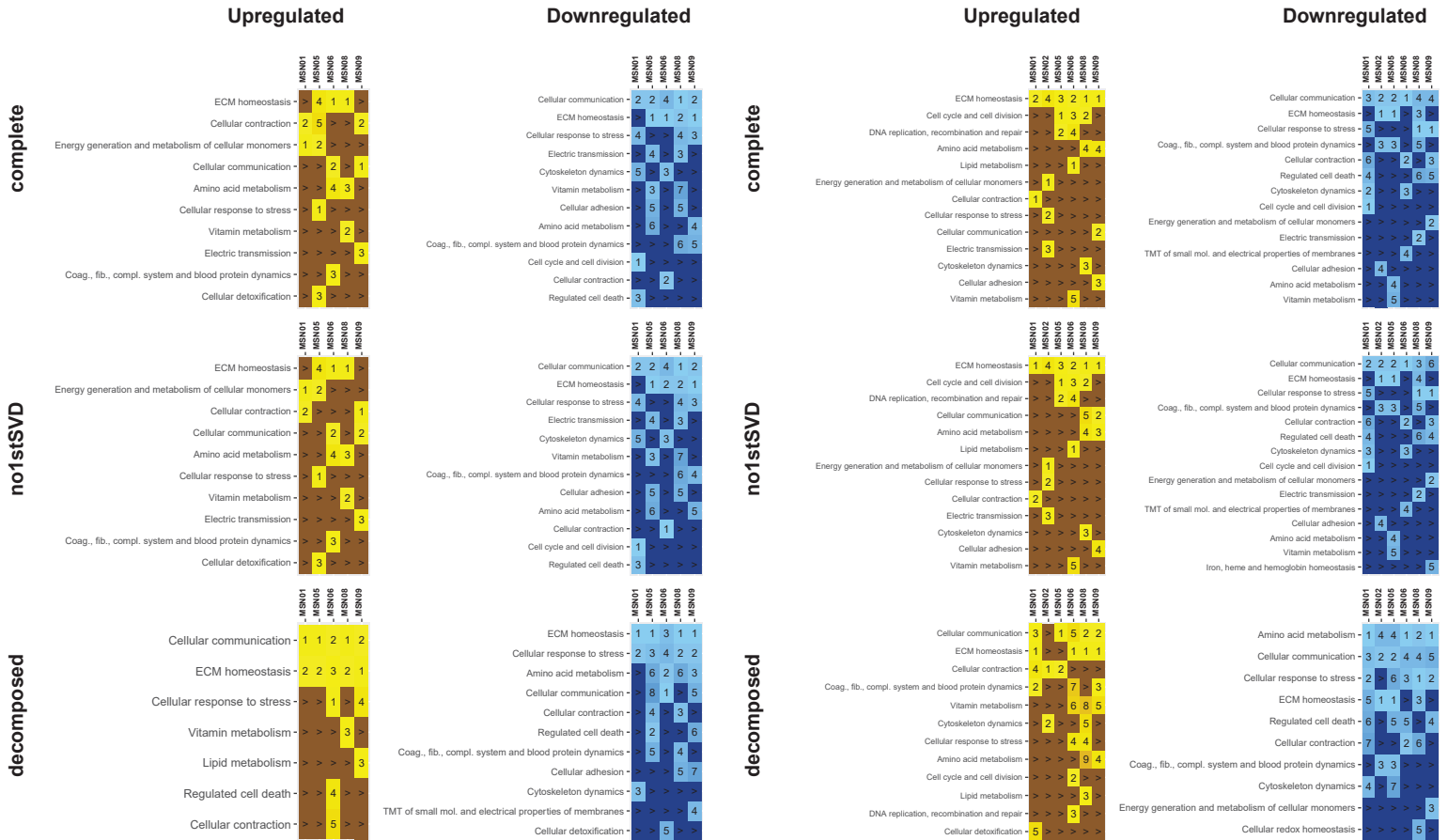
**MBCOL1
diclofenac
(is c.toxic: nd)**

**MBCOL1
endothelin-1
(is c.toxic: nd)**



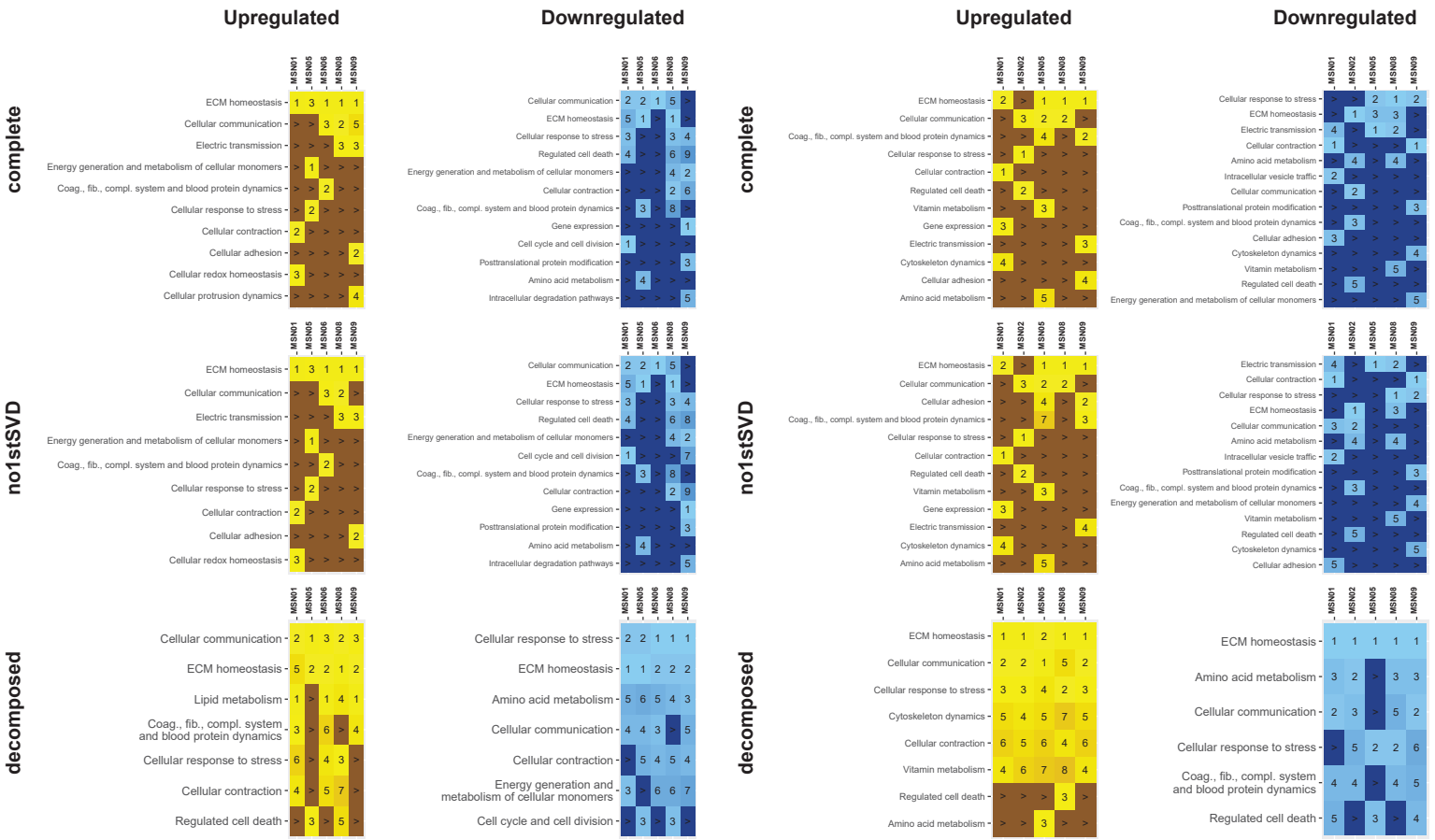
**MBCOL1
estradiol
(is c.toxic: nd)**

**MBCOL1
insulin-like growth factor 1
(is c.toxic: nd)**



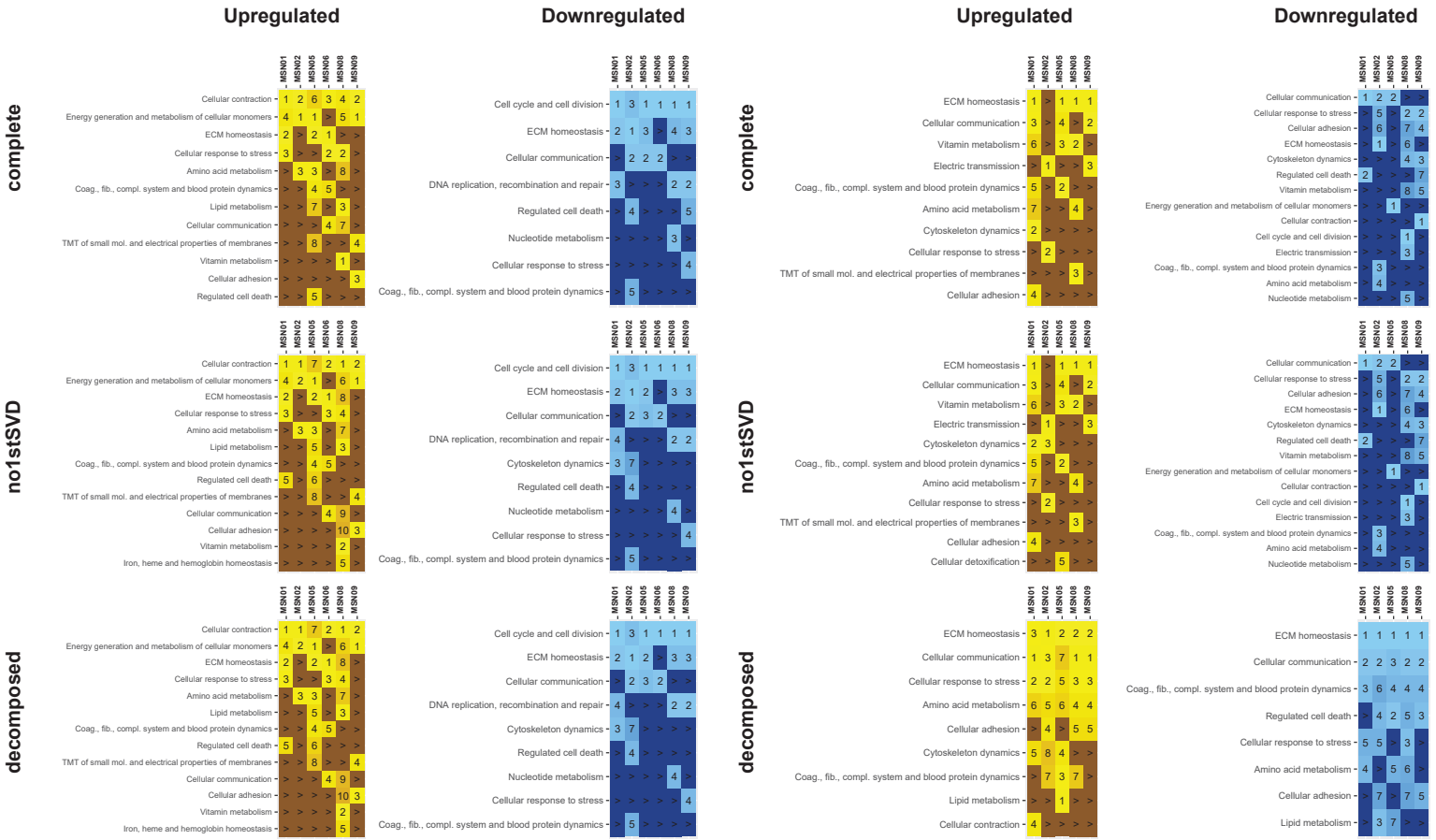
**MBCOL1
olmesartan
(is c.toxic: nd)**

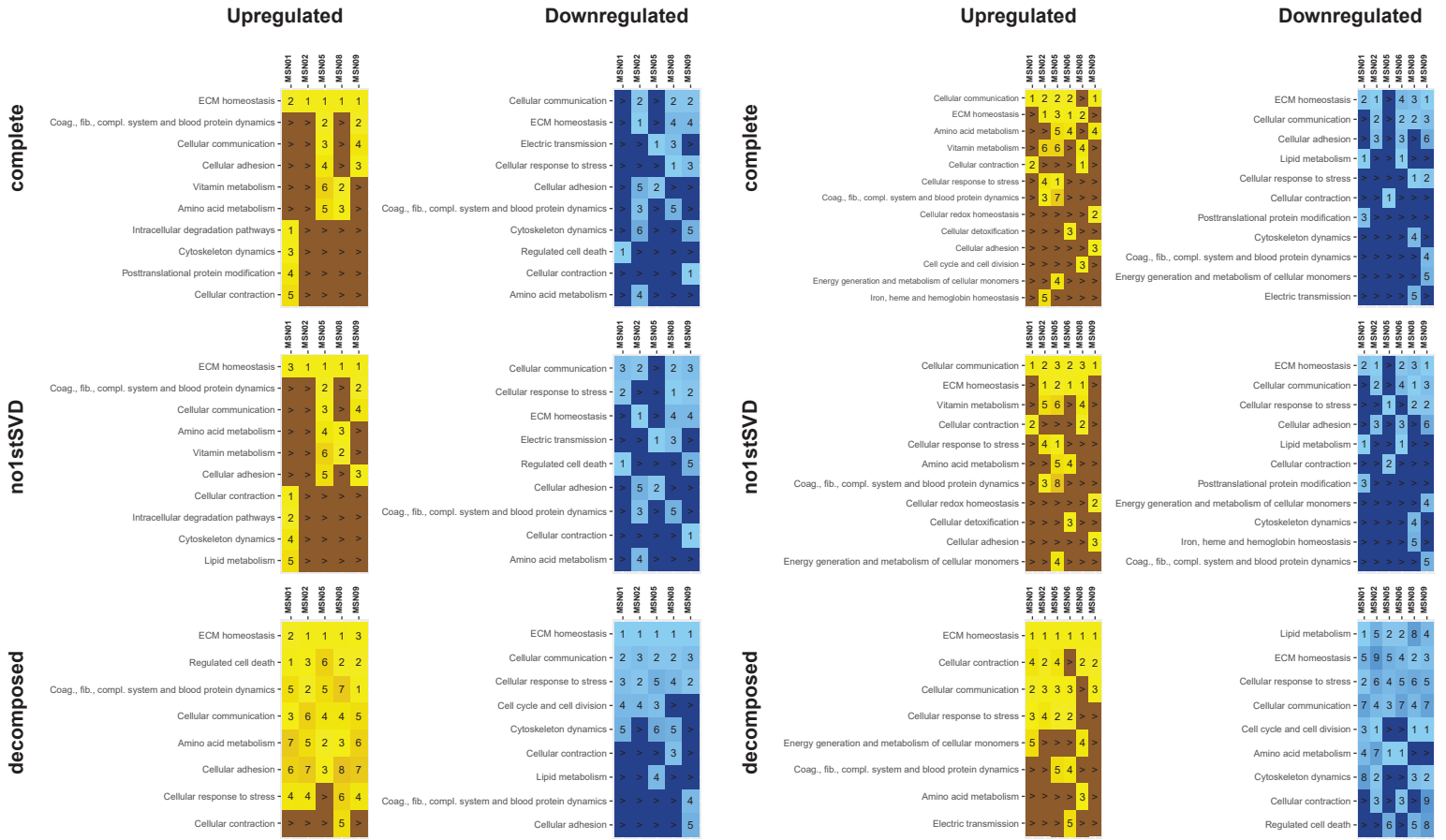
**MBCOL1
pioglitazone
(is c.toxic: nd)**



**MBCOL1
prednisolone
(is c.toxic: nd)**

**MBCOL1
rosiglitazone
(is c.toxic: nd)**





**MBCOL2
afatinib**
(is c.toxic: no)

**MBCOL2
axitinib**
(is c.toxic: no)

Upregulated

Downregulated

Upregulated

Downregulated

complete

complete

complete

no1stSD

no1stSD

decomposed

decomposed

decomposed

**MBCOL2
bosutinib**
(is c.toxic: no)

**MBCOL2
cabozantinib**
(is c.toxic: no)

Upregulated

Downregulated

Upregulated

Downregulated

complete

complete

complete

no1stSD

no1stSD

decomposed

decomposed

decomposed

MBCOL2
ceritinib
(is c.toxic: no)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN09
ECM breakdown	1	3	2	3	4
Apoptosis	7	1	3	2	4
Signaling pathways involved in glucose and lipid homeostasis	3	9	>	1	
Interferon signaling	1	2	12	>	1
Sig. pathways that control cell prol. and diff.	3	7	6	>	1
Pattern recognition signaling	4	6	>	14	3
Signaling pathways involved in hematopoiesis	10	13	2	>	1
Actin filament dynamics	9	3	12	>	5
Elastogenesis	13	13	4	>	1
Matricellular protein signaling	>	4	2	>	1
Collagen biosynthesis	>	5	1	>	1
Cellular response to hypoxia	3	4	>	>	1
Metabolism and transport of cholesterol, steroids and bile acids	>	1	>	7	1
Metabolism of non-essential amino acids	>	2	>	>	1
Complement pathway and regulation	>	7	5	>	1
Cellular response to oxidative stress	5	>	>	>	1
Antigen presentation	5	>	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Mitotic cell cycle checkpoints	2	4	4	2	2
Centrosome cycle	3	3	3	4	4
Cytokinesis	4	5	2	5	3
Microtubule dynamics	7	10	5	>	8
Eukaryotic DNA replication	>	2	>	>	5
Carbohydrate metabolism and transport	>	>	>	>	4
Cardiomyocyte action potential generation and propagation	>	>	>	>	>

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN09
ECM breakdown	6	3	3	5	5
Pattern recognition signaling	4	6	13	15	2
Sig. pathways that control cell prol. and diff.	2	7	3	>	1
Signaling pathways involved in glucose and lipid homeostasis	4	7	1	>	1
Collagen biosynthesis	10	9	5	>	1
Matricellular protein signaling	11	4	2	>	1
Interferon signaling	8	7	>	4	1
Apoptosis	12	8	4	>	1
Elastogenesis	>	12	14	2	1
Signaling pathways involved in hematopoiesis	>	1	>	12	14
Actin filament dynamics	1	1	>	>	1
Metabolism and transport of cholesterol, steroids and bile acids	>	1	>	7	1
Cellular response to hypoxia	7	2	>	>	1
Epidermal growth factor family signaling	>	3	11	>	1
Metabolism of non-essential amino acids	>	2	>	13	1
Complement pathway and regulation	>	3	10	>	1
Cellular response to oxidative stress	>	5	>	>	1
Metabolism of tryptophan products	5	5	>	>	1
Antigen presentation	5	>	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Mitotic cell cycle checkpoints	2	4	4	>	2
Centrosome cycle	4	3	3	>	3
Cytokinesis	3	5	2	>	4
Microtubule dynamics	6	6	5	>	8
Eukaryotic DNA replication	>	2	>	>	7
Carbohydrate metabolism and transport	>	>	>	>	6
Signaling pathways regulating water homeostasis	>	>	>	>	3
Cellular response to hypoxia	>	>	>	>	5
Cardiomyocyte action potential generation and propagation	>	>	>	>	>

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN09
Sig. pathways that control cell prol. and diff.	9	11	9	7	1
Signaling pathways involved in hematopoiesis	14	5	11	10	2
ECM breakdown	6	2	4	6	1
Interferon signaling	3	1	10	>	7
Complement pathway and regulation	11	4	5	9	1
Epidermal growth factor family signaling	13	3	6	4	1
Metabolism and transport of cholesterol, steroids and bile acids	13	12	1	1	5
Matricellular protein signaling	1	8	2	>	8
Cellular response to hypoxia	7	2	>	>	8
Elastogenesis	4	>	16	3	1
Collagen biosynthesis	>	3	1	>	1
Metabolism of non-essential amino acids	>	2	5	>	1
Apoptosis	12	4	>	>	3
Myofibril formation and organization	>	>	>	>	3
Cellular response to oxidative stress	5	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Mitotic cell cycle checkpoints	3	3	4	3	3
Centrosome cycle	5	4	3	2	2
Cytokinesis	2	5	2	4	4
Eukaryotic DNA replication	4	2	>	5	1
Heme, hemoglobin and bilirubin metabolism	>	>	>	>	5

complete

	MSN01	MSN05	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	1	1	2	1	1
Cellular response to oxidative stress	6	2	4	10	5
Signaling pathways involved in hematopoiesis	8	5	9	3	1
Apoptosis	3	6	12	9	1
Sig. pathways that control cell prol. and diff.	8	8	>	2	1
Matricellular protein signaling	7	5	8	>	1
PT protein modification and QC during secretory pathway	2	1	>	1	1
Metabolism and transport of cholesterol, steroids and bile acids	3	3	>	2	1
ECM breakdown	4	>	3	>	1
Glycosaminoglycan metabolism	10	>	6	4	1
Collagen biosynthesis	3	7	>	>	1
Intracellular common signaling cascades of multiple pathways	5	10	>	>	1
Signaling by extracellular matrix components	>	4	>	>	1
Basement membrane dynamics	4	>	>	>	1
Neuronal signaling pathways	>	5	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Myofibril formation and organization	3	2	1	6	3
Metabolism of fat-soluble vitamins	9	6	4	5	1
Cardiomyocyte action potential generation and propagation	4	2	5	>	1
Cellular response to hypoxia	>	2	1	>	1
Apoptosis	5	>	3	>	4
Matricellular protein signaling	3	7	7	>	3
Collagen biosynthesis	2	7	3	>	1
ECM breakdown	3	9	4	>	1
Centrosome cycle	10	4	>	>	1
Epidermal growth factor family signaling	1	1	>	>	1
Complement pathway and regulation	>	1	>	>	1
Chromosome segregation by mitotic spindle	1	1	>	>	1
Eukaryotic DNA replication	1	2	>	>	1
Carbohydrate metabolism and transport	>	3	>	>	2
Neuronal action potential generation and propagation	>	3	>	>	1
Mitotic cell cycle checkpoints	1	3	>	>	1
Metabolism of tryptophan products	3	5	>	>	1
Cytokinesis	5	>	>	>	1

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	1	1	2	1	1
Cellular response to oxidative stress	8	2	6	11	4
Signaling pathways involved in hematopoiesis	10	5	8	3	1
ECM breakdown	4	4	>	6	1
Apoptosis	3	5	>	9	1
Matricellular protein signaling	7	4	8	>	1
Sig. pathways that control cell prol. and diff.	9	11	>	2	1
Collagen biosynthesis	3	7	>	12	1
PT protein modification and QC during secretory pathway	2	1	>	1	1
Metabolism and transport of cholesterol, steroids and bile acids	3	3	>	2	1
Glycosaminoglycan metabolism	>	6	3	>	1
Actin filament dynamics	5	>	>	5	10
Neuronal signaling pathways	>	5	>	>	1
Signaling by extracellular matrix components	>	4	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Myofibril formation and organization	3	2	6	4	1
Metabolism of fat-soluble vitamins	9	6	4	5	1
Cardiomyocyte action potential generation and propagation	4	1	5	>	1
Cellular response to hypoxia	>	2	1	>	1
Apoptosis	5	>	3	>	3
Matricellular protein signaling	2	7	7	>	3
Collagen biosynthesis	2	7	3	>	1
ECM breakdown	3	10	4	>	1
Epidermal growth factor family signaling	1	1	>	>	1
Complement pathway and regulation	>	1	>	>	1
Chromosome segregation by mitotic spindle	1	1	>	>	1
Eukaryotic DNA replication	1	2	>	>	1
Carbohydrate metabolism and transport	>	3	>	>	2
Neuronal action potential generation and propagation	>	3	>	>	1
Mitotic cell cycle checkpoints	1	3	>	>	1
Metabolism of tryptophan products	3	5	>	>	1
Cytokinesis	5	>	>	>	1

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	1	1	2	1	1
Cellular response to oxidative stress	8	2	6	11	4
Signaling pathways involved in hematopoiesis	10	5	8	3	1
ECM breakdown	4	4	>	6	1
Apoptosis	3	5	>	9	1
Matricellular protein signaling	7	4	8	>	1
Sig. pathways that control cell prol. and diff.	9	11	>	2	1
Collagen biosynthesis	3	7	>	12	1
PT protein modification and QC during secretory pathway	2	1	>	1	1
Metabolism and transport of cholesterol, steroids and bile acids	3	3	>	2	1
Glycosaminoglycan metabolism	>	6	3	>	1
Actin filament dynamics	5	>	>	5	10
Neuronal signaling pathways	>	5	>	>	1
Signaling by extracellular matrix components	>	4	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Myofibril formation and organization	3	2	6	4	1
Metabolism of fat-soluble vitamins	9	6	4	5	1
Cardiomyocyte action potential generation and propagation	4	1	5	>	1
Cellular response to hypoxia	>	2	1	>	1
Apoptosis	5	>	3	>	3
Matricellular protein signaling	2	7	7	>	3
Collagen biosynthesis	2	7	3	>	1
ECM breakdown	3	10	4	>	1
Epidermal growth factor family signaling	1	1	>	>	1
Complement pathway and regulation	>	1	>	>	1
Chromosome segregation by mitotic spindle	1	1	>	>	1
Eukaryotic DNA replication	1	2	>	>	1
Carbohydrate metabolism and transport	>	3	>	>	2
Neuronal action potential generation and propagation	>	3	>	>	1
Mitotic cell cycle checkpoints	1	3	>	>	1
Metabolism of tryptophan products	3	5	>	>	1
Cytokinesis	5	>	>	>	1

MBCOL2
crizotinib
(is c.toxic: no)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN09
Matricellular protein signaling	1	2	3	10	1
Collagen biosynthesis	>	1	2	>	1
Myofibril formation and organization	>	1	3	>	1
Cellular response to hypoxia	>	7	3	>	1
Elastogenesis	>	3	5	>	1
Signaling pathways involved in glucose and lipid homeostasis	>	1	>	1	1
ECM breakdown	>	2	>	1	1
Metabolism of glutamate and histidine products	2	>	>	>	1
Ribonucleoprotein biosynthesis	>	2	>	>	1
Cellular response to radiation	>	2	>	>	1
Cellular antioxidant systems	>	2	>	>	1
Vesicle traffic between ER and Golgi	>	3	>	>	1
Cortical cytoskeleton dynamics	3	>	>	>	1
Metabolism of tryptophan products	>	4	>	>	1
Epidermal growth factor family signaling	>	4	>	>	1
Complement pathway and regulation	>	4	>	>	1
Cellular response to oxidative stress	>	4	>	>	1
Coagulation cascade and fibrinolysis	>	5	>	>	1
Apoptosis	5	>	>	>	1

	MSN01	MSN05	MSN06	MSN08	MSN09
Signaling pathways involved in hematopoiesis	5	9	1	8	1
Matricellular protein signaling	3	4	1	3	1
Collagen biosynthesis	1	7	3	>	1
Cytosolic intermediate filament and septin dynamics	6	10	5	>	1
Elastogenesis	6	10	5	>	1
Sig. pathways that control cell prol. and diff.	4	8	1	>	1
ECM breakdown	2	7	>	>	1
Metabolism and transport of cholesterol, steroids and bile acids	3	1	>	4	1
Carbohydrate metabolism and transport	1	2	4	>	1
TGF-beta superfamily signaling	2	1	>	>	1
Cellular response to hypoxia	1	8	>	>	1
Amyloid generation and aggregation	1	8	>	>	1
Basement membrane dynamics	>	1	>	3	1
Chromosome segregation by mitotic spindle	>	1	>	>	1
Neuronal signaling pathways	>	2	>	>	1
Cytokinesis	>	2	>	>	1
Complement pathway and regulation	>	2	>	>	1
Cardiomyocyte action potential generation and propagation	>	5	>	>	1

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN09
Matricellular protein signaling	1	2	3	10	1
Myofibril formation and organization	>	1	3	>	1
Collagen biosynthesis	>	1	2	>	1
Elastogenesis	>	3	5	>	1
Signaling pathways involved in glucose and lipid homeostasis	>	1	>	1	1
ECM breakdown	>	2	>	>	1
Metabolism of glutamate and histidine products	2	>	>	>	1
Ribonucleoprotein biosynthesis	>	2	>	>	1
Cellular response to radiation	>	2	>	>	1
Cellular antioxidant systems	>	2	>	>	1
Vesicle traffic between ER and Golgi	>	3	>	>	1
Cortical cytoskeleton dynamics	3	>	>	>	1
Metabolism of tryptophan products	>	4	>	>	1
Epidermal growth factor family signaling	>	4	>	></	

**MBCOL2
erlotinib**
(is c.toxic: no)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN09
Metabolism of non-essential amino acids	1	1	4	1
Cellular response to oxidative stress	2	3	1	2
Apoptosis	3	3	4	
Cellular response to hypoxia	7	2	>	>
Cellular antioxidant systems	>	6	3	>
Carbohydrate metabolism and transport	2	>	>	>
Iron homeostasis	4	>	>	>
Basement membrane dynamics	4	>	>	>
Cellular response to radiation	>	5	>	>
Ammonium metabolism	>	>	5	>

	MSN01	MSN05	MSN06	MSN09
Chromosome segregation by mitotic spindle	1	1	2	1
Eukaryotic DNA replication	6	7	1	2
Cytokinesis	2	5	4	5
Mitotic cell cycle checkpoints	3	4	6	3
Centrosome cycle	4	9	5	4
DNA interstrand cross-links repair	5	12	3	8
Matricellular protein signaling	7	3	12	9
Collagen biosynthesis	2	9	16	>

no1stSVD

	MSN01	MSN05	MSN06	MSN09
Metabolism of non-essential amino acids	1	1	4	1
Cellular response to oxidative stress	5	3	1	2
Apoptosis	2	3	3	
Myofibril formation and organization	3	5	>	>
Cellular response to hypoxia	7	2	>	>
Carbohydrate metabolism and transport	2	>	>	>
TM ion transport involved in membrane potential generation	>	>	4	>
Basement membrane dynamics	4	>	>	>
Cellular antioxidant systems	>	5	>	>

	MSN01	MSN05	MSN06	MSN09
Chromosome segregation by mitotic spindle	1	1	2	1
Mitotic cell cycle checkpoints	3	4	8	3
Cytokinesis	2	5	7	5
Centrosome cycle	4	9	5	4
DNA interstrand cross-links repair	8	12	3	7
Matricellular protein signaling	5	3	15	8
Microtubule dynamics	6	2	4	11
Eukaryotic DNA replication	7	1	2	>
Collagen biosynthesis	2	6	16	>

decomposed

	MSN01	MSN05	MSN06	MSN09
Metabolism of non-essential amino acids	1	1	1	1
Cellular response to oxidative stress	3	2	3	2
Apoptosis	4	3	2	3
Cellular antioxidant systems	10	5	8	6
Myofibril formation and organization	7	5	4	>
Cellular response to hypoxia	9	4	7	>
ECM breakdown	2	6	>	>
DNA recombination	6	5	>	>
Cellular response to radiation	>	4	>	>
Metabolism and transport of cholesterol, steroids and bile acids	5	>	>	>

	MSN01	MSN05	MSN06	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1
Eukaryotic DNA replication	2	2	2	2
Mitotic cell cycle checkpoints	3	5	3	3
Cytokinesis	4	3	4	4
Centrosome cycle	5	6	5	5
Matricellular protein signaling	4	6	7	>

complete

	MSN01	MSN05	MSN06	MSN09
Collagen biosynthesis	7	1	3	1
Epidermal growth factor family signaling	2	2	4	2
TM ion transport involved in membrane potential generation	2	2	4	2
Matricellular protein signaling	1	1	6	1
Myofibril formation and organization	1	1	6	1
Cellular response to hypoxia	1	1	6	1
Apoptosis	1	1	6	1
Complement pathway and regulation	1	1	6	1
Cellular response to oxidative stress	2	2	4	2
Signaling pathways involved in hematopoiesis	3	3	4	3
Pattern recognition signaling	3	3	4	3
Elastogenesis	4	4	3	4
Interphase nucleus and nuclear chromatin organization	4	4	3	4
Neoptosis	5	5	1	5
Cellular response to energy deprivation	5	5	1	5

no1stSVD

	MSN01	MSN05	MSN06	MSN09
Collagen biosynthesis	6	1	3	1
TM ion transport involved in membrane potential generation	1	1	5	1
Matricellular protein signaling	1	1	2	4
Cellular response to hypoxia	1	1	2	4
Apoptosis	1	1	2	4
Pattern recognition signaling	3	3	2	1
Complement pathway and regulation	3	3	2	1
Cellular response to oxidative stress	2	2	4	2
Cell-cell adhesion	2	2	4	2
Signaling pathways involved in hematopoiesis	3	3	4	3
Cardiomyocyte action potential generation and propagation	4	4	3	4
Interphase nucleus and nuclear chromatin organization	4	4	3	4
Elastogenesis	5	5	4	5
Neoptosis	5	5	1	5
Cellular response to energy deprivation	5	5	1	5

decomposed

	MSN01	MSN05	MSN06	MSN09
ECM breakdown	7	3	6	3
Cellular response to oxidative stress	2	6	4	8
Collagen biosynthesis	3	7	1	9
Complement pathway and regulation	1	2	1	1
Metabolism of non-essential amino acids	2	2	3	2
Matricellular protein signaling	5	5	4	5
Apoptosis	4	4	5	7
Sig. pathways that control cell prol. and diff.	4	4	9	4
Myofibril formation and organization	1	7	10	>

**MBCOL2
gefitinib**
(is c.toxic: no)

Upregulated

Downregulated

	MSN01	MSN05	MSN06	MSN09
Matricellular protein signaling	8	2	7	2
Chromosome segregation by mitotic spindle	1	1	1	1
Mitotic cell cycle checkpoints	3	5	4	2
Centrosome cycle	4	3	4	3
Cytokinesis	2	4	5	5
Microtubule dynamics	5	8	6	11
Collagen biosynthesis	1	6	10	14
Metabolism and transport of cholesterol, steroids and bile acids	7	2	7	7
ECM breakdown	6	4	>	13
Carbohydrate metabolism and transport	>	11	>	3
Elastogenesis	14	3	>	>
Metabolism of fat-soluble vitamins	5	>	>	>

	MSN01	MSN05	MSN06	MSN09
Matricellular protein signaling	8	2	7	2
Chromosome segregation by mitotic spindle	1	1	1	1
Centrosome cycle	4	3	3	3
Cytokinesis	2	4	5	4
Mitotic cell cycle checkpoints	3	5	4	6
Microtubule dynamics	5	6	10	15
Collagen biosynthesis	1	9	10	15
Metabolism and transport of cholesterol, steroids and bile acids	6	2	7	7
Sig. pathways that control cell prol. and diff.	11	4	>	7
Elastogenesis	14	3	>	>
Cellular response to hypoxia	13	>	>	5
Carbohydrate metabolism and transport	>	>	>	2
Metabolism of fat-soluble vitamins	5	>	>	>

	MSN01	MSN05	MSN06	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1
Cytokinesis	2	2	3	2
Mitotic cell cycle checkpoints	3	3	5	4
Centrosome cycle	4	4	3	5
Matricellular protein signaling	5	5	4	5

**MBCOL2
imatinib**
(is c.toxic: no)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	5	1	2	1
Chromosome segregation by mitotic spindle	1	3	1	>
Centrosome cycle	3	6	3	>
Mitotic cell cycle checkpoints	2	7	4	>
Fatty acid metabolism	8	4	2	>
Mitochondrial energy production	6	2	7	>
Cytokinesis	4	8	5	>
Cardiomyocyte action potential generation and propagation	>	>	3	>
Signaling pathways involved in glucose and lipid homeostasis	>	>	4	>
ECM breakdown	>	>	5	>
Carbohydrate metabolism and transport	5	>	>	>

	MSN01	MSN05	MSN06	MSN09
Collagen biosynthesis	1	2	6	>
Matricellular protein signaling	3	2	5	>
Epidermal growth factor family signaling	5	8	1	>
Elastogenesis	4	5	7	>
ECM breakdown	2	3	>	>
Sig. pathways that control cell prol. and diff.	4	4	3	>
Cellular response to hypoxia	6	1	1	>
Myofibril formation and organization	>	3	8	>
Metabolism of fat-soluble vitamins	9	4	4	>
Fibronectin matrix dynamics	1	>	>	>
Carbohydrate metabolism and transport	>	>	2	>
Cell-cell adhesion	4	4	>	>

no1stSVD

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	5	1	2	1
Chromosome segregation by mitotic spindle	1	3	1	>
Mitotic cell cycle checkpoints	2	5	4	>
Centrosome cycle	4	4	3	>
Mitochondrial energy production	6	2	7	>
Fatty acid metabolism	8	6	2	>
Cytokinesis	3	8	5	>
Cardiomyocyte action potential generation and propagation	>	>	3	>
Signaling pathways involved in glucose and lipid homeostasis	>	>	4	>
Signaling pathways involved in hematopoiesis	>	>	5	>

	MSN01	MSN05	MSN06	MSN09
Collagen biosynthesis	1	2	6	>
Epidermal growth factor family signaling	1	8	1	>
Matricellular protein signaling	4	2	5	>
Elastogenesis	5	5	7	>
ECM breakdown	3	3	>	>
Sig. pathways that control cell prol. and diff.	4	4	3	>
Cellular response to hypoxia	6	1	1	>
Metabolism of fat-soluble vitamins	9	4	4	>
Fibronectin matrix dynamics	2	>	>	>
Carbohydrate metabolism and transport	>	>	2	>

decomposed

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	2	2	2	1
Chromosome segregation by mitotic spindle	1	1	1	>
Mitotic cell cycle checkpoints	4	5	3	>
Centrosome cycle	3	4	5	>
Cytokinesis	6	3	4	>
Fatty acid metabolism	8	9	2	>
Cellular antioxidant systems	7	>	3	>
Cellular response to oxidative stress	5	9	>	>
ECM breakdown	>	11	4	>
Metabolism of glutamate and histidine products	>	>	5	>

	MSN01	MSN05	MSN06	MSN09
Sig. pathways that control cell prol. and diff.	4	5	2	3
Matricellular protein signaling	3	2	6	>
Cellular response to hypoxia	2	8	1	>
ECM breakdown	12	3	4	>
Epidermal growth factor family signaling	15	12	3	>
Metabolism of non-essential amino acids	1	1	1	5
Collagen biosynthesis	1	>	5	>
Metabolism of fat-soluble vitamins	5	>	4	>
Carbohydrate metabolism and transport	>	>	2	>
Elastogenesis	4	>	>	>

complete

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	4	1	1	1
Interferon signaling	5	8	2	2
Cellular response to oxidative stress	8	8	11	2
Collagen biosynthesis	2	7	4	4
Fatty acid metabolism	2	7	4	4
Complement pathway and regulation	2	9	4	3
Gastrointestinal hormone signaling	2	9	4	3
ECM breakdown	2	2	4	2
Steroid and sex hormone signaling	2	2	4	2
Signaling pathways involved in hematopoiesis	3	3	4	3
Pattern recognition signaling	3	3	4	3
Elastogenesis	4	3	4	3
Lipid droplet dynamics	4	3	4	3
Amyloid generation and aggregation	4	3	4	3
Matricellular protein signaling	4	3	4	3
Apoptosis	4	3	4	3
Antigen presentation	4	3	4	3

no1stSVD

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	1	1	1	1
Interferon signaling	2	2	2	4
Cellular response to oxidative stress	8	7	6	3
Collagen biosynthesis	11	8	6	5
Complement pathway and regulation	11	8	6	5
Amyloid generation and aggregation	11	8	6	5
Gastrointestinal hormone signaling	12	5	3	4
ECM breakdown	2	2	4	2
Steroid and sex hormone signaling	2	2	4	2
Pattern recognition signaling	3	3	4	3
Lipid droplet dynamics	4	3	4	3
Elastogenesis	4	3	4	3
Signaling pathways involved in hematopoiesis	4	3	4	3
Matricellular protein signaling	4	3	4	3
Cardiomyocyte action potential generation and propagation	4	3	4	3
Antigen presentation	4	3	4	3

decomposed

	MSN01	MSN05	MSN06	MSN09
Metabolism and transport of cholesterol, steroids and bile acids	1	1	1	1
Interferon signaling	2	2	2	4
Sig. pathways that control cell prol. and diff.	8	7	6	3
Collagen biosynthesis	11	8	6	5
Cellular response to hypoxia	3	3	8	5
Gastrointestinal hormone signaling	12	5	3	4
Signaling pathways involved in hematopoiesis	5	10	12	>
Cellular response to oxidative stress	4	5	3	>
Complement pathway and regulation	4	4	6	>
Cardiomyocyte action potential generation and propagation	4	4	7	>
Amyloid generation and aggregation	3	4	10	>
Apoptosis	3	4	10	>
Matricellular protein signaling	3	4	10	>
Metabolism of tryptophan products	3	4	10	>

**MBCOL2
lapatinib**

**MBCOL2
nilotinib
(is c.toxic: no)**

Upregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	9	1	1	1	1
Metabolism of non-essential amino acids	5	2	5	3	5
Centrosome cycle	14	6	2	2	2
Cytokinesis	9	3	5	4	
Mitotic cell cycle checkpoints	13	4	4	4	3
Cellular response to hypoxia	1	>	>	>	>
Collagen biosynthesis	13	>	>	>	>
Rolling cell adhesion	3	>	>	>	>
Myofibril formation and organization	3	>	>	>	>
Metabolism of glutamate and histidine products	4	>	>	>	>
Elastogenesis	4	>	>	>	>
Metabolism and transport of cholesterol, steroids and bile acids	5	>	>	>	>

Downregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Myofibril formation and organization	7	1	1	1	1
Neuronal action potential generation and propagation	6	3	14	11	
Sig. pathways that control cell prol. and diff.	2	8	5	>	>
Actin filament dynamics	9	2	5	>	>
Cytosolic intermediate filament and septin dynamics	10	>	4	4	
Amyloid generation and aggregation	3	13	14	>	>
Cellular response to hypoxia	3	>	3	>	>
Collagen biosynthesis	1	6	>	>	>
Signaling pathways involved in hematopoiesis	1	7	3	>	>
Cardiomyocyte action potential generation and propagation	1	9	>	>	>
Fibronectin matrix dynamics	9	5	8	>	>
Epidermal growth factor family signaling	2	11	8	>	>
Metabolism of fat-soluble vitamins	4	12	>	>	>
Carbohydrate metabolism and transport	4	>	2	>	>
Intracellular common signaling cascades of multiple pathways	4	>	>	>	>
Elastogenesis	4	>	>	>	>

complete

no1stSVD

decomposed

	MSN01	MSN02	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	9	1	1	1	1
Metabolism of non-essential amino acids	5	2	5	4	5
Centrosome cycle	14	6	2	2	2
Mitotic cell cycle checkpoints	13	3	3	3	
Cytokinesis	9	4	5	4	
Myofibril formation and organization	1	>	>	>	>
Collagen biosynthesis	2	>	>	>	>
Rolling cell adhesion	3	5	>	>	>
Cellular response to hypoxia	3	>	>	>	>
Metabolism of glutamate and histidine products	4	>	>	>	>
Elastogenesis	4	>	>	>	>
Metabolism and transport of cholesterol, steroids and bile acids	5	>	>	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09
Myofibril formation and organization	3	1	1	1	1
Neuronal action potential generation and propagation	5	2	10	11	
Sig. pathways that control cell prol. and diff.	2	8	5	>	>
Cytosolic intermediate filament and septin dynamics	10	>	2	4	
Actin filament dynamics	9	3	6	>	>
Amyloid generation and aggregation	3	13	8	>	>
Cellular response to hypoxia	2	4	3	>	>
Collagen biosynthesis	1	4	>	>	>
Cardiomyocyte action potential generation and propagation	1	9	>	>	>
Fibronectin matrix dynamics	9	5	7	>	>
Metabolism of fat-soluble vitamins	4	11	>	>	>
Carbohydrate metabolism and transport	4	11	5	>	>
Epidermal growth factor family signaling	3	2	>	>	>
Elastogenesis	4	>	>	>	>
Autophagy	4	>	>	>	>
Intracellular common signaling cascades of multiple pathways	4	>	>	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Cytokinesis	2	2	3	4	2
Mitotic cell cycle checkpoints	3	3	4	3	3
Centrosome cycle	4	4	2	2	4
Metabolism of non-essential amino acids	7	5	5	5	5
Cellular response to oxidative stress	5	6	6	6	6

	MSN01	MSN02	MSN06	MSN08	MSN09
Collagen biosynthesis	7	1	2	6	6
Sig. pathways that control cell prol. and diff.	3	9	11	7	4
Myofibril formation and organization	2	2	1	1	1
ECM breakdown	2	11	4	3	
Cardiomyocyte action potential generation and propagation	6	5	8	2	
Signaling pathways involved in hematopoiesis	6	12	3	2	
Amyloid generation and aggregation	8	4	8	12	
Phase II biotransformation	7	4	4	8	
Microtubule protein signaling	1	>	3	>	>
Metabolism of fat-soluble vitamins	3	5	>	>	>
Elastogenesis	4	10	>	>	>
Steroid hormone metabolism	5	5	>	>	>
Signaling by extracellular matrix components	5	5	>	>	>
Cellular response to hypoxia	5	>	>	5	>

**MBCOL2
pazopanib
(is c.toxic: yes)**

Upregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	2	2	1	2	
Carbohydrate metabolism and transport	3	4	10	3	
Fatty acid metabolism	11	6	1	3	
PT protein modification in mitochondria	4	5	11	5	
Mitochondrial energy production	1	1	8	4	
Metabolism and transport of cholesterol, steroids and bile acids	8	>	2	5	1
Degradation by lysosomal enzymes	5	4	8	>	>
Ammonium metabolism	9	>	5	8	>
Collagen biosynthesis	>	>	3	>	>
Cellular antioxidant systems	>	>	3	>	>

Downregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Sig. pathways that control cell prol. and diff.	4	1	7	3	
ECM breakdown	6	3	4	10	
Cell-cell adhesion	2	6	3	12	
Cellular response to hypoxia	11	6	1	1	
Cardiomyocyte action potential generation and propagation	5	1	4	2	
Collagen biosynthesis	2	1	7	1	
Myofibril formation and organization	5	1	8	2	
Apoptosis	5	1	5	5	
Cellular response to radiation	3	9	>	>	>
Epidermal growth factor family signaling	4	9	>	>	>
Signaling by extracellular matrix components	>	>	4	12	>
TGF-beta superfamily signaling	>	>	3	2	>
Neuronal signaling pathways	>	>	2	5	>
Elastogenesis	5	>	>	>	>

complete

no1stSVD

decomposed

	MSN01	MSN02	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	3	2	1	2	
Mitochondrial energy production	1	1	8	2	
Carbohydrate metabolism and transport	2	3	11	4	
Fatty acid metabolism	12	4	5	1	
PT protein modification in mitochondria	4	6	10	5	
Metabolism and transport of cholesterol, steroids and bile acids	9	>	1	5	1
Degradation by lysosomal enzymes	5	4	8	>	>
Cellular antioxidant systems	7	5	>	>	>
Collagen biosynthesis	>	>	3	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09
Sig. pathways that control cell prol. and diff.	4	1	4	4	3
ECM breakdown	3	3	2	6	
Signaling pathways involved in hematopoiesis	3	7	10	3	
Cell-cell adhesion	6	5	7	8	
Cellular response to hypoxia	12	15	1	1	
Cardiomyocyte action potential generation and propagation	5	1	9	5	
Apoptosis	5	1	10	5	
Collagen biosynthesis	2	7	7	1	
Epidermal growth factor family signaling	4	6	>	>	>
Cellular response to radiation	2	9	>	>	>
Microtubule dynamics	>	4	12	>	>
Myofibril formation and organization	>	13	>	>	>
Neuronal signaling pathways	>	2	5	>	>
TGF-beta superfamily signaling	>	5	>	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09
Metabolism of non-essential amino acids	3	2	2	3	
Mitochondrial energy production	1	1	8	2	
Carbohydrate metabolism and transport	2	3	11	4	
Fatty acid metabolism	12	4	5	1	
PT protein modification in mitochondria	4	6	10	5	
Metabolism and transport of cholesterol, steroids and bile acids	9	>	1	5	1
Degradation by lysosomal enzymes	5	4	8	>	>
Cellular antioxidant systems	7	5	>	>	>
Collagen biosynthesis	>	>	3	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09
Sig. pathways that control cell prol. and diff.	4	1	4	4	3
ECM breakdown	3	3	2	6	
Signaling pathways involved in hematopoiesis	3	7	10	3	
Cell-cell adhesion	6	5	7	8	
Cellular response to hypoxia	12	15	1	1	
Cardiomyocyte action potential generation and propagation	5	1	9	5	
Apoptosis	5	1	10	5	
Collagen biosynthesis	2	7	7	1	
Epidermal growth factor family signaling	4	6	>	>	>
Cellular response to radiation	2	9	>	>	>
Microtubule dynamics	>	4	12	>	>
Myofibril formation and organization	>	13	>	>	>
Neuronal signaling pathways	>	2	5	>	>
TGF-beta superfamily signaling	>	5	>	>	>

**MBCOL2
ponatinib
(is c.toxic: yes)**

Upregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Centrosome cycle	3	2	2	2	2
Cytokinesis	4	3	4	4	3
Mitotic cell cycle checkpoints	5	3	3	3	4
Microtubule organization center dynamics	17	7	7	5	10
Microtubule dynamics	13	>	5	6	6
Metabolism of non-essential amino acids	2	4	6	>	>
Cellular response to hypoxia	15	1	>	>	>
Carbohydrate metabolism and transport	3	2	>	>	>
Vesicle exocytosis	3	3	>	>	>
Prostanoid receptor signaling	3	4	>	>	>
Ribonucleoprotein biogenesis	3	>	>	5	>
Drug and toxin export	3	5	>	>	>

Downregulated

	MSN01	MSN02	MSN06	MSN08	MSN09
Myofibril formation and organization	1	0	1	1	1
Signaling pathways involved in hematopoiesis	4	16	12	10	8
ECM breakdown	3	5	6	9	
Sig. pathways that control cell prol. and diff.	9	4	7	4	4
Microtubule protein signaling	6	2	14	4	6
Basement membrane dynamics	5	4	7	11	6
Elastogenesis	5	4	7	11	6
Cytosolic intermediate filament and septin dynamics	11	3	5	11	
Actin filament dynamics	5	4	5	8	15
Cellular response to hypoxia	1	1	1	12	
Collagen biosynthesis	5	12	2	1	
Cellular response to energy deprivation	5	12	2	3	
Apoptosis	9	3	15	4	5
Cardiomyocyte action potential generation and propagation	9	3	15	4	5
Fibronectin matrix dynamics	9	3	15	4	5
Metabolism and transport of cholesterol, steroids and bile acids	9	3	15	4	5
Cellular response to oxidative stress	3	7	4	3	
Carbohydrate metabolism and transport	3	7	4	3	

complete

no1stSVD

decomposed

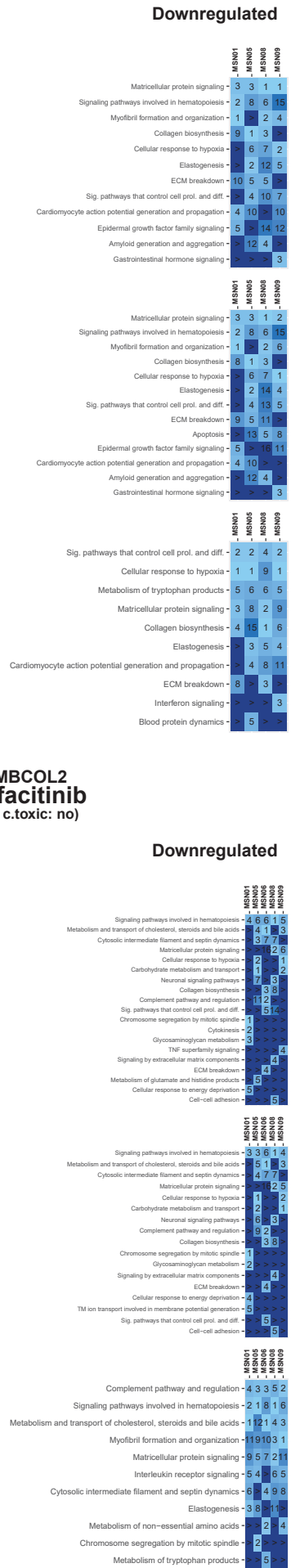
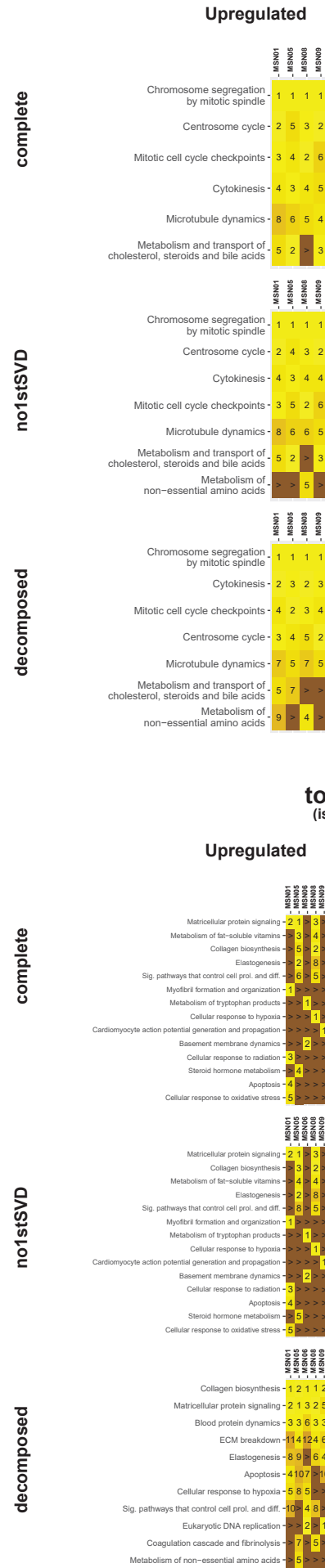
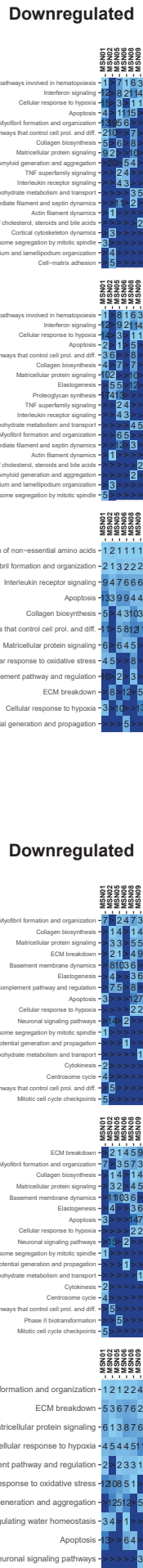
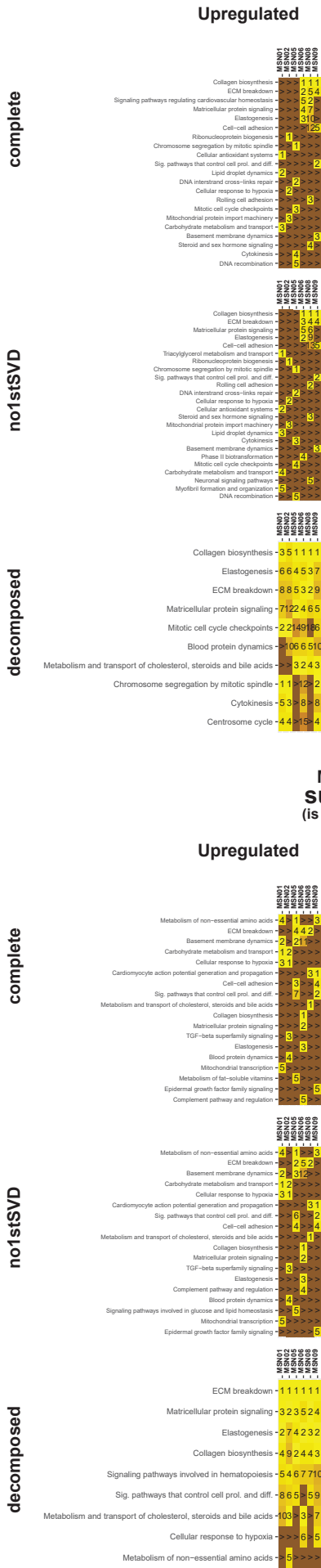
	MSN01	MSN02	MSN06	MSN08	MSN09
Chromosome segregation by mitotic spindle	1	1	1	1	1
Centrosome cycle	3	2	2	2	2
Cytokinesis	5	3	4	3	3
Mitotic cell cycle checkpoints	4	4	3	4	4
Microtubule organization center dynamics	8	7	7	5	10
Microtubule dynamics	12	8	5	6	6
Metabolism of non-essential amino acids	2	5	6	>	>
Cellular response to hypoxia	10	1	>	>	>
Carbohydrate metabolism and transport	3	2	>	>	>
Vesicle exocytosis	3	3	>	>	>
Prostanoid receptor signaling	3	4	>	>	>
Ribonucleoprotein biogenesis	3	>	>	5	>
Drug and toxin export	3	5	>	>	>

	MSN01	MSN02	MSN06	MSN08	MSN09	
Signaling pathways involved in hematopoiesis	4	17	12	6	13	8
Myofibril formation and organization	1	8	1	1	2	
Sig. pathways that control cell prol. and diff.	9	4	7	4	6	
Microtubule protein signaling	6	2	15	4	6	
Basement membrane dynamics	5	4	7	3	6	7
ECM breakdown	3	5	10	8		
Elastogenesis	5	4	7	10		
Cytosolic intermediate filament and septin dynamics	11	3	5	11		
Actin filament dynamics	6	4	7	15		
Cellular response to hypoxia	7	3	2	1		
Collagen biosynthesis	1	1	1	11		
Cellular response to energy deprivation	5	12	2	3		
Apoptosis	9	3	15	4	5	
Neuronal action potential generation and propagation	9	3	15	4	5	
Fibronectin matrix dynamics	9	3	15	4	5	
Metabolism and transport of cholesterol, steroids and bile acids	9	3	15	4	5	
Cellular response to oxidative stress	3	7	4	3		
Cardiomyocyte action potential generation and propagation	9	3	15	4	5	
Carbohydrate metabolism and transport	3	7	4	3		

	MSN01
--	-------

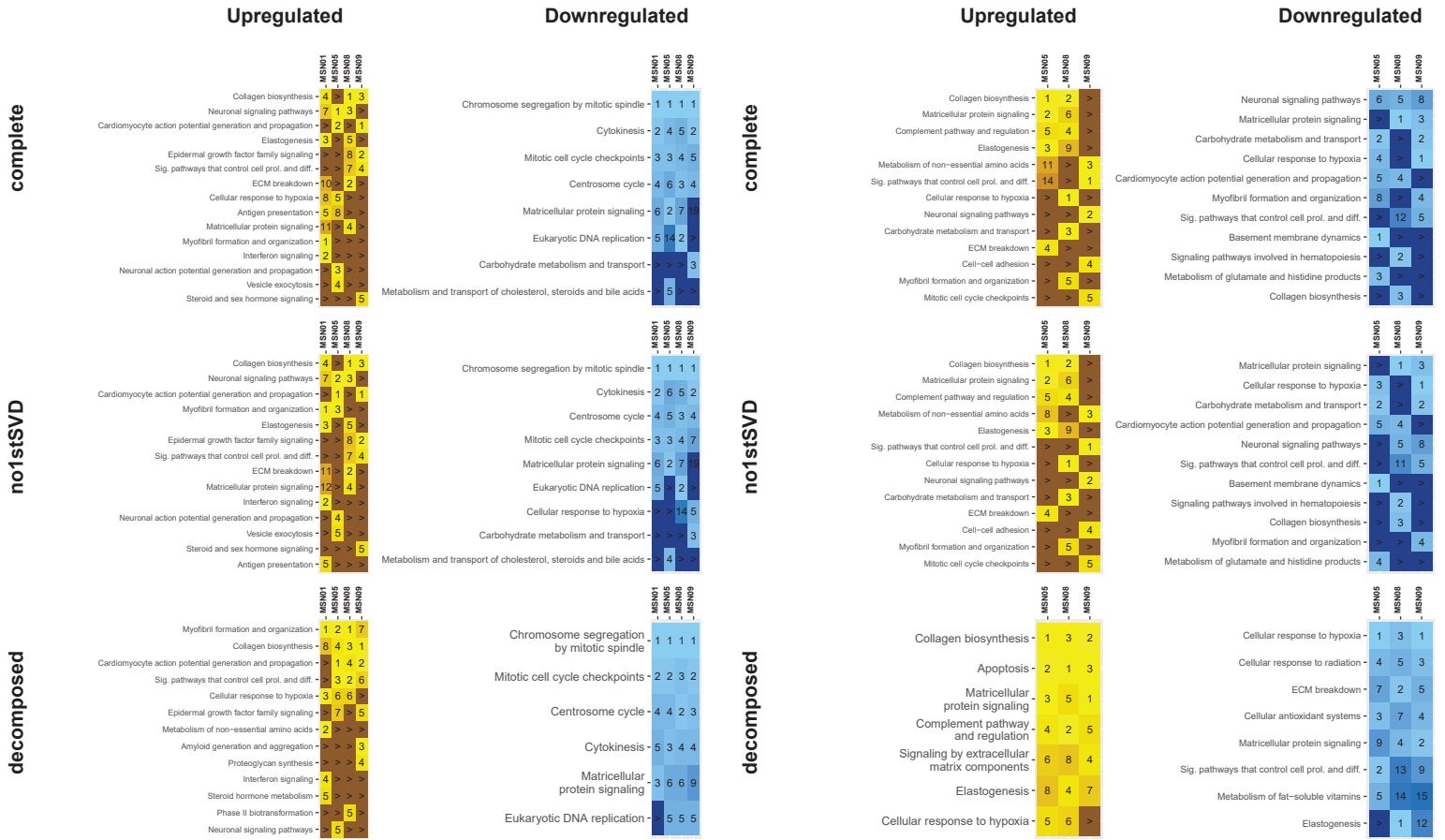
**MBCOL2
ruxolitinib
(is c.toxic: no)**

**MBCOL2
sorafenib
(is c.toxic: yes)**



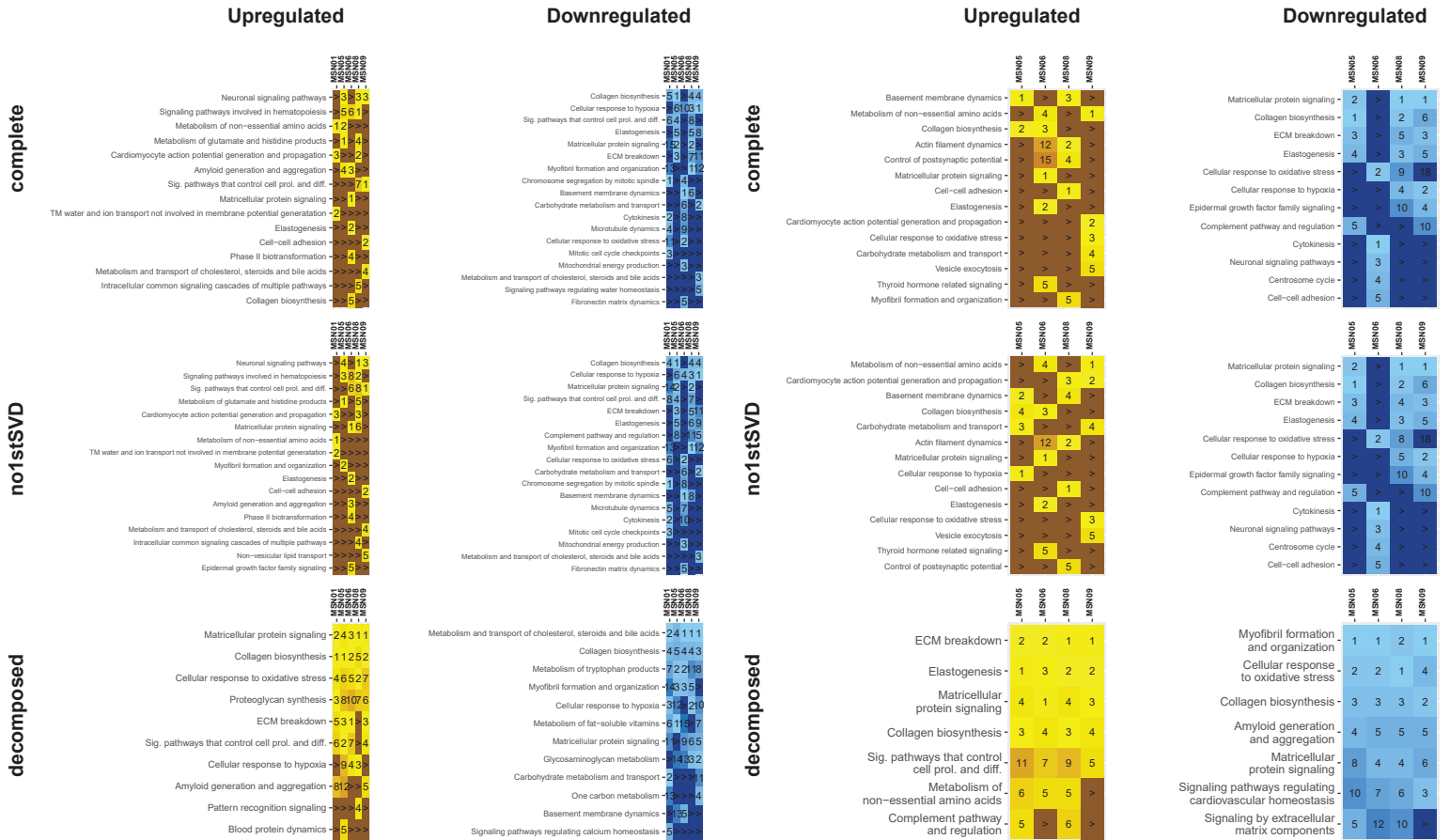
**MBCOL2
trametinib
(is c.toxic: yes)**

**MBCOL2
vandetanib
(is c.toxic: yes)**



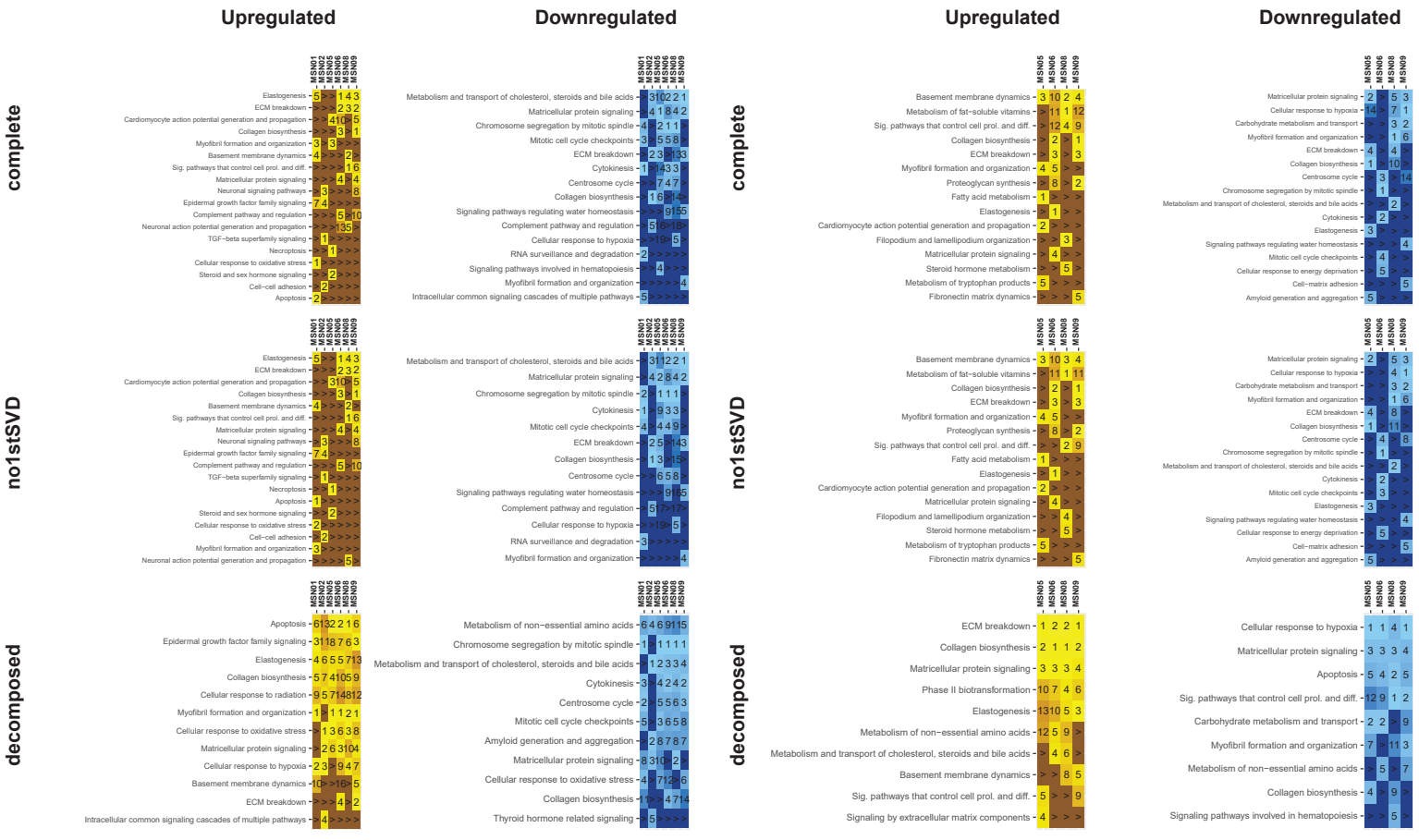
**MBCOL2
vemurafenib
(is c.toxic: no)**

**MBCOL2
bevacizumab
(is c.toxic: yes)**



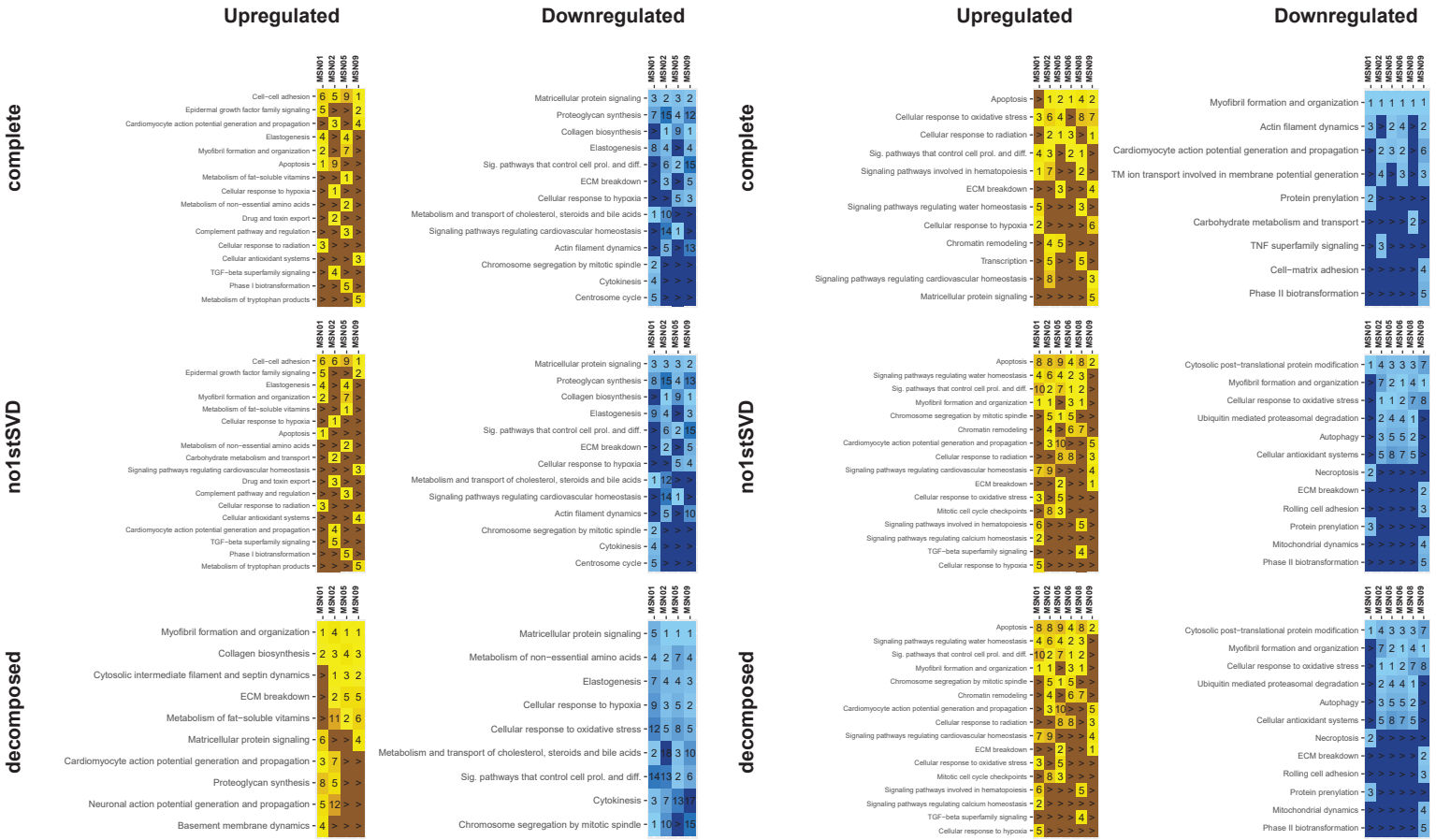
**MBCOL2
cetuximab
(is c.toxic: no)**

**MBCOL2
rituximab
(is c.toxic: no)**



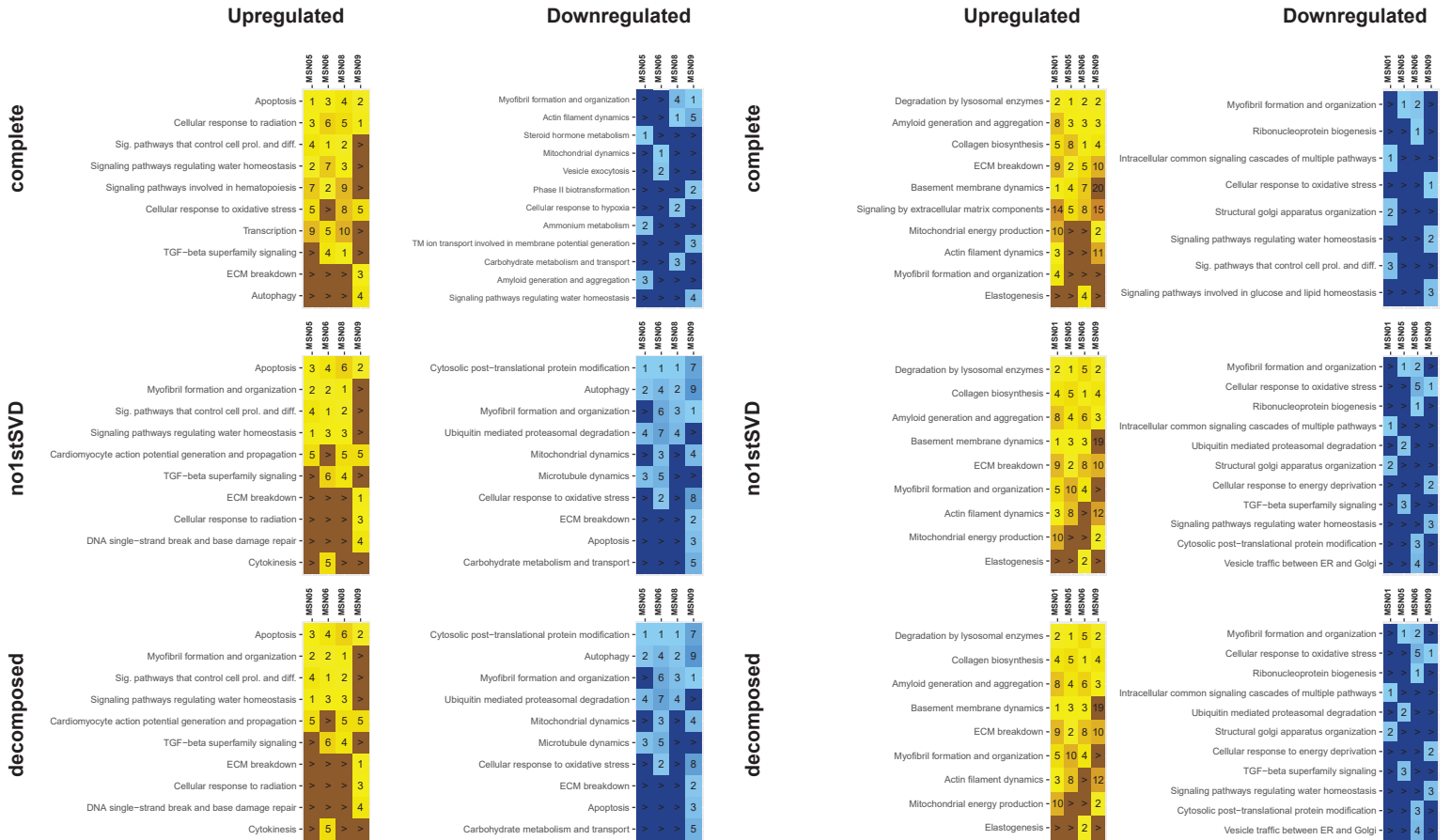
**MBCOL2
trastuzumab
(is c.toxic: yes)**

**MBCOL2
daunorubicin
(is c.toxic: yes)**



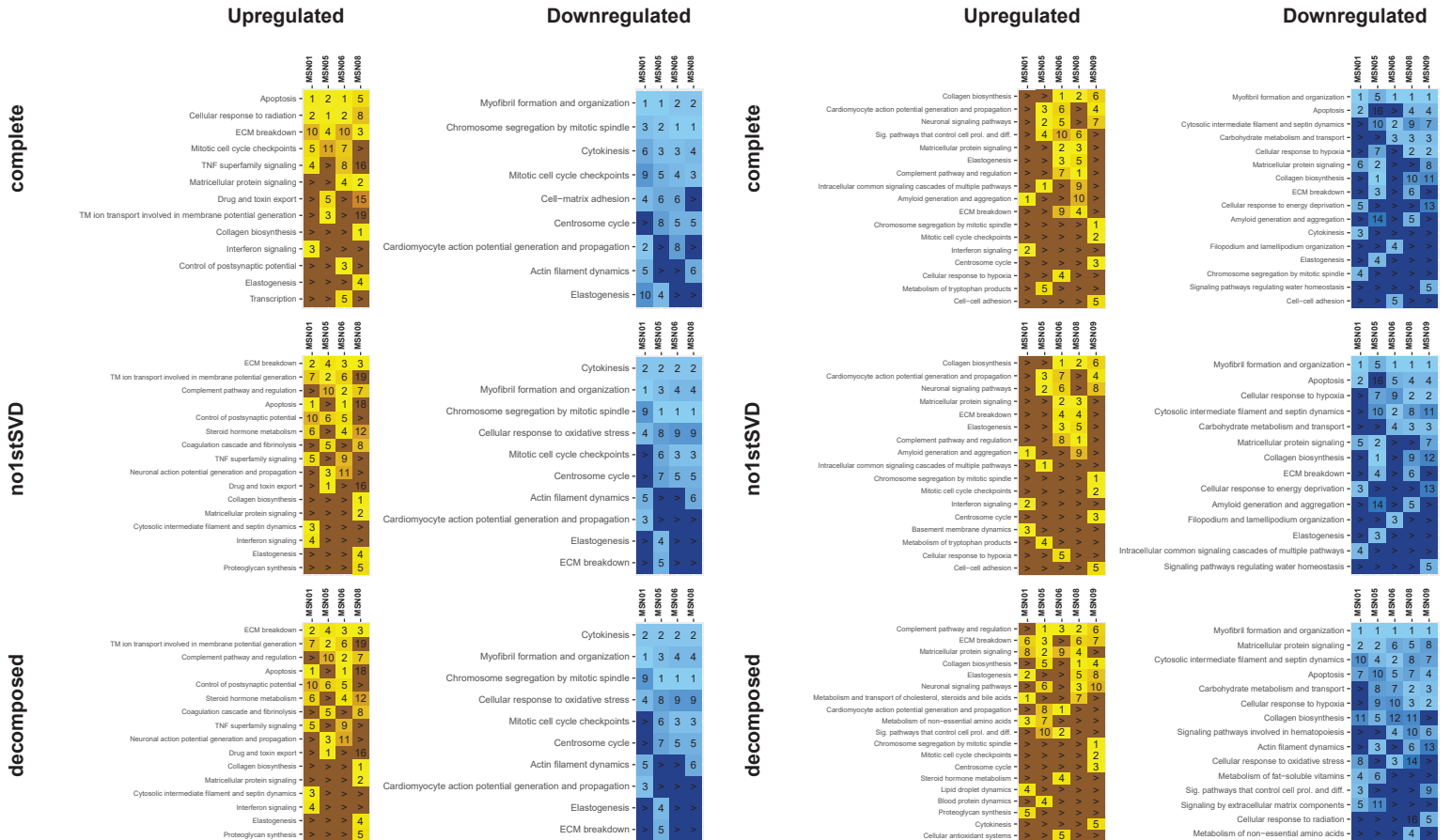
**MBCOL2
doxorubicin**
(is c.toxic: yes)

**MBCOL2
epirubicin**
(is c.toxic: yes)



**MBCOL2
idarubicin**
(is c.toxic: yes)

**MBCOL2
amiodarone**
(is c.toxic: nd)



MBCOL2
dobutamine
(is c.toxic: nd)

MBCOL2
flecainide
(is c.toxic: nd)

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	7	1	4	1	1
Carbohydrate metabolism and transport	2	2	1	9	2
Sig. pathways that control cell prol. and diff.	8	8	3	3	3
Basement membrane dynamics	1	1	4	4	4
Matricellular protein signaling	2	1	1	6	6
Elastogenesis	3	3	5	5	5
Cardiomyocyte action potential generation and propagation	2	2	7	7	7
Control of postsynaptic potential	5	5	5	5	5
Photolytic synthesis	1	1	5	10	10
Puynergic signaling	1	1	1	1	1
Cellular response to hypoxia	1	1	1	2	2
Actin filament dynamics	3	3	3	3	3
Signaling pathways involved in hematopoiesis	3	3	3	3	3
Mitochondrial dynamics	3	3	3	3	3
Metabolism of glutamate and histidine products	3	3	3	3	3
Neuronal signaling pathways	4	4	4	4	4
Myofibril formation and organization	4	4	4	4	4
Metabolism and transport of cholesterol, steroids and bile acids	4	4	4	4	4
TM water and ion transport not involved in membrane potential generation	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
Matricellular protein signaling	8	2	1	1	6
Cellular response to oxidative stress	10	2	12	3	3
Mitotic cell cycle checkpoints	3	1	14	2	2
Collagen biosynthesis	1	1	5	1	1
Centrosome cycle	4	1	4	4	4
Cytokinesis	2	6	7	4	4
Complement pathway and regulation	6	6	4	4	4
Sig. pathways that control cell prol. and diff.	4	10	11	11	11
Basement membrane dynamics	5	10	10	10	10
Signaling pathways involved in hematopoiesis	5	11	11	11	11
Chromosome segregation by mitotic spindle	1	1	1	1	1
Cellular antioxidant systems	1	1	2	2	2
Myofibril formation and organization	1	2	2	2	2
Phase II biotransformation	3	3	3	3	3
Metabolism and transport of cholesterol, steroids and bile acids	3	3	3	3	3
ECM breakdown	3	3	3	3	3
Amyloid generation and aggregation	4	4	4	4	4
Mitochondrial energy production	4	4	4	4	4
Fatty acid metabolism	5	5	5	5	5

complete

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	2	2	1	1	1
Matricellular protein signaling	1	1	1	1	1
Chromosome segregation by mitotic spindle	4	4	4	4	4
ECM breakdown	4	4	4	4	4
Elastogenesis	4	4	4	4	4
Mitotic cell cycle checkpoints	7	7	7	7	7
Complement pathway and regulation	1	1	1	1	1
Signaling pathways regulating cardiovascular homeostasis	1	1	1	1	1
Thyroid hormone related signaling	1	1	1	1	1
Metabolism of hypphoph products	2	2	2	2	2
Interphase nucleus and nuclear chromatin organization	2	2	2	2	2
Protein prenylation	2	2	2	2	2
Cellular response to radiation	3	3	3	3	3
Carbohydrate metabolism and transport	3	3	3	3	3
Microtubule dynamics	3	3	3	3	3
Apoptosis	4	4	4	4	4
Myofibril formation and organization	4	4	4	4	4
Metabolism of fat-soluble vitamins	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	1	1	1	1	1
Cellular response to hypoxia	6	6	2	2	2
Sig. pathways that control cell prol. and diff.	4	1	7	7	7
Neuronal signaling pathways	3	3	6	6	6
Basement membrane dynamics	5	5	5	5	5
Elastogenesis	5	5	5	5	5
Matricellular protein signaling	5	5	2	2	2
Myofibril formation and organization	1	1	1	1	1
Intracellular common signaling cascades of multiple pathways	1	1	1	1	1
Carbohydrate metabolism and transport	2	2	2	2	2
Steroid and sex hormone signaling	2	2	2	2	2
Cellular response to energy deprivation	2	2	2	2	2
TM ion transport involved in membrane potential generation	3	3	3	3	3
RNA surveillance and degradation	3	3	3	3	3
ECM breakdown	3	3	3	3	3
TM water and ion transport not involved in membrane potential generation	4	4	4	4	4
Centrosome cycle	4	4	4	4	4
Actin filament dynamics	4	4	4	4	4
Endoplasmic reticulum and nuclear envelope organization	5	5	5	5	5

no1stSD

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	7	1	4	1	1
Carbohydrate metabolism and transport	2	2	1	9	2
Sig. pathways that control cell prol. and diff.	8	8	3	3	3
Basement membrane dynamics	1	1	4	4	4
Matricellular protein signaling	2	1	1	6	6
Elastogenesis	3	3	5	5	5
Cardiomyocyte action potential generation and propagation	2	2	7	7	7
Control of postsynaptic potential	5	5	5	5	5
Photolytic synthesis	1	1	5	10	10
Puynergic signaling	1	1	1	1	1
Cellular response to hypoxia	1	1	1	2	2
Actin filament dynamics	3	3	3	3	3
Signaling pathways involved in hematopoiesis	3	3	3	3	3
Mitochondrial dynamics	3	3	3	3	3
Metabolism of glutamate and histidine products	3	3	3	3	3
Neuronal signaling pathways	4	4	4	4	4
Myofibril formation and organization	4	4	4	4	4
Metabolism and transport of cholesterol, steroids and bile acids	4	4	4	4	4
TM water and ion transport not involved in membrane potential generation	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
Matricellular protein signaling	8	2	1	1	6
Cellular response to oxidative stress	10	2	12	3	3
Mitotic cell cycle checkpoints	3	1	14	2	2
Collagen biosynthesis	1	1	5	1	1
Centrosome cycle	4	1	4	4	4
Cytokinesis	2	6	7	4	4
Complement pathway and regulation	6	6	4	4	4
Sig. pathways that control cell prol. and diff.	4	10	11	11	11
Basement membrane dynamics	5	10	10	10	10
Signaling pathways involved in hematopoiesis	5	11	11	11	11
Chromosome segregation by mitotic spindle	1	1	1	1	1
Cellular antioxidant systems	1	1	2	2	2
Myofibril formation and organization	1	2	2	2	2
Phase II biotransformation	3	3	3	3	3
Metabolism and transport of cholesterol, steroids and bile acids	3	3	3	3	3
ECM breakdown	3	3	3	3	3
Amyloid generation and aggregation	4	4	4	4	4
Mitochondrial energy production	4	4	4	4	4
Fatty acid metabolism	5	5	5	5	5

no1stSD

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	2	2	1	1	1
Matricellular protein signaling	1	1	1	1	1
Chromosome segregation by mitotic spindle	4	4	4	4	4
ECM breakdown	4	4	4	4	4
Elastogenesis	4	4	4	4	4
Mitotic cell cycle checkpoints	7	7	7	7	7
Complement pathway and regulation	1	1	1	1	1
Signaling pathways regulating cardiovascular homeostasis	1	1	1	1	1
Thyroid hormone related signaling	1	1	1	1	1
Metabolism of hypphoph products	2	2	2	2	2
Interphase nucleus and nuclear chromatin organization	2	2	2	2	2
Protein prenylation	2	2	2	2	2
Cellular response to radiation	3	3	3	3	3
Carbohydrate metabolism and transport	3	3	3	3	3
Microtubule dynamics	3	3	3	3	3
Apoptosis	4	4	4	4	4
Myofibril formation and organization	4	4	4	4	4
Metabolism of fat-soluble vitamins	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	1	1	1	1	1
Cellular response to hypoxia	6	6	1	2	2
Sig. pathways that control cell prol. and diff.	4	1	7	7	7
Neuronal signaling pathways	3	3	6	6	6
Basement membrane dynamics	5	5	5	5	5
Elastogenesis	5	5	5	5	5
Matricellular protein signaling	5	5	2	2	2
Myofibril formation and organization	1	1	1	1	1
Intracellular common signaling cascades of multiple pathways	1	1	1	1	1
Carbohydrate metabolism and transport	2	2	2	2	2
Steroid and sex hormone signaling	2	2	2	2	2
Cellular response to energy deprivation	2	2	2	2	2
TM ion transport involved in membrane potential generation	3	3	3	3	3
RNA surveillance and degradation	3	3	3	3	3
ECM breakdown	3	3	3	3	3
TM water and ion transport not involved in membrane potential generation	4	4	4	4	4
Centrosome cycle	4	4	4	4	4
Actin filament dynamics	4	4	4	4	4
Endoplasmic reticulum and nuclear envelope organization	5	5	5	5	5

decomposed

	MS101	MS105	MS106	MS108	MS109
ECM breakdown	3	4	4	1	3
Signaling pathways involved in hematopoiesis	4	2	5	4	1
Sig. pathways that control cell prol. and diff.	2	5	1	8	6
Matricellular protein signaling	6	1	3	2	10
Collagen biosynthesis	1	6	2	5	9
Cellular response to hypoxia	7	7	10	3	12
Elastogenesis	5	5	6	5	5
Apoptosis	8	8	8	2	2
Signaling by extracellular matrix components	3	3	6	6	6
Pattern recognition signaling	4	4	4	4	4

	MS101	MS105	MS106	MS108	MS109
Matricellular protein signaling	1	2	2	1	3
Cellular response to hypoxia	4	8	1	3	2
Myofibril formation and organization	5	5	9	4	7
Cellular response to oxidative stress	8	11	5	5	11
Collagen biosynthesis	1	7	2	1	1
ECM breakdown	3	3	3	14	14
Metabolism of fat-soluble vitamins	6	4	4	12	12
Apoptosis	12	12	5	5	5
Signaling pathways regulating water homeostasis	2	2	4	4	4
Complement pathway and regulation	3	3	10	10	10
Neuronal signaling pathways	4	4	4	4	4

decomposed

	MS101	MS105	MS106	MS108	MS109
Matricellular protein signaling	11	1	2	6	4
Chromosome segregation by mitotic spindle	8	1	1	1	1
Mitotic cell cycle checkpoints	12	4	2	2	2
ECM breakdown	1	7	8	11	7
Cellular response to oxidative stress	4	7	6	10	10
Collagen biosynthesis	3	3	7	7	11
Elastogenesis	5	5	10	9	9
Microtubule dynamics	3	3	4	3	3
Cytokinesis	6	6	5	6	6
Proteoglycan synthesis	4	4	9	8	5
Centrosome cycle	14	3	5	5	5
Complement pathway and regulation	2	2	9	9	9
Interferon signaling	2	2	2	2	2
Carbohydrate metabolism and transport	3	3	3	3	3
Rolling cell adhesion	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
ECM breakdown	1	10	1	4	4
Metabolism of non-essential amino acids	2	4	3	8	8
ECM breakdown	4	6	13	13	9
Cellular response to hypoxia	1	6	5	2	1
Matricellular protein signaling	7	5	2	1	1
Carbohydrate metabolism and transport	2	9	6	6	6
Interferon signaling	5	2	3	3	3
Myofibril formation and organization	3	7	3	3	3
Metabolism of fat-soluble vitamins	8	4	5	5	5
Metabolism and transport of cholesterol, steroids and bile acids	11	11	11	11	11
Sig. pathways that control cell prol. and diff.	3	3	3	3	3
Complement pathway and regulation	5	5	5	5	5

MBCOL2
isoprenaline
(is c.toxic: nd)

MBCOL2
milrinone
(is c.toxic: nd)

Upregulated

Downregulated

Upregulated

Downregulated

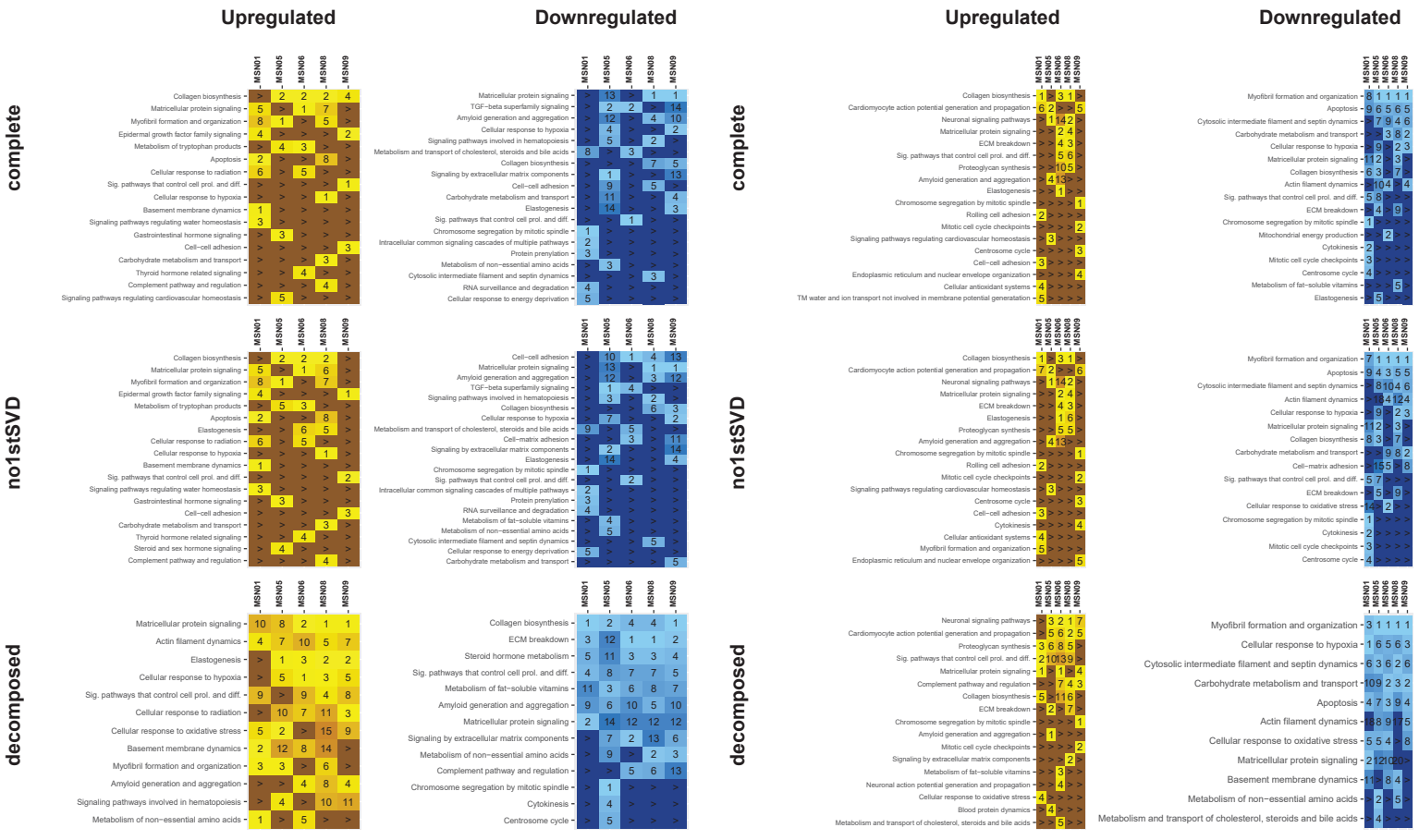
complete

	MS101	MS105	MS106	MS108	MS109
Collagen biosynthesis	1	1	4	4	4
Myofibril formation and organization	1	5	4	4	4
Sig. pathways that control cell prol. and diff.	6	6	1	1	1
Elastogenesis	5	5	2	2	2
Basement membrane dynamics	4	4	8	8	8
Matricellular protein signaling	10	3	3	3	3
Cellular response to hypoxia	12	2	2	2	2
ECM breakdown	1	1	4	4	4
Eukaryotic DNA replication	1	1	1	1	1
Metabolism and transport of cholesterol, steroids and bile acids	2	2	2	2	2
Actin filament dynamics	2	2	3	3	3
Control of postsynaptic potential	3	3	3	3	3
Apoptosis	3	3	3	3	3
Cardiomyocyte action potential generation and propagation	3	3	4	4	4
Steroid and sex hormone signaling	4	4	5	5	5
Cell-matrix adhesion	5	5	5	5	5

	MS101	MS105	MS106	MS108	MS109
Cardiomyocyte action					

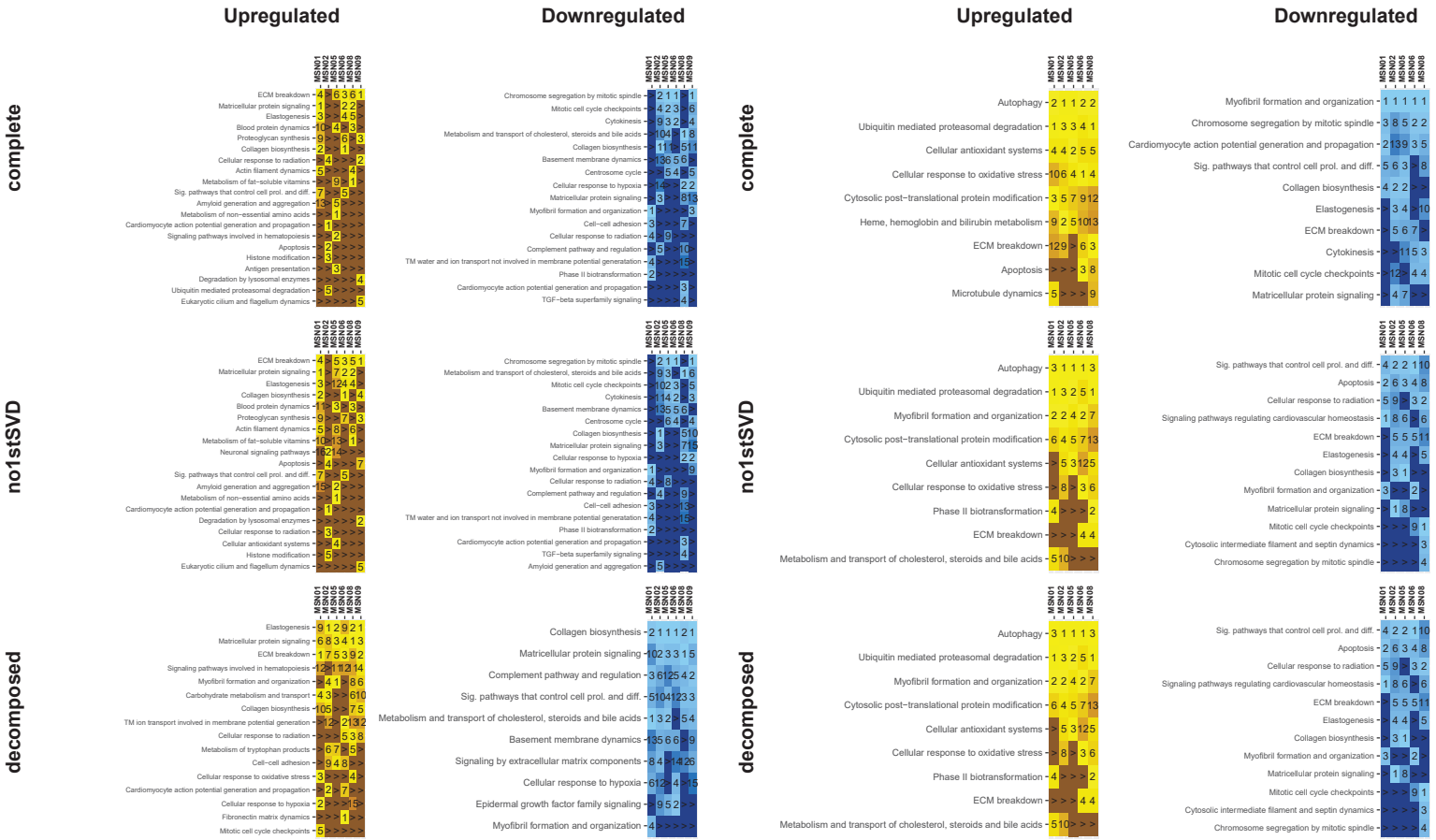
**MBCOL2
phenylephrine**
(is c.toxic: nd)

**MBCOL2
verapamil**
(is c.toxic: nd)



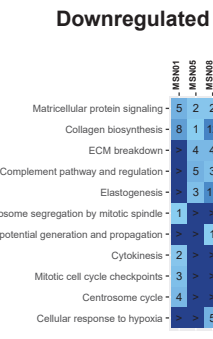
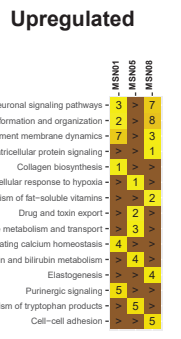
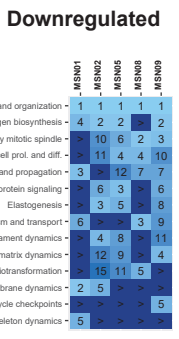
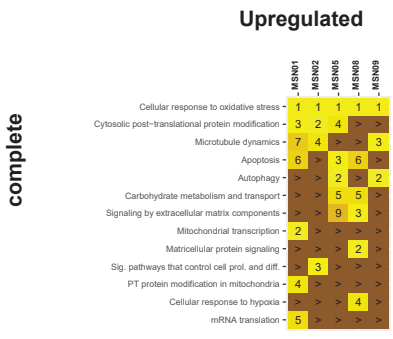
**MBCOL2
azacitidine**
(is c.toxic: nd)

**MBCOL2
bortezomib**
(is c.toxic: yes)



**MBCOL2
carfilzomib
(is c.toxic: yes)**

**MBCOL2
cyclosporine
(is c.toxic: nd)**



complete

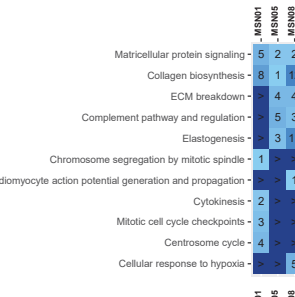
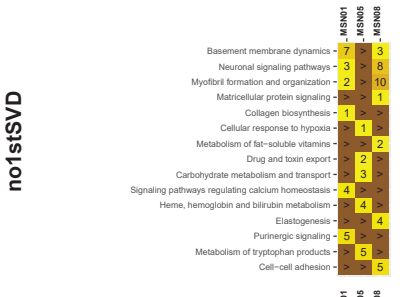
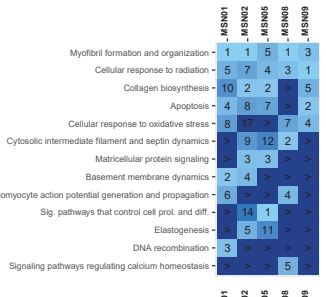
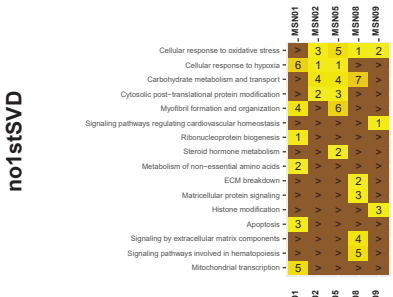
complete

no1stSVD

no1stSVD

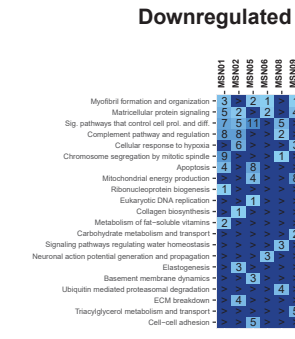
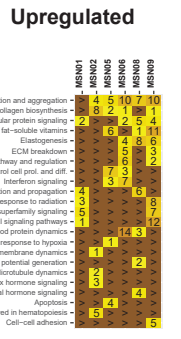
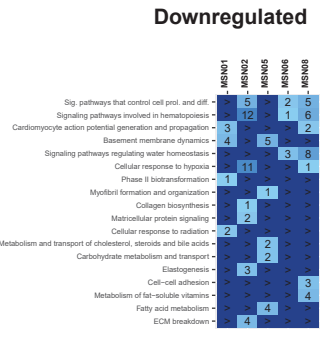
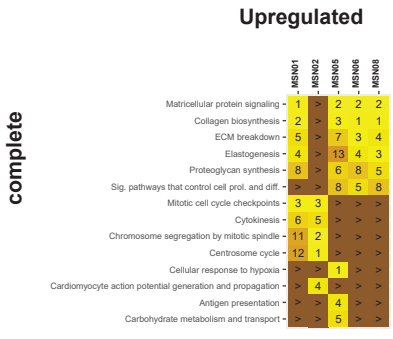
decomposed

decomposed



**MBCOL2
decitabine
(is c.toxic: nd)**

**MBCOL2
delavirdine
(is c.toxic: nd)**



complete

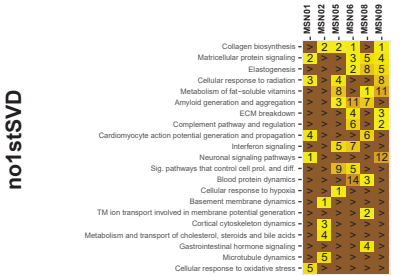
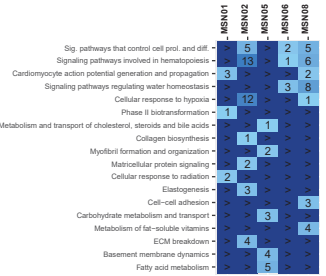
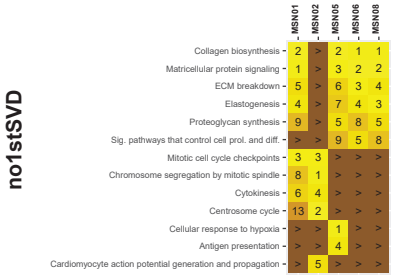
complete

no1stSVD

no1stSVD

decomposed

decomposed



**MBCOL2
diclofenac**
(is c.toxic: nd)

**MBCOL2
endothelin-1**
(is c.toxic: nd)

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Basement membrane dynamics	5	10	10	8					
Sig. pathways that control cell prol. and diff.	3	6	9	3					
Collagen biosynthesis	2	1	1	1					
Matricellular protein signaling	3	3	2	2					
ECM breakdown	1	4	3	3					
Elastogenesis	4	4	4	4					
Complement pathway and regulation	7	2	5	5					
Proteoglycan synthesis	7	7	5	5					
Cardiomyocyte action potential generation and propagation	2	2	1	1					
Cell-cell adhesion	10	2	2	2					
Neuronal signaling pathways	1	1	1	1					
Cellular response to hypoxia	2	2	2	2					
Cellular response to oxidative stress	3	4	5	5					
Metabolism of fat-soluble vitamins	5	5	5	5					
Control of postsynaptic potential	2	2	2	2					

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Sig. pathways that control cell prol. and diff.	2	2	2	2					
Matricellular protein signaling	2	2	2	2					
Signaling pathways regulating water homeostasis	1	1	1	1					
Cellular response to hypoxia	1	1	1	1					
Neuronal signaling pathways	3	3	2	2					
Mitochondrial energy production	3	4	3	3					
ECM breakdown	3	1	1	1					
Apoptosis	1	1	1	1					
Thyroid hormone related signaling	1	1	1	1					
Cell-matrix adhesion	1	1	1	1					
Collagen biosynthesis	1	1	1	1					
Cellular response to radiation	1	1	1	1					
Cardiomyocyte action potential generation and propagation	2	2	1	1					
PT protein modification in mitochondria	2	2	2	2					
Myofibril formation and organization	2	2	2	2					
Ribonucleoprotein biogenesis	3	3	3	3					
Metabolism of fat-soluble vitamins	3	3	3	3					
Carbohydrate metabolism and transport	3	3	3	3					
Signaling pathways involved in hematopoiesis	3	4	4	4					
Cell-cell adhesion	4	4	4	4					
Actin filament dynamics	4	4	4	4					
Microtubule organization center dynamics	4	4	4	4					
Complement pathway and regulation	5	5	5	5					

complete

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Carbohydrate metabolism and transport	5	1	1	2					
Matricellular protein signaling	10	2	2	2					
ECM breakdown	6	3	3	3					
Metabolism of non-essential amino acids	7	2	2	2					
Myofibril formation and organization	13	3	3	3					
Cellular response to hypoxia	5	2	2	2					
Elastogenesis	4	4	4	4					
Collagen biosynthesis	7	7	7	7					
Cardiomyocyte action potential generation and propagation	4	4	4	4					
Signaling pathways regulating water homeostasis	3	3	3	3					
Sig. pathways that control cell prol. and diff.	5	5	5	5					
Fatty acid metabolism	11	4	4	4					
Metabolism and transport of cholesterol, steroids and bile acids	3	1	1	1					
Actin filament dynamics	2	2	2	2					
Complement pathway and regulation	5	5	5	5					

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
ECM breakdown	5	3	4	9					
Collagen biosynthesis	1	1	1	1					
Apoptosis	10	2	1	1					
Amayloid generation and aggregation	1	1	1	1					
Elastogenesis	5	7	7	7					
Matricellular protein signaling	2	2	2	2					
Cardiomyocyte action potential generation and propagation	2	2	2	2					
Sig. pathways that control cell prol. and diff.	4	3	3	3					
Chromosome segregation by mitotic spindle	1	1	1	1					
Neuronal action potential generation and propagation	3	3	3	3					
Intracellular common signaling cascades of multiple pathways	3	3	3	3					
TM ion transport involved in membrane potential generation	4	4	4	4					
Phase II biotransformation	5	5	5	5					

no1stSVD

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Basement membrane dynamics	4	3	12	11	8				
Collagen biosynthesis	2	1	1	1					
Matricellular protein signaling	3	3	2	2					
ECM breakdown	1	4	3	3					
Elastogenesis	8	5	4	4					
Complement pathway and regulation	6	2	5	5					
Sig. pathways that control cell prol. and diff.	3	6	9	3					
Proteoglycan synthesis	10	7	5	5					
Cardiomyocyte action potential generation and propagation	2	1	1	1					
Cell-cell adhesion	10	2	2	2					
Cellular response to hypoxia	10	2	2	2					
Cellular response to oxidative stress	3	4	4	4					
Metabolism of fat-soluble vitamins	5	5	5	5					
Control of postsynaptic potential	2	2	2	2					
Actin filament dynamics	5	5	5	5					

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Sig. pathways that control cell prol. and diff.	2	2	2	2					
Matricellular protein signaling	2	2	2	2					
Signaling pathways regulating water homeostasis	1	1	1	1					
Cellular response to hypoxia	1	1	1	1					
Neuronal signaling pathways	3	3	2	2					
Mitochondrial energy production	3	4	3	3					
ECM breakdown	3	1	1	1					
Cell-matrix adhesion	1	1	1	1					
Collagen biosynthesis	1	1	1	1					
Cellular response to radiation	1	1	1	1					
Cardiomyocyte action potential generation and propagation	2	2	1	1					
Ribonucleoprotein biogenesis	2	2	2	2					
PT protein modification in mitochondria	2	2	2	2					
Cellular response to oxidative stress	2	2	2	2					
Metabolism of fat-soluble vitamins	3	3	3	3					
Ubiquitin mediated proteasomal degradation	3	3	3	3					
Signaling pathways involved in hematopoiesis	3	4	4	4					
Cell-cell adhesion	4	4	4	4					
Microtubule organization center dynamics	4	4	4	4					
Complement pathway and regulation	5	5	5	5					

no1stSVD

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Carbohydrate metabolism and transport	3	1	1	2					
Matricellular protein signaling	10	2	2	2					
ECM breakdown	6	3	3	3					
Metabolism of non-essential amino acids	7	2	2	2					
Myofibril formation and organization	13	3	3	3					
Cellular response to hypoxia	5	2	2	2					
Elastogenesis	4	4	4	4					
Collagen biosynthesis	7	7	7	7					
Cardiomyocyte action potential generation and propagation	3	4	5	5					
Signaling pathways regulating water homeostasis	3	3	3	3					
Sig. pathways that control cell prol. and diff.	5	5	5	5					
Fatty acid metabolism	15	3	3	3					
Metabolism and transport of cholesterol, steroids and bile acids	3	1	1	1					
Actin filament dynamics	2	2	2	2					
Complement pathway and regulation	5	5	5	5					

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
ECM breakdown	5	3	5	8					
Collagen biosynthesis	1	1	2	4					
Amayloid generation and aggregation	1	1	1	1					
Elastogenesis	5	4	7	7					
Complement pathway and regulation	6	6	6	6					
Matricellular protein signaling	2	2	2	2					
Cardiomyocyte action potential generation and propagation	1	3	3	3					
Sig. pathways that control cell prol. and diff.	4	3	3	3					
Chromosome segregation by mitotic spindle	2	2	2	2					
Neuronal action potential generation and propagation	3	3	3	3					
TM ion transport involved in membrane potential generation	4	4	4	4					
Phase II biotransformation	4	4	4	4					

decomposed

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Matricellular protein signaling	2	1	2	1	1				
Collagen biosynthesis	1	2	1	2	3				
Cardiomyocyte action potential generation and propagation	3	4	6	5	2				
Elastogenesis	4	5	3	3	2				
Cellular response to oxidative stress	3	8	4	4	3				
Sig. pathways that control cell prol. and diff.	1	12	4	12	13				
Amayloid generation and aggregation	5	12	5	14	14				
Signaling pathways regulating cardiovascular homeostasis	5	5	5	5	12				

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Cellular response to hypoxia	1	1	1	1	1				
Collagen biosynthesis	2	3	2	10	4				
Sig. pathways that control cell prol. and diff.	7	2	2	4	2				
Cellular response to radiation	4	6	3	3	5				
Proteoglycan synthesis	5	7	5	4	6				
Metabolism of fat-soluble vitamins	10	10	9	2	2				
Matricellular protein signaling	3	4	4	4	2				
Metabolism and transport of cholesterol, steroids and bile acids	8	7	5	3	3				
ECM breakdown	1	11	3	1	3				
Myofibril formation and organization	5	12	9	9	9				
Signaling pathways involved in hematopoiesis	11	13	13	3	3				
Signaling by extracellular matrix components	5	5	5	5	5				

decomposed

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Collagen biosynthesis	2	5	2	4	3				
Matricellular protein signaling	8	2	5	2	15				
Complement pathway and regulation	10	10	3	9	9				
Apoptosis	5	4	9	5	12				
Metabolism and transport of cholesterol, steroids and bile acids	1	1	1	1	2				
Cellular response to hypoxia	3	1	4	3	1				
Chromosome segregation by mitotic spindle	7	3	3	1	1				
Cytokinesis	4	6	5	5	5				
Mitotic cell cycle checkpoints	4	4	6	4	6				

	MS101	MS102	MS103	MS104	MS105	MS106	MS107	MS108	MS109
Collagen biosynthesis	1	1	1	1	1				
Sig. pathways that control cell prol. and diff.	2	5	4	3	5				
Elastogenesis	4	9	2	2	2				
Signaling by extracellular matrix components	4	7	6	5	8				
Metabolism of non-essential amino acids	3	6	5	8	8				
Amayloid generation and aggregation	3	12	7	3	4				
Cellular response to oxidative stress	5	9	6	6	6				

MBCOL2
saxagliptin
(is c.toxic: nd)

MBCOL2
tnf-alpha
(is c.toxic: nd)

complete

no1stSD

decomposed

Upregulated

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
ECM breakdown	-4	1	2	1	1	1	1	1	1
Collagen biosynthesis	-10	1	2	1	1	1	1	1	1
Elastogenesis	-4	4	4	4	4	4	4	4	4
Matricellular protein signaling	-2	3	3	3	3	3	3	3	3
Metabolism of fat-soluble vitamins	-7	1	1	1	1	1	1	1	1
Complement pathway and regulation	-3	5	5	5	5	5	5	5	5
Signaling pathways involved in hematopoiesis	-1	9	9	9	9	9	9	9	9
Fibronectin matrix dynamics	-13	4	4	4	4	4	4	4	4
Steroid hormone metabolism	-15	5	5	5	5	5	5	5	5
Ubiquitin mediated proteasomal degradation	-1	>>	>>	>>	>>	>>	>>	>>	>>
Cellular response to oxidative stress	-2	>>	>>	>>	>>	>>	>>	>>	>>
Basement membrane dynamics	->	3	3	3	3	3	3	3	3
Signaling pathways regulating water homeostasis	->	3	3	3	3	3	3	3	3
Myofibril formation and organization	-3	>>	>>	>>	>>	>>	>>	>>	>>
Apoptosis	-5	>>	>>	>>	>>	>>	>>	>>	>>

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Collagen biosynthesis	-7	4	4	4	4	4	4	4	4
ECM breakdown	-8	5	5	5	5	5	5	5	5
Elastogenesis	-4	4	4	4	4	4	4	4	4
Sig. pathways that control cell prol. and diff.	-1	9	9	9	9	9	9	9	9
Matricellular protein signaling	-2	4	4	4	4	4	4	4	4
Metabolism of fat-soluble vitamins	-7	1	1	1	1	1	1	1	1
Complement pathway and regulation	-3	5	5	5	5	5	5	5	5
Signaling pathways involved in hematopoiesis	-2	8	8	8	8	8	8	8	8
Fibronectin matrix dynamics	-13	4	4	4	4	4	4	4	4
Steroid hormone metabolism	-15	5	5	5	5	5	5	5	5
Ubiquitin mediated proteasomal degradation	-1	>>	>>	>>	>>	>>	>>	>>	>>
Myofibril formation and organization	->	3	3	3	3	3	3	3	3
Basement membrane dynamics	->	3	3	3	3	3	3	3	3
Signaling pathways regulating water homeostasis	->	3	3	3	3	3	3	3	3
Cellular response to oxidative stress	-3	>>	>>	>>	>>	>>	>>	>>	>>
Phase II biotransformation	-4	>>	>>	>>	>>	>>	>>	>>	>>
Microtubule dynamics	-5	>>	>>	>>	>>	>>	>>	>>	>>

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Complement pathway and regulation	-3	1	4	8	1	1	1	1	1
Metabolism of non-essential amino acids	-5	3	2	3	6	6	6	6	6
Apoptosis	-1	7	9	1	3	3	3	3	3
Collagen biosynthesis	-6	5	4	4	4	4	4	4	4
Eukaryotic DNA replication	-4	2	1	5	5	5	5	5	5
ECM breakdown	-7	8	3	9	9	9	9	9	9
Cellular response to hypoxia	-2	4	>>	2	2	2	2	2	2
Matricellular protein signaling	-6	3	>>	2	2	2	2	2	2
TGF-beta superfamily signaling	-10	>>	5	5	5	5	5	5	5

Downregulated

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Cardiomyocyte action potential generation and propagation	-1	1	2	8	8	8	8	8	8
Matricellular protein signaling	-2	2	2	2	2	2	2	2	2
Cellular response to hypoxia	-1	4	4	4	4	4	4	4	4
Sig. pathways that control cell prol. and diff.	-2	5	>>	1	1	1	1	1	1
Signaling pathways involved in hematopoiesis	-1	3	3	3	3	3	3	3	3
Amyloid generation and aggregation	-9	5	5	5	5	5	5	5	5
Cell-matrix adhesion	-14	>>	3	3	3	3	3	3	3
Myofibril formation and organization	->	1	>>	1	1	1	1	1	1
Collagen biosynthesis	-1	>>	>>	>>	>>	>>	>>	>>	>>
Apoptosis	-1	>>	>>	>>	>>	>>	>>	>>	>>
Metabolism of glutamate and histidine products	-2	>>	2	2	2	2	2	2	2
Elastogenesis	-3	>>	3	3	3	3	3	3	3
Cellular response to radiation	->	3	3	3	3	3	3	3	3
Neuronal signaling pathways	->	4	4	4	4	4	4	4	4
ECM breakdown	-4	>>	4	4	4	4	4	4	4
Cellular response to oxidative stress	->	5	5	5	5	5	5	5	5

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Cardiomyocyte action potential generation and propagation	-1	2	10	10	10	10	10	10	10
Amyloid generation and aggregation	-13	4	5	5	5	5	5	5	5
Matricellular protein signaling	-2	2	2	2	2	2	2	2	2
Sig. pathways that control cell prol. and diff.	-3	5	1	3	3	3	3	3	3
Apoptosis	-1	>>	7	7	7	7	7	7	7
Cellular response to radiation	-2	>>	9	9	9	9	9	9	9
Signaling pathways involved in hematopoiesis	-10	3	3	3	3	3	3	3	3
Myofibril formation and organization	->	1	1	1	1	1	1	1	1
Collagen biosynthesis	-1	>>	3	3	3	3	3	3	3
Cell-matrix adhesion	-1	>>	2	2	2	2	2	2	2
Elastogenesis	-3	>>	3	3	3	3	3	3	3
Control of postsynaptic potential	->	3	3	3	3	3	3	3	3
Neuronal signaling pathways	->	4	4	4	4	4	4	4	4
ECM breakdown	-4	>>	4	4	4	4	4	4	4
Cellular response to oxidative stress	->	4	4	4	4	4	4	4	4
Thyroid hormone related signaling	->	5	5	5	5	5	5	5	5
Metabolism of glutamate and histidine products	-5	>>	5	5	5	5	5	5	5

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Matricellular protein signaling	-3	1	1	2	1	1	1	1	1
Collagen biosynthesis	-1	3	2	2	1	1	1	1	1
Elastogenesis	-2	2	3	4	3	3	3	3	3
Fibronectin matrix dynamics	-4	4	4	4	4	4	4	4	4
Signaling pathways involved in hematopoiesis	-5	6	3	6	6	6	6	6	6
ECM breakdown	-5	7	5	5	5	5	5	5	5
Sig. pathways that control cell prol. and diff.	-10	>>	5	5	5	5	5	5	5
Metabolism and transport of cholesterol, steroids and bile acids	->	510	510	510	510	510	510	510	510

complete

no1stSD

decomposed

Upregulated

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Matricellular protein signaling	-2	2	2	3	1	1	1	1	1
Collagen biosynthesis	-4	2	1	3	1	1	1	1	1
Elastogenesis	-4	4	3	3	3	3	3	3	3
Cardiomyocyte action potential generation and propagation	-7	7	1	1	1	1	1	1	1
Metabolism of fat-soluble vitamins	-6	4	1	12	8	8	8	8	8
ECM breakdown	-5	16	4	4	4	4	4	4	4
Metabolism of tryptophan products	->	5	2	2	2	2	2	2	2
TGF-beta superfamily signaling	->	8	9	9	9	9	9	9	9
Myofibril formation and organization	->	1	>>	1	1	1	1	1	1
Cellular response to hypoxia	->	1	>>	1	1	1	1	1	1
Epidermal growth factor family signaling	->	>>	2	2	2	2	2	2	2
Lipid droplet dynamics	->	>>	3	3	3	3	3	3	3
Carbohydrate metabolism and transport	->	3	4	4	4	4	4	4	4
Phase II biotransformation	->	4	4	4	4	4	4	4	4
One carbon metabolism	->	4	4	4	4	4	4	4	4
Cell-cell adhesion	->	4	4	4	4	4	4	4	4
Blood protein dynamics	->	5	5	5	5	5	5	5	5

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Matricellular protein signaling	-2	6	1	3	1	1	1	1	1
Collagen biosynthesis	-4	2	3	11	1	1	1	1	1
ECM breakdown	-5	12	6	4	4	4	4	4	4
Elastogenesis	-6	6	2	8	8	8	8	8	8
Cardiomyocyte action potential generation and propagation	-3	5	8	1	1	1	1	1	1
Metabolism of fat-soluble vitamins	-6	4	10	2	2	2	2	2	2
Sig. pathways that control cell prol. and diff.	->	3	11	3	8	8	8	8	8
Metabolism of tryptophan products	->	1	5	2	2	2	2	2	2
Signaling pathways regulating cardiovascular homeostasis	->	1	>>	7	4	4	4	4	4
Gastrointestinal hormone signaling	->	2	9	9	9	9	9	9	9
Apoptosis	-2	9	>>	>>	>>	>>	>>	>>	>>
TGF-beta superfamily signaling	->	9	5	1	1	1	1	1	1
Myofibril formation and organization	->	9	5	5	5	5	5	5	5
Cellular response to hypoxia	->	1	>>	2	2	2	2	2	2
One carbon metabolism	->	3	3	3	3	3	3	3	3
Cell-cell adhesion	->	3	3	3	3	3	3	3	3
Carbohydrate metabolism and transport	->	3	3	3	3	3	3	3	3
Phase II biotransformation	->	4	4	4	4	4	4	4	4
Neuronal signaling pathways	->	4	5	5	5	5	5	5	5

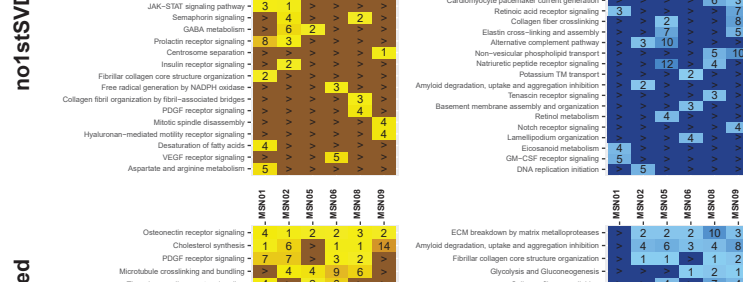
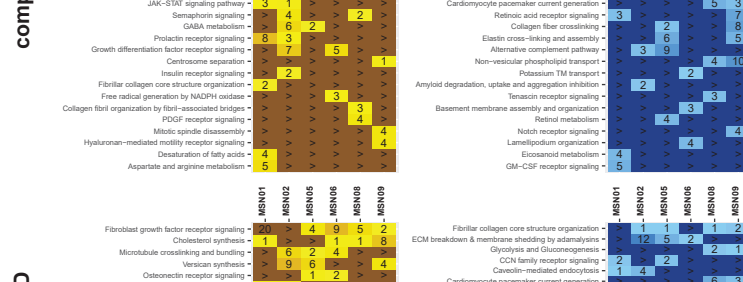
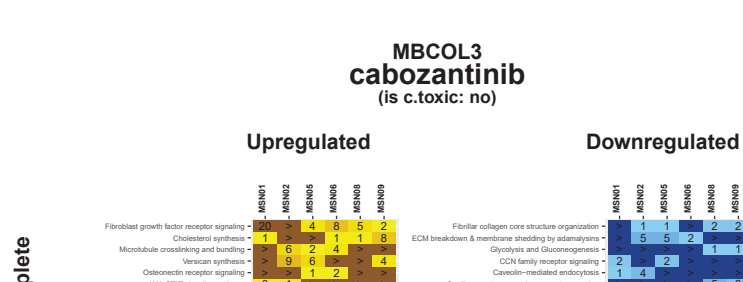
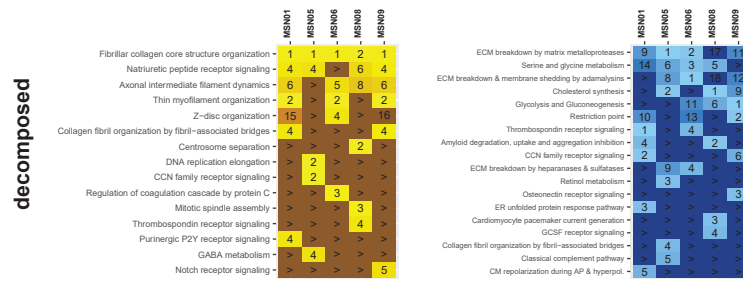
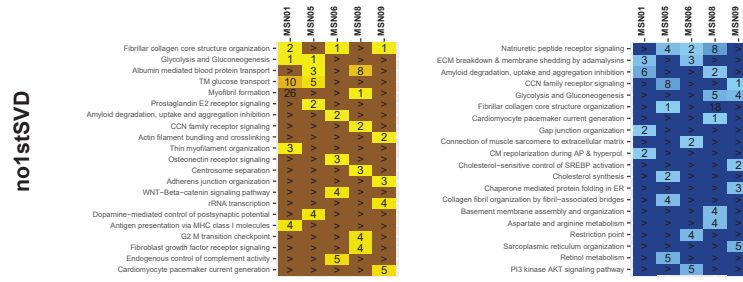
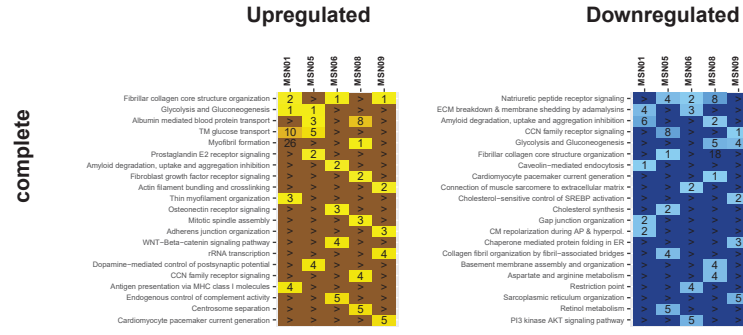
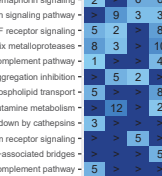
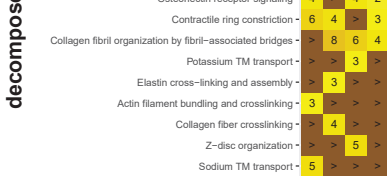
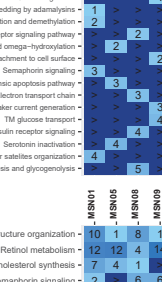
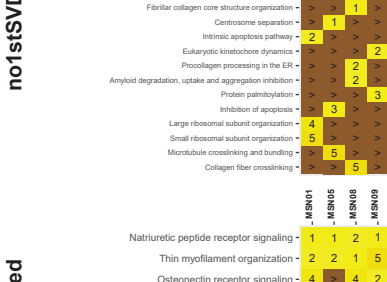
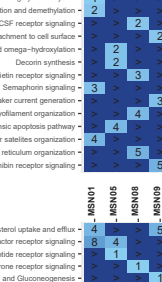
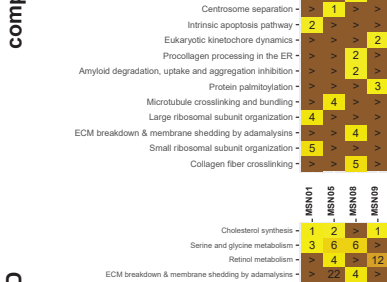
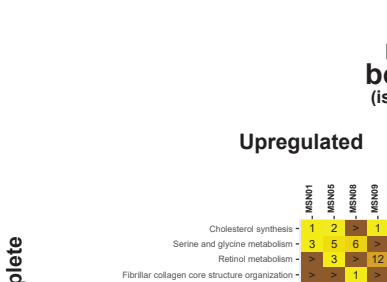
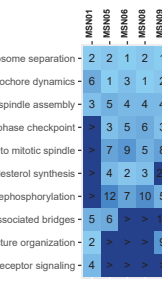
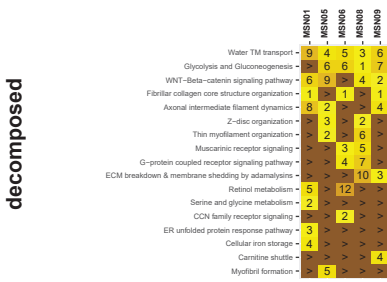
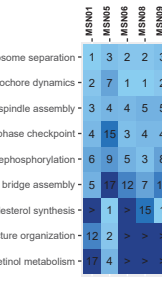
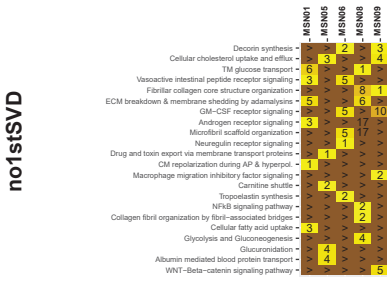
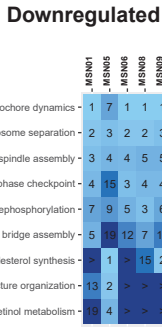
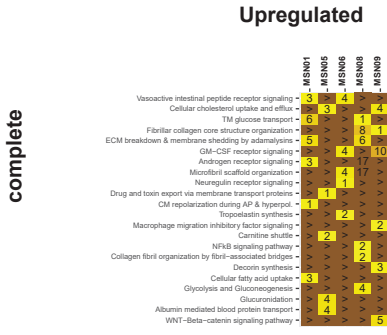
	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Collagen biosynthesis	-2	1	2	1	1	1	1	1	1
Myofibril formation and organization	-6	4	5	2	2	2	2	2	2
Cellular response to hypoxia	-1	7	3	3	8	8	8	8	8
Amyloid generation and aggregation	-13	3	5	4	3	3	3	3	3
ECM breakdown	-9	2	11	6	4	4	4	4	4
Cardiomyocyte action potential generation and propagation	-10	6	10	5	5	5	5	5	5
Sig. pathways that control cell prol. and diff.	->	5	14	7	7	7	7	7	7
Elastogenesis	-12	15	4	7	7	7	7	7	7
Matricellular protein signaling	-3	1	2	>>	>>	>>	>>	>>	>>
Signaling pathways involved in hematopoiesis	-14	4	7	>>	>>	>>	>>	>>	>>
Carbohydrate metabolism and transport	-8	19	3	>>	>>	>>	>>	>>	>>
Interferon signaling	-4	6	>>	>>	>>	>>	>>	>>	>>

Downregulated

	MSNO1	MSNO2	MSNO3	MSNO4	MSNO5	MSNO6	MSNO7	MSNO8	MSNO9
Cellular response to oxidative stress	-10	9	4	7	7	7	7	7	7
Sig. pathways that control cell prol. and diff.	-3	3	2	2	2	2	2	2	2
Basement membrane dynamics	-1	3	4	5	5	5	5	5	5
ECM breakdown	-2	2	2	2	2	2	2	2	2
Amyloid generation and aggregation	-4	1	1	3	3	3	3	3	3
Metabolism and transport of cholesterol, steroids and bile acids	-1	1	1	6	10	10	10	10	10
Cellular response to hypoxia	-1	1	1	1	3	3	3	3	3
Matricellular protein signaling	-6	6	6	6	6	6	6	6	6
Carbohydrate metabolism and transport	->	5	5	5	5	5	5	5	5
Neuronal signaling pathways	->	9	9	9	9	9	9	9	9
Cell-cell adhesion	->	12	2	14	14	14	14	14	14
Myofibril formation and organization	->	2	2	2	2	2	2	2	2
Metabolism of tryptophan products	->	3	3	3	3	3	3	3	3
PT protein modification and QC during secretory pathway	->	3	3						

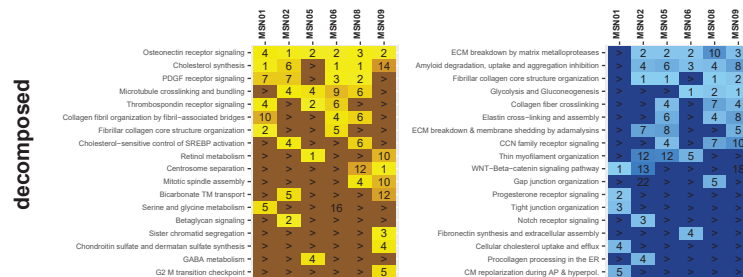
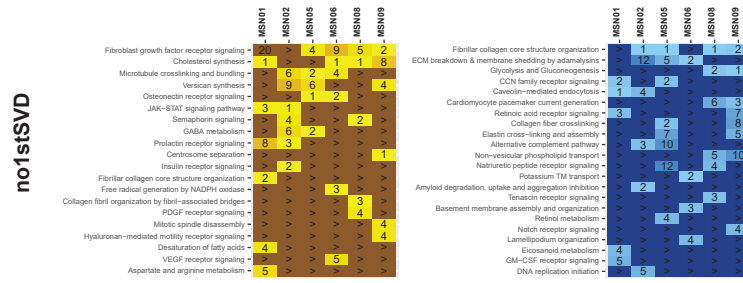
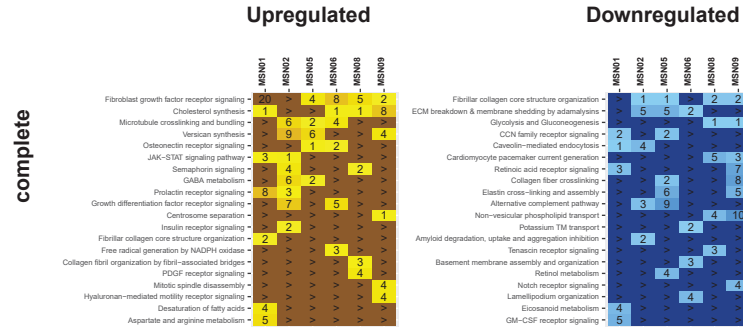
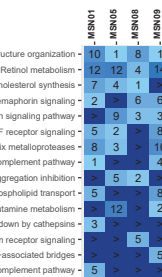
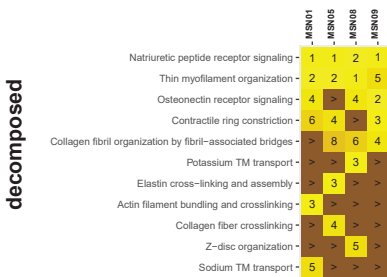
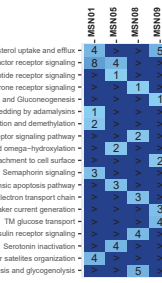
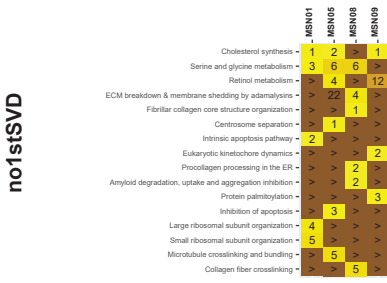
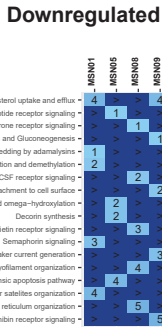
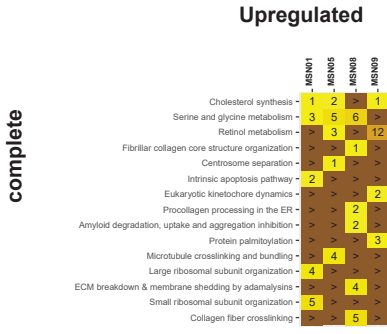
**MBCOL3
afatinib**
(is c.toxic: no)

**MBCOL3
axitinib**
(is c.toxic: no)



**MBCOL3
bosutinib**
(is c.toxic: no)

**MBCOL3
cabozantinib**
(is c.toxic: no)



MBCOL3
ceritinib
(is c.toxic: no)

MBCOL3
crizotinib
(is c.toxic: no)

Upregulated

Downregulated

Upregulated

Downregulated

complete

Heatmap showing upregulated pathways for ceritinib in the 'complete' group. Pathways include Amyloid degradation, Actin filament bundling, Fibroblast collagen core structure organization, and others. Values range from 1 to 10.

Heatmap showing downregulated pathways for ceritinib in the 'complete' group. Pathways include Eukaryotic kinetochore dynamics, Centrosome separation, Mitotic spindle assembly, and others. Values range from 1 to 12.

complete

Heatmap showing upregulated pathways for crizotinib in the 'complete' group. Pathways include Fibroblast collagen core structure organization, CCN family receptor signaling, and others. Values range from 1 to 5.

Heatmap showing downregulated pathways for crizotinib in the 'complete' group. Pathways include Fibroblast collagen core structure organization, Cholesterol synthesis, and others. Values range from 1 to 10.

no1stSVD

Heatmap showing upregulated pathways for ceritinib in the 'no1stSVD' group. Pathways include Fibroblast collagen core structure organization, Amyloid degradation, and others. Values range from 1 to 20.

Heatmap showing downregulated pathways for ceritinib in the 'no1stSVD' group. Pathways include Centrosome separation, Mitotic spindle assembly, and others. Values range from 1 to 6.

no1stSVD

Heatmap showing upregulated pathways for crizotinib in the 'no1stSVD' group. Pathways include Fibroblast collagen core structure organization, CCN family receptor signaling, and others. Values range from 1 to 5.

Heatmap showing downregulated pathways for crizotinib in the 'no1stSVD' group. Pathways include Fibroblast collagen core structure organization, Cholesterol synthesis, and others. Values range from 1 to 10.

decomposed

Heatmap showing upregulated pathways for ceritinib in the 'decomposed' group. Pathways include Amyloid degradation, Cellular cholesterol uptake, and others. Values range from 1 to 11.

Heatmap showing downregulated pathways for ceritinib in the 'decomposed' group. Pathways include Centrosome separation, Eukaryotic kinetochore dynamics, and others. Values range from 1 to 12.

decomposed

Heatmap showing upregulated pathways for crizotinib in the 'decomposed' group. Pathways include ECM breakdown by heparanases, Natriuretic peptide receptor signaling, and others. Values range from 1 to 13.

Heatmap showing downregulated pathways for crizotinib in the 'decomposed' group. Pathways include Fibroblast collagen core structure organization, Elastin cross-linking, and others. Values range from 1 to 11.

MBCOL3
dabrafenib
(is c.toxic: yes)

MBCOL3
dasatinib
(is c.toxic: no)

Upregulated

Downregulated

Upregulated

Downregulated

complete

Heatmap showing upregulated pathways for dabrafenib in the 'complete' group. Pathways include Serine and glycine metabolism, ER unfolded protein response pathway, and others. Values range from 1 to 12.

Heatmap showing downregulated pathways for dabrafenib in the 'complete' group. Pathways include Retinol metabolism, Myofibril formation, and others. Values range from 1 to 10.

complete

Heatmap showing upregulated pathways for dasatinib in the 'complete' group. Pathways include Calcitonin receptor signaling, ECM breakdown, and others. Values range from 1 to 15.

Heatmap showing downregulated pathways for dasatinib in the 'complete' group. Pathways include Fibroblast collagen core structure organization, Bicyclic synthesis, and others. Values range from 1 to 10.

no1stSVD

Heatmap showing upregulated pathways for dabrafenib in the 'no1stSVD' group. Pathways include Serine and glycine metabolism, ER unfolded protein response pathway, and others. Values range from 1 to 6.

Heatmap showing downregulated pathways for dabrafenib in the 'no1stSVD' group. Pathways include Retinol metabolism, Z-disc organization, and others. Values range from 1 to 6.

no1stSVD

Heatmap showing upregulated pathways for dasatinib in the 'no1stSVD' group. Pathways include Calcitonin receptor signaling, ECM breakdown, and others. Values range from 1 to 15.

Heatmap showing downregulated pathways for dasatinib in the 'no1stSVD' group. Pathways include Fibroblast collagen core structure organization, Bicyclic synthesis, and others. Values range from 1 to 10.

decomposed

Heatmap showing upregulated pathways for dabrafenib in the 'decomposed' group. Pathways include Serine and glycine metabolism, ER unfolded protein response pathway, and others. Values range from 1 to 5.

Heatmap showing downregulated pathways for dabrafenib in the 'decomposed' group. Pathways include Retinol metabolism, Z-disc organization, and others. Values range from 1 to 5.

decomposed

Heatmap showing upregulated pathways for dasatinib in the 'decomposed' group. Pathways include Calcitonin receptor signaling, ECM breakdown, and others. Values range from 1 to 15.

Heatmap showing downregulated pathways for dasatinib in the 'decomposed' group. Pathways include Fibroblast collagen core structure organization, Restriction point, and others. Values range from 1 to 12.

**MBCOL3
erlotinib**
(is c.toxic: no)

**MBCOL3
gefitinib**
(is c.toxic: no)

Upregulated

Downregulated

complete

	MSNB1	MSNB5	MSNB6	MSNB9
Serine and glycine metabolism	2	1	2	1
ER unfolded protein response pathway	1	4	1	2
Aspartate and arginine metabolism	4	6	>	5
Cellular iron storage	3	>	>	3
Glutamate and glutamine metabolism	>	>	5	4
Intrinsic apoptosis pathway	>	>	4	8
Vimentin-like intermediate filament dynamics	5	>	>	16
TM glucose transport	>	2	>	>
Thin myofilament organization	>	3	>	>
Heme degradation to bilirubin	>	>	3	>
Phase I biotransformation via cytochrome P450	>	4	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
Eukaryotic kinetochore dynamics	1	4	3	2
DNA replication initiation	11	2	1	1
Centrosome separation	4	3	5	3
Fanconi anemia interstrand cross-link repair pathway	12	11	4	10
Mitotic spindle assembly	3	8	27	7
DNA replication elongation	>	5	2	5
Metaphase to anaphase checkpoint	2	6	>	6
Intracellular bridge assembly	5	18	>	22
Fibrillar collagen core structure organization	>	1	20	>
Glycolysis and Gluconeogenesis	>	>	>	4

no1stSVD

	MSNB1	MSNB5	MSNB6	MSNB9
Serine and glycine metabolism	2	1	2	1
ER unfolded protein response pathway	1	6	1	2
Aspartate and arginine metabolism	6	2	>	5
Cellular iron storage	3	>	>	3
Thin myofilament organization	4	5	>	>
Intrinsic apoptosis pathway	>	>	3	8
Glutamate and glutamine metabolism	>	>	7	4
TM glucose transport	8	3	>	>
Z-disc organization	>	>	4	>
Urea cycle	>	4	>	>
Androgen synthesis	>	>	5	>

	MSNB1	MSNB5	MSNB6	MSNB9
Eukaryotic kinetochore dynamics	1	4	4	2
Centrosome separation	4	3	5	3
DNA replication initiation	2	2	1	1
Fanconi anemia interstrand cross-link repair pathway	12	11	3	9
Mitotic spindle assembly	3	8	26	7
DNA replication elongation	>	5	2	5
Metaphase to anaphase checkpoint	2	6	>	6
Intracellular bridge assembly	5	18	>	22
Fibrillar collagen core structure organization	>	1	20	>
Glycolysis and Gluconeogenesis	>	>	>	4

decomposed

	MSNB1	MSNB5	MSNB6	MSNB9
ER unfolded protein response pathway	1	1	1	2
Serine and glycine metabolism	2	2	2	1
Vasoactive intestinal peptide receptor signaling	3	6	7	10
Aspartate and arginine metabolism	7	3	>	3
Protein polyubiquitination	>	4	>	7
Glutamate and glutamine metabolism	9	>	>	5
Fibrillar collagen core structure organization	>	>	3	2
Neuregulin receptor signaling	>	>	>	4
ECM breakdown by matrix metalloproteinases	4	>	>	>
Decorin synthesis	>	>	>	4
Intrinsic apoptosis pathway	>	>	>	5
Cholesterol synthesis	5	>	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
DNA replication initiation	2	1	1	1
Eukaryotic kinetochore dynamics	1	4	3	2
Centrosome separation	3	2	2	3
DNA replication elongation	4	3	4	4
Metaphase to anaphase checkpoint	5	7	5	5
Mitotic spindle assembly	6	5	6	8

complete

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	2	1	1	1
Centrosome separation	1	3	3	4
Metaphase to anaphase checkpoint	3	7	4	>
Sister chromatid segregation	6	4	10	>
Cholesterol-sensitive control of SREBP activation	4	4	17	2
Eukaryotic kinetochore dynamics	4	2	>	2
Mitotic spindle assembly	5	5	>	>
Citric acid cycle	8	2	>	>
Tropoelastin synthesis	>	>	24	4
Decorin synthesis	>	>	24	4
Phosphoglyceride biosynthesis	>	>	>	3

Downregulated

	MSNB1	MSNB5	MSNB6	MSNB9
Collagen fibril organization by fibril-associated bridges	2	1	1	8
Blycyl synthesis	4	17	>	14
Fibrillar collagen core structure organization	2	1	>	>
WNT-Beta-catenin signaling pathway	>	4	>	6
Retinol metabolism	8	9	>	2
MicrorRNA scaffold organization	8	9	>	3
Tropoelastin synthesis	4	17	>	>
Progesterone receptor signaling	>	17	4	>
Glycolysis and Gluconeogenesis	>	>	>	1
Fibronectin synthesis and extracellular assembly	1	>	>	1
Potassium TM transport	>	>	2	>
Neuregulin receptor signaling	>	>	2	>
Hepatocyte growth factor receptor signaling	>	3	>	4
Fibrin synthesis	>	>	>	4
Tenascin receptor signaling	>	>	>	5
Semaphorin signaling	>	>	>	5
PI3 kinase AKT signaling pathway	5	>	>	>
Amyloid degradation, uptake and aggregation inhibition	>	5	>	>

no1stSVD

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	2	1	1	1
Centrosome separation	1	3	3	4
Metaphase to anaphase checkpoint	3	7	4	>
Sister chromatid segregation	6	4	10	>
Cholesterol-sensitive control of SREBP activation	4	4	17	2
Eukaryotic kinetochore dynamics	4	2	>	2
Mitotic spindle assembly	5	5	>	>
Citric acid cycle	8	2	>	>
Tropoelastin synthesis	>	>	24	4
Decorin synthesis	>	>	24	4
Phosphoglyceride biosynthesis	>	>	>	3

	MSNB1	MSNB5	MSNB6	MSNB9
Collagen fibril organization by fibril-associated bridges	2	1	1	8
Blycyl synthesis	4	17	>	14
Fibrillar collagen core structure organization	2	1	>	>
WNT-Beta-catenin signaling pathway	>	4	>	6
Retinol metabolism	8	9	>	2
MicrorRNA scaffold organization	8	9	>	3
Tropoelastin synthesis	4	17	>	>
Progesterone receptor signaling	>	17	4	>
Glycolysis and Gluconeogenesis	>	>	>	1
Fibronectin synthesis and extracellular assembly	1	>	>	1
Potassium TM transport	>	>	2	>
Neuregulin receptor signaling	>	>	2	>
Hepatocyte growth factor receptor signaling	>	3	>	4
Fibrin synthesis	>	>	>	4
Tenascin receptor signaling	>	>	>	5
Semaphorin signaling	>	>	>	5
PI3 kinase AKT signaling pathway	5	>	>	>
Amyloid degradation, uptake and aggregation inhibition	>	5	>	>

decomposed

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	1	1	1	1
Cholesterol-sensitive control of SREBP activation	9	8	20	2
Centrosome separation	2	2	2	2
Metaphase to anaphase checkpoint	3	4	3	>
Centrosome maturation	4	5	8	>
Mitotic spindle assembly	5	3	9	>
Eukaryotic kinetochore dynamics	10	6	4	>
Transamination pathways	>	>	22	4
GABA metabolism	>	>	>	2
ECM breakdown & membrane shedding by adamalysins	>	>	>	5

	MSNB1	MSNB5	MSNB6	MSNB9
Collagen fibril organization by fibril-associated bridges	2	4	4	4
WNT-Beta-catenin signaling pathway	>	6	3	2
Serine and glycine metabolism	1	>	1	3
Retinol metabolism	2	>	>	3
ECM breakdown & membrane shedding by adamalysins	>	4	8	>
Chaperone mediated protein folding in ER	5	>	12	>
Hepatocyte growth factor receptor signaling	>	5	16	>
Glycolysis and Gluconeogenesis	>	>	>	1
Fibrillar collagen core structure organization	>	1	>	>
Neuregulin receptor signaling	>	>	2	>
Thrombospondin receptor signaling	3	>	>	>
CCN family receptor signaling	>	3	>	>
Urea cycle	4	>	>	>
Tenascin receptor signaling	>	>	>	5
ECM breakdown by cathepsins	>	>	>	5

complete

	MSNB1	MSNB5	MSNB6	MSNB9
Semaphorin signaling	6	2	3	2
Alternative complement pathway	1	4	4	1
Classical complement pathway	3	5	4	3
Serine and glycine metabolism	7	2	2	6
ECM breakdown & membrane shedding by adamalysins	5	6	5	5
Water TM transport	2	4	>	4
Fibrillar collagen core structure organization	3	>	1	>
Osteonectin receptor signaling	1	>	>	>
Albumin mediated blood protein transport	4	>	>	>
Inhibition of apoptosis	5	>	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	1	1	1	1
Cholesterol-sensitive control of SREBP activation	2	4	3	5
Lipogenesis	4	15	15	10
Leptin receptor signaling	6	3	5	5
ECM breakdown & membrane shedding by adamalysins	13	6	10	3
JAK-STAT signaling pathway	16	11	2	10
Interferon beta receptor signaling	11	5	7	>
Amyloid degradation, uptake and aggregation inhibition	>	2	>	4
Desaturation of fatty acids	3	>	4	>
WNT-Beta-catenin signaling pathway	>	>	17	4
Hepatocyte growth factor receptor signaling	>	>	>	2
ER unfolded protein response pathway	>	>	>	2
Heme degradation to bilirubin	>	>	>	4

decomposed

	MSNB1	MSNB5	MSNB6	MSNB9
Natriuretic peptide receptor signaling	7	16	13	4
DNA replication initiation	>	5	3	1
Eukaryotic kinetochore dynamics	2	3	1	6
Centrosome separation	3	1	4	15
Fanconi anemia interstrand cross-link repair pathway	4	10	10	3
DNA replication elongation	>	14	12	2
Mitotic spindle assembly	5	6	2	>
Metaphase to anaphase checkpoint	6	2	5	>
Glycolysis and Gluconeogenesis	>	4	>	1
Contactin ring constriction	2	14	>	11
Collagen fibril organization by fibril-associated bridges	>	14	13	4
Glycolysis and Gluconeogenesis	>	4	>	1
Intracellular bridge assembly	>	3	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
Natriuretic peptide receptor signaling	7	16	13	4
DNA replication initiation	>	5	3	1
Eukaryotic kinetochore dynamics	2	3	1	6
Centrosome separation	3	1	4	15
Fanconi anemia interstrand cross-link repair pathway	4	10	10	3
DNA replication elongation	>	14	12	2
Mitotic spindle assembly	5	6	2	>
Metaphase to anaphase checkpoint	6	2	5	>
Glycolysis and Gluconeogenesis	>	4	>	1
Contactin ring constriction	2	14	>	11
Collagen fibril organization by fibril-associated bridges	>	14	13	4
Glycolysis and Gluconeogenesis	>	4	>	1
Intracellular bridge assembly	>	3	>	>

decomposed

	MSNB1	MSNB5	MSNB6	MSNB9
Natriuretic peptide receptor signaling	5	9	8	9
Contactin ring constriction	7	2	5	2
Glutamate and glutamine metabolism	4	6	9	9
Eukaryotic kinetochore dynamics	>	2	2	3
DNA replication initiation	>	4	4	9
Metaphase to anaphase checkpoint	>	3	3	15
Mitotic spindle assembly	>	5	6	10
Collagen fibril organization by fibril-associated bridges	>	16	5	9
Centrosome separation	>	1	1	1
Intracellular bridge assembly	>	6	>	4
Elastin cross-linking and assembly	>	14	>	4
Collagen fiber crosslinking	>	16	>	4
ECM breakdown & membrane shedding by adamalysins	>	4	>	2
Cellular cholesterol uptake and efflux	>	4	>	2
Serine and glycine metabolism	1	2	>	>
Classical complement pathway	2	>	>	>
ECM breakdown by matrix metalloproteinases	>	3	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	1	1	1	1
Cholesterol-sensitive control of SREBP activation	2	4	3	5
Lipogenesis	4	15	15	10
Leptin receptor signaling	6	3	5	5
ECM breakdown & membrane shedding by adamalysins	13	6	10	3
JAK-STAT signaling pathway	16	11	2	10
Interferon beta receptor signaling	11	5	7	>
Amyloid degradation, uptake and aggregation inhibition	>	2	>	4
Desaturation of fatty acids	3	>	4	>
WNT-Beta-catenin signaling pathway	>	>	17	4
Hepatocyte growth factor receptor signaling	>	>	>	2
ER unfolded protein response pathway	>	>	>	2
Heme degradation to bilirubin	>	>	>	4

decomposed

	MSNB1	MSNB5	MSNB6	MSNB9
Centrosome separation	1	2	1	3
Metaphase to anaphase checkpoint	4	5	3	5
Mitotic spindle assembly	2	3	6	6
Eukaryotic kinetochore dynamics	2	4	7	4
Centrosome maturation	12	12	2	16
G2 M transition checkpoint	12	12	2	16
Cholesterol synthesis	5	1	1	1
G2 M transition checkpoint	12	12	2	16
Collagen fiber crosslinking	3	6	>	24
Fibrillar collagen core structure organization	>	1	25	24
Tenascin receptor signaling	>	12	>	5
Glycolysis and Gluconeogenesis	>	25	>	2
ECM breakdown by matrix metalloproteinases	28	5	>	>
Retinol metabolism	2	>	>	>
Amyloid degradation, uptake and aggregation inhibition	4	>	>	>

	MSNB1	MSNB5	MSNB6	MSNB9
Cholesterol synthesis	1	1	1	1
Decorin synthesis	4	4	6	2
Androgen receptor signaling	4	2	10	>
Procollagen cleavage into collagen				

**MBCOL3
nilotinib
(is c.toxic: no)**

**MBCOL3
pazopanib
(is c.toxic: yes)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN09
Centrosome separation	1	8	2	1	2
Serine and glycine metabolism	4	1	5	4	8
Eukaryotic kinetochore dynamics	>	16	1	2	1
Metaphase to anaphase checkpoint	>	16	4	3	4
Mitotic spindle assembly	>	17	3	5	3
Sister chromatid segregation	>	3	9	16	12
Centrosome maturation	>	3	11	10	12
Cholesterol synthesis	18	5	>	>	>
Glycolysis and Gluconeogenesis	2	>	>	>	>
Selectin-mediated Leukocyte rolling	>	>	>	>	>
GABA metabolism	>	>	>	>	>
Fibrillar collagen core structure organization	3	>	>	>	>
Fibronectin synthesis and extracellular assembly	5	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN09
Z-disc organization	>	9	1	2	3
Thin myofibril organization	>	5	2	3	>
Thick myofibril organization	>	2	5	5	>
Epithelial intermediate filament dynamics	>	6	>	4	4
Fibrillar collagen core structure organization	>	1	>	13	12
GM-CSF receptor signaling	>	11	3	7	>
Collagen fibril organization by fibril-associated bridges	>	2	>	10	>
Potassium TM transport	>	4	>	10	>
Gap junction organization	>	2	>	20	>
Glycolysis and Gluconeogenesis	>	>	>	>	1
CM repolarization during AP & hyperpol.	>	2	>	>	>
ECM breakdown & membrane shedding by adamalysins	>	2	>	>	>
Microtubule crosslinking and bundling	>	3	>	>	>
Connection of muscle sarcomere to plasma membrane	>	3	>	>	>
Tenascin receptor signaling	>	4	>	>	>
Hepatocyte growth factor receptor signaling	>	4	>	>	>
Amyloid plaque organization	>	4	>	>	>
Thick myofibril organization	>	4	>	>	5
Glycogen synthesis and glycogenolysis	>	5	>	>	>
Fibroblast growth factor receptor signaling	>	5	>	>	>

complete

	MSN01	MSN05	MSN06	MSN08	MSN09
Serine and glycine metabolism	3	1	3	4	1
Lysosomal glycoprotein degradation	8	4	4	6	4
Cholesterol-sensitive control of SREBP activation	8	4	8	6	4
Citric acid cycle	1	2	>	14	8
ER unfolded protein response pathway	14	7	5	2	>
Mammalian target of rapamycin signaling pathway	>	9	7	5	10
Cholesterol synthesis	10	>	2	>	2
Desaturation of fatty acids	>	>	10	1	6
Protein folding in mitochondria	>	4	14	>	14
Electron transport chain	5	>	>	12	>
Fibrillar collagen core structure organization	>	>	1	>	>
Glycolysis and Gluconeogenesis	2	>	>	>	>
Fatty acid elongation	>	>	>	3	>

	MSN01	MSN05	MSN06	MSN08	MSN09
WNT-Beta-catenin signaling pathway	>	3	>	>	6
Hippo signaling	>	6	1	>	6
CCN family receptor signaling	1	8	>	>	3
HIF-1 receptor signaling pathway	4	5	6	>	3
ECM breakdown & membrane shedding by adamalysins	>	4	5	6	>
HIF-1 receptor signaling pathway	>	7	8	>	1
Fibrillar collagen core structure organization	>	1	>	2	1
Gap junction organization	>	1	>	2	4
Macrophage migration inhibitory factor signaling	>	8	>	1	4
Microtubule crosslinking and bundling	>	12	3	11	4
Microtubule crosslinking and bundling	>	12	4	>	4
Collagen fibril organization by fibril-associated bridges	>	2	>	>	2
Retinol metabolism	>	2	>	>	2
Caveolin-mediated endocytosis	>	2	>	>	2
Tenascin receptor signaling	>	3	>	>	3
Adherens junction organization	>	3	>	>	4
Tight junction organization	>	4	>	>	5
Water TM transport	>	4	>	>	5
Leukocyte transmigration through endothelium	>	5	>	>	5

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN09
Centrosome separation	1	8	2	1	2
Serine and glycine metabolism	9	1	5	4	8
Eukaryotic kinetochore dynamics	>	16	1	2	1
Metaphase to anaphase checkpoint	>	16	3	3	4
Mitotic spindle assembly	>	17	4	5	3
Sister chromatid segregation	>	3	11	20	12
Centrosome maturation	>	3	11	10	12
Cholesterol synthesis	18	5	>	>	>
Glycolysis and Gluconeogenesis	2	>	>	>	>
Selectin-mediated Leukocyte rolling	>	>	>	>	>
GABA metabolism	>	>	>	>	>
Fibrillar collagen core structure organization	3	>	>	>	>
Fibronectin synthesis and extracellular assembly	5	>	>	>	>
Thin myofibril organization	5	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN09
Z-disc organization	>	5	1	1	2
Thin myofibril organization	>	3	4	2	3
Epithelial intermediate filament dynamics	>	6	>	3	4
Fibrillar collagen core structure organization	>	1	>	11	12
Collagen fibril organization by fibril-associated bridges	>	2	>	7	8
Potassium TM transport	>	2	5	10	>
Gap junction organization	>	2	>	18	>
Glycolysis and Gluconeogenesis	>	>	>	>	1
CM repolarization during AP & hyperpol.	>	2	>	>	>
ECM breakdown & membrane shedding by adamalysins	>	2	>	>	>
Microtubule crosslinking and bundling	>	3	>	>	>
Connection of muscle sarcomere to plasma membrane	>	3	>	>	>
Tenascin receptor signaling	>	4	>	>	>
Hepatocyte growth factor receptor signaling	>	4	>	>	>
Amyloid plaque organization	>	4	>	>	>
Thick myofibril organization	>	4	>	>	5
Glycogen synthesis and glycogenolysis	>	5	>	>	>
Fibroblast growth factor receptor signaling	>	5	>	>	>

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN09
Serine and glycine metabolism	4	1	3	5	1
Lysosomal glycoprotein degradation	8	4	4	8	4
Cholesterol-sensitive control of SREBP activation	8	4	8	8	4
Citric acid cycle	1	2	>	1	3
ER unfolded protein response pathway	>	7	5	3	>
Cholesterol synthesis	13	>	2	>	2
Desaturation of fatty acids	>	>	10	2	6
Electron transport chain	3	8	>	13	>
Protein folding in mitochondria	5	15	>	>	12
Fibrillar collagen core structure organization	>	>	1	>	>
Glycolysis and Gluconeogenesis	2	>	>	>	>
Fatty acid elongation	>	>	>	4	>

	MSN01	MSN05	MSN06	MSN08	MSN09
CCN family receptor signaling	1	8	>	>	3
HIF-1 receptor signaling pathway	>	6	1	>	6
WNT-Beta-catenin signaling pathway	>	3	5	7	>
Gap junction organization	>	1	1	3	>
Fibrillar collagen core structure organization	>	1	>	7	4
Microtubule polymerization	>	8	>	1	4
Macrophage migration inhibitory factor signaling	>	8	>	1	4
ECM breakdown & membrane shedding by adamalysins	>	4	5	>	3
Semaphorin signaling	>	12	3	9	>
Collagen fibril organization by fibril-associated bridges	>	12	3	>	4
Tenascin receptor signaling	>	2	>	>	2
Retinol metabolism	>	2	>	>	2
Caveolin-mediated endocytosis	>	2	>	>	2
Tight junction organization	>	3	>	>	4
Water TM transport	>	4	>	>	5
Intrinsic apoptosis pathway	>	4	>	>	5
Cardiomyocyte pacemaker current generation	>	5	>	>	5

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN09
Centrosome separation	1	1	1	1	1
Metaphase to anaphase checkpoint	3	3	3	3	3
Eukaryotic kinetochore dynamics	2	7	2	2	2
Mitotic spindle assembly	4	6	4	4	4
Serine and glycine metabolism	10	4	5	5	5
Mitotic H3 phosphorylation and dephosphorylation	5	8	6	6	6
Contractile ring constriction	13	2	6	18	6
Cholesterol synthesis	>	5	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN09
Fibrillar collagen core structure organization	10	1	3	10	3
Z-disc organization	>	4	1	1	1
Thin myofibril organization	>	2	6	2	>
Epithelial intermediate filament dynamics	>	5	6	4	4
ECM breakdown & membrane shedding by adamalysins	>	8	>	2	6
Cardiomyocyte pacemaker current generation	>	6	8	4	>
Thick myofibril organization	>	4	3	3	>
Retinol metabolism	>	3	4	4	>
Collagen fibril organization by fibril-associated bridges	>	2	5	>	>
Amyloid degradation, uptake and aggregation inhibition	>	1	>	>	>
Thrombospondin receptor signaling	>	2	>	>	>
Osteonectin receptor signaling	>	2	>	>	>
Muscarinic receptor signaling	>	4	>	>	>
CCN family receptor signaling	>	4	>	5	>

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN09
Serine and glycine metabolism	4	1	3	5	1
Lysosomal glycoprotein degradation	8	4	4	8	4
Cholesterol-sensitive control of SREBP activation	8	4	8	8	4
Citric acid cycle	1	2	>	1	3
ER unfolded protein response pathway	>	7	5	3	>
Cholesterol synthesis	13	>	2	>	2
Desaturation of fatty acids	>	>	10	2	6
Electron transport chain	3	8	>	13	>
Protein folding in mitochondria	5	15	>	>	12
Fibrillar collagen core structure organization	>	>	1	>	>
Glycolysis and Gluconeogenesis	2	>	>	>	>
Fatty acid elongation	>	>	>	4	>

	MSN01	MSN05	MSN06	MSN08	MSN09
CCN family receptor signaling	1	8	>	>	3
HIF-1 receptor signaling pathway	>	6	1	>	6
WNT-Beta-catenin signaling pathway	>	3	5	7	>
Gap junction organization	>	1	1	3	>
Fibrillar collagen core structure organization	>	1	>	7	4
Microtubule polymerization	>	8	>	1	4
Macrophage migration inhibitory factor signaling	>	8	>	1	4
ECM breakdown & membrane shedding by adamalysins	>	4	5	>	3
Semaphorin signaling	>	12	3	9	>
Collagen fibril organization by fibril-associated bridges	>	12	3	>	4
Tenascin receptor signaling	>	2	>	>	2
Retinol metabolism	>	2	>	>	2
Caveolin-mediated endocytosis	>	2	>	>	2
Tight junction organization	>	3	>	>	4
Water TM transport	>	4	>	>	5
Intrinsic apoptosis pathway	>	4	>	>	5
Cardiomyocyte pacemaker current generation	>	5	>	>	5

**MBCOL3
ponatinib
(is c.toxic: yes)**

**MBCOL3
regorafenib
(is c.toxic: no)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MSN01	MSN02	MSN05	MSN06	MSN08	MSN09
Centrosome separation	1	1	1	3	3	3
Mitotic spindle assembly	4	2	4	2	2	2
Metaphase to anaphase checkpoint	8	5	3	4	4	4
Centrosome maturation	14	4	5	5	6	6
Sister chromatid segregation	5	7	6	8	16	16
Serine and glycine metabolism	2	3	13	24	26	26
Eukaryotic kinetochore dynamics	6	7	2	1	1	1
Albumin mediated blood protein transport	12	4	>	>	>	>
Contractile ring constriction	>	>	15	5	>	>
Glycolysis and Gluconeogenesis	>	1	>	>	>	>
Prostaglandin E2 receptor signaling	>	2	>	>	>	>
Fibrillar collagen core structure organization	3	>	>	>	>	>
Carnitine shuttle	>	3	>	>	>	>
Verhagen synthesis	>	4	>	>	>	>

	MSN01	MSN02	MSN05	MSN06	MSN08	MSN09
Z-disc organization	>	9	1	2	3	>
Thin myofibril organization	>	5	2	3	>	>
VEGF receptor signaling	>	11	3	7	4	>
Fibrillar collagen core structure organization	>	4	4	3	3	>
CCN family receptor signaling	>	4	4	3	3	>
GM-CSF receptor signaling	>	11	3	4	14	>
Natriuretic peptide receptor signaling	>	6	3	10	5	>
ECM breakdown & membrane shedding by adamalysins	>	6	3	10	5	>
Collagen fibril organization by fibril-associated bridges	>	6	3	10	5	>
Caveolin-mediated endocytosis	>	2	10	>	>	>
Glycolysis and Gluconeogenesis	>	1	>	1	>	>
Cholesterol synthesis	>	1	>	1	>	>
Anchoring of nuclear membrane to cytoskeleton	>	2	>	>	1	>
Amyloid degradation, uptake and aggregation inhibition	>	2	>	>	2	>
Fibronectin synthesis and extracellular assembly	>	2	>	>	2	>
Non-vesicular phospholipid transport	>	2	>	>	4	>
Hemidesmosome organization	>	2	>	>	4	

**MBCOL3
ruxolitinib
(is c.toxic: no)**

**MBCOL3
sorafenib
(is c.toxic: yes)**

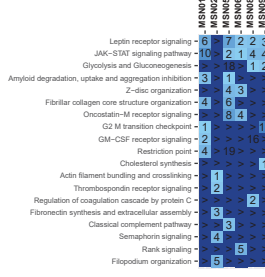
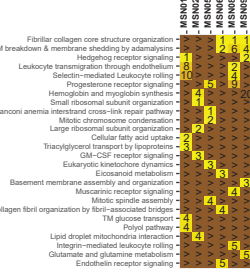
Upregulated

Downregulated

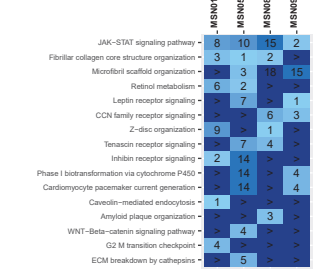
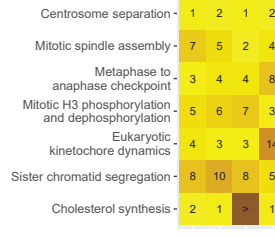
Upregulated

Downregulated

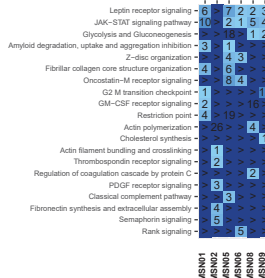
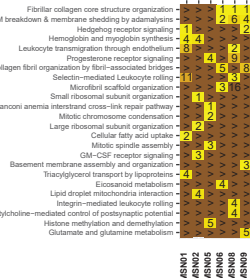
complete



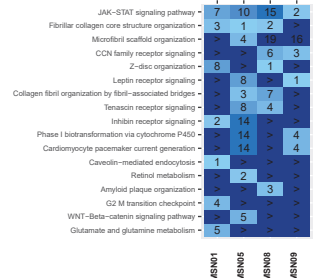
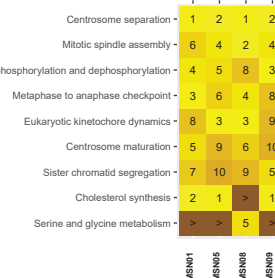
complete



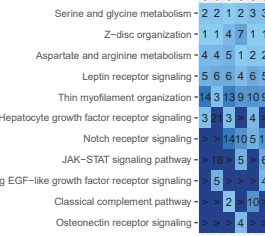
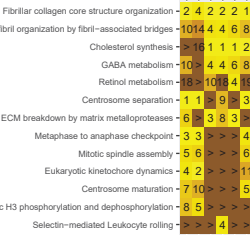
no1stSVD



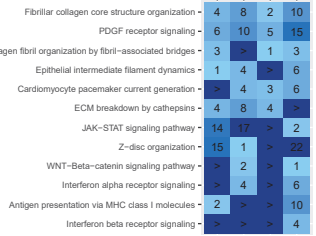
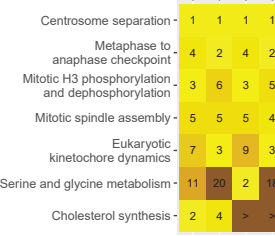
no1stSVD



decomposed



decomposed



**MBCOL3
sunitinib
(is c.toxic: yes)**

**MBCOL3
tofacitinib
(is c.toxic: no)**

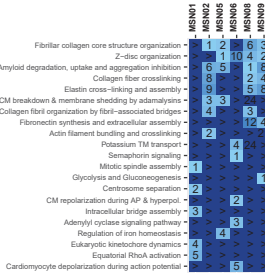
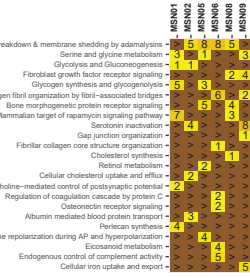
Upregulated

Downregulated

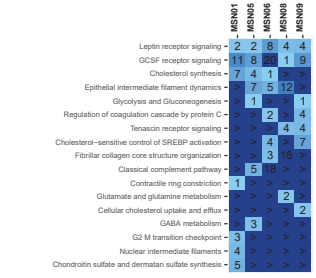
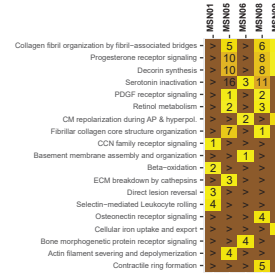
Upregulated

Downregulated

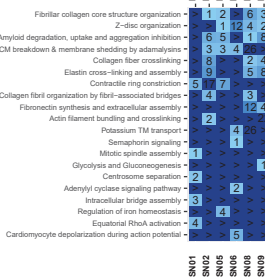
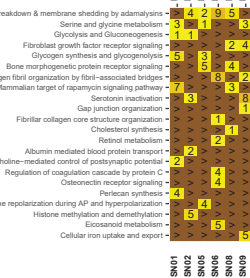
complete



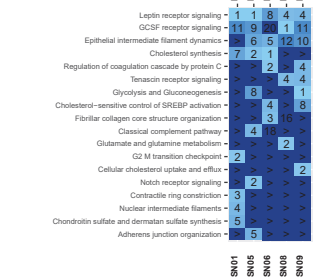
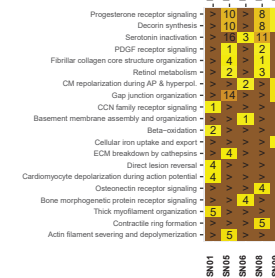
complete



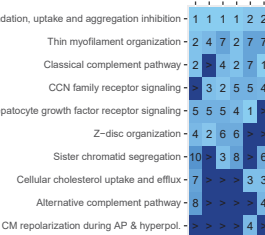
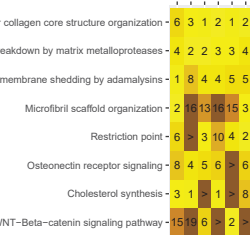
no1stSVD



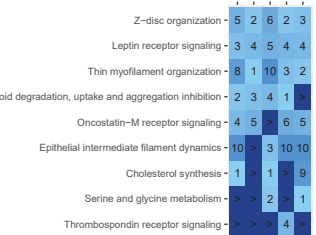
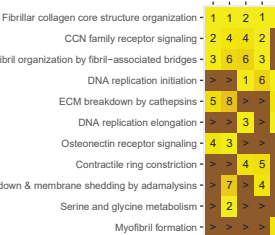
no1stSVD



decomposed

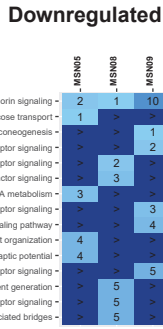
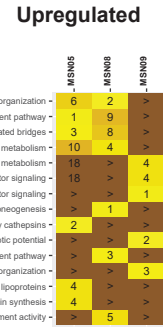
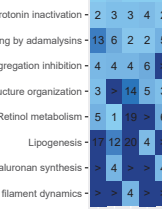
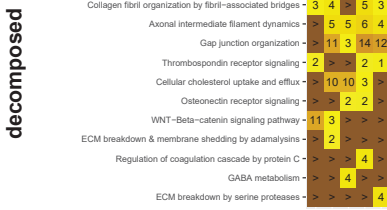
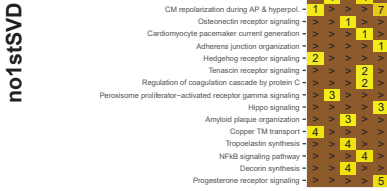
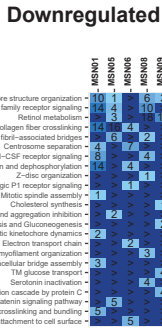
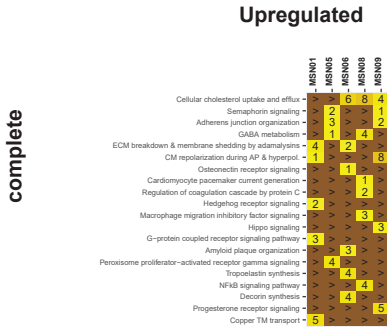
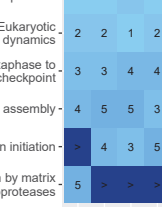
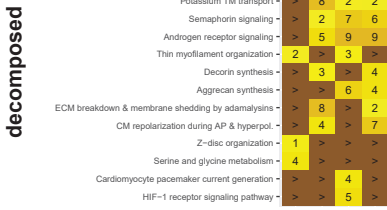
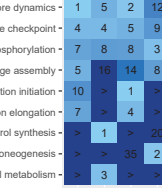
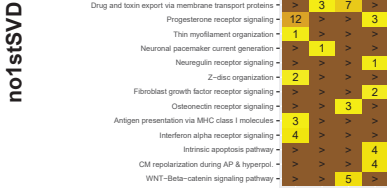
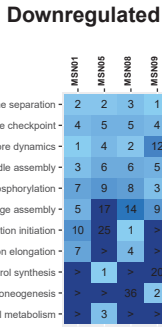
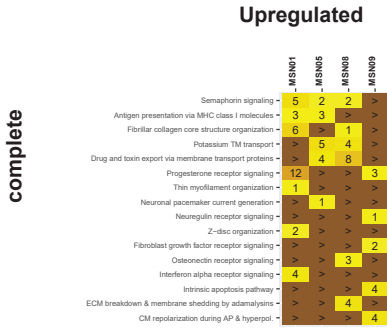


decomposed



**MBCOL3
trametinib
(is c.toxic: yes)**

**MBCOL3
vandetanib
(is c.toxic: yes)**



complete

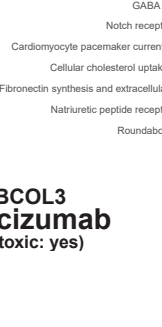
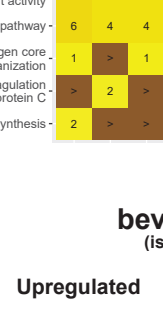
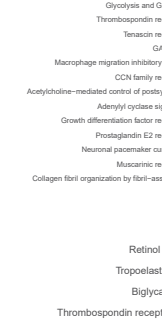
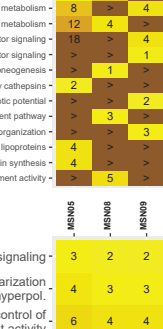
no1stSVD

decomposed

complete

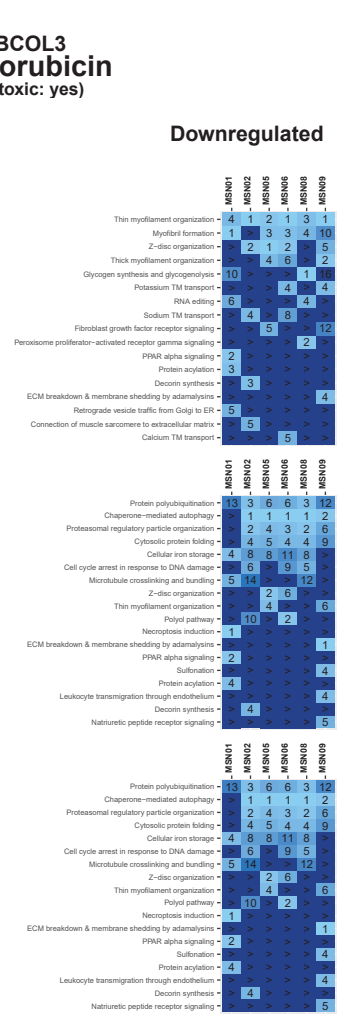
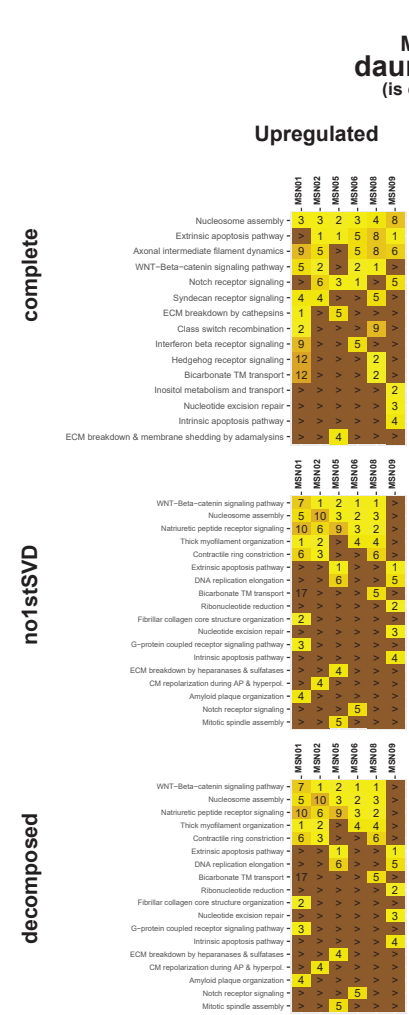
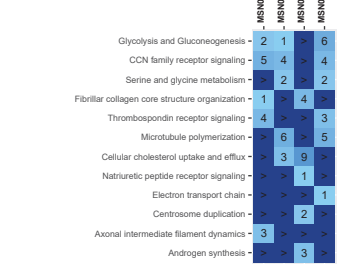
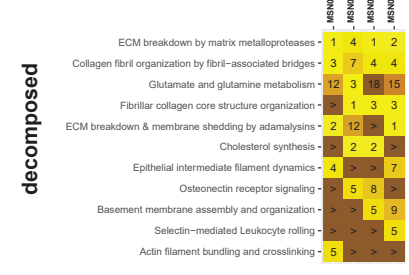
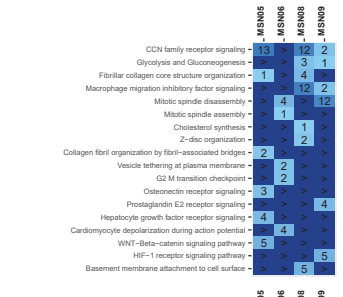
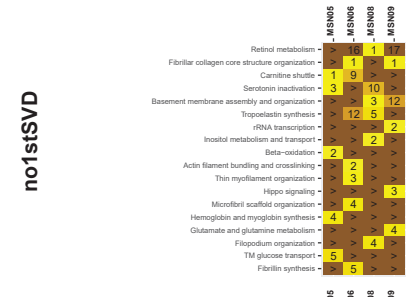
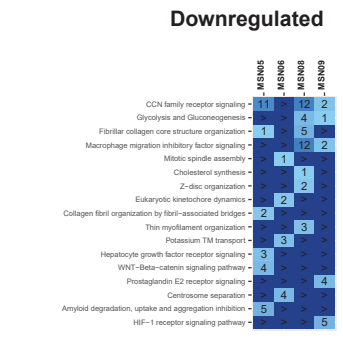
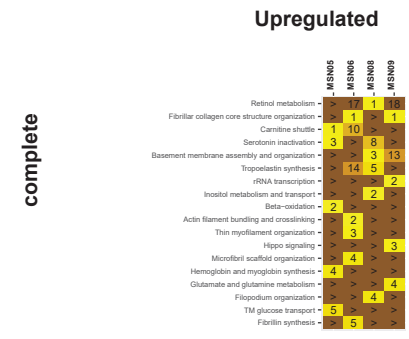
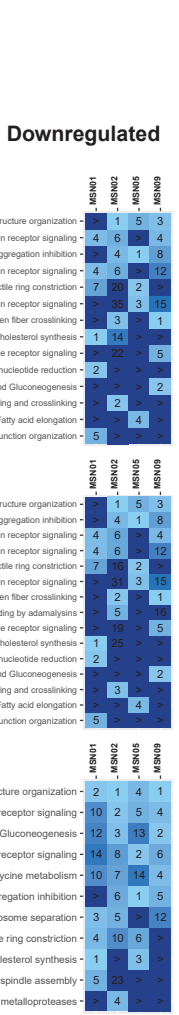
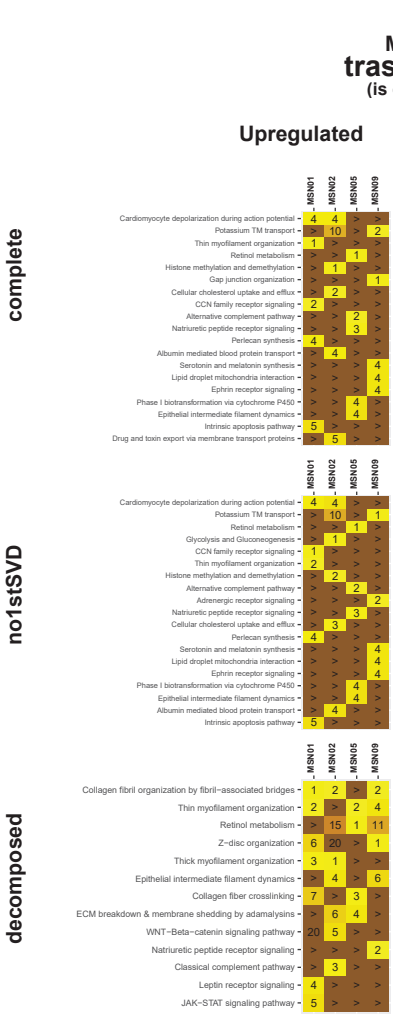
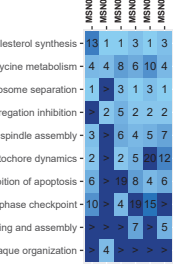
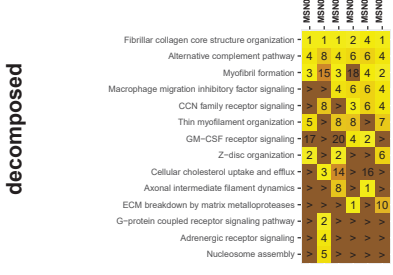
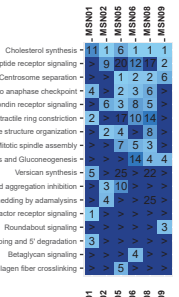
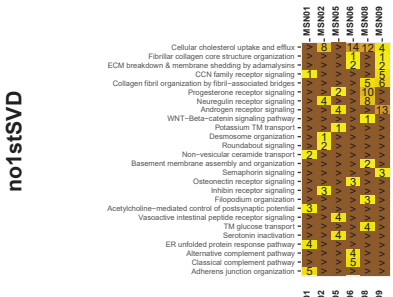
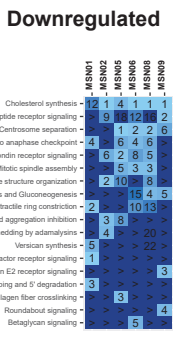
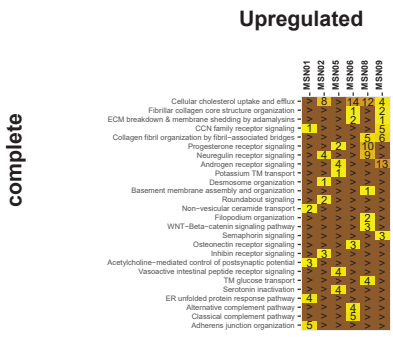
no1stSVD

decomposed



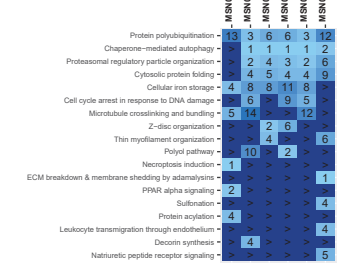
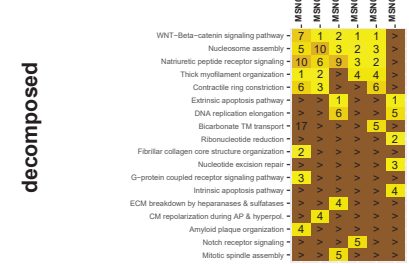
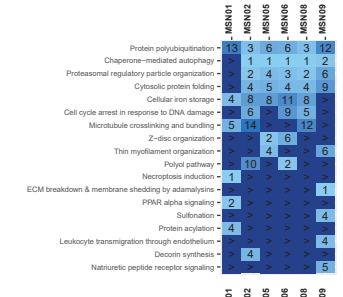
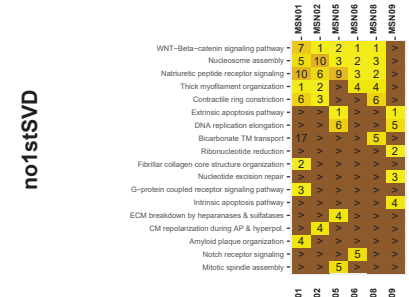
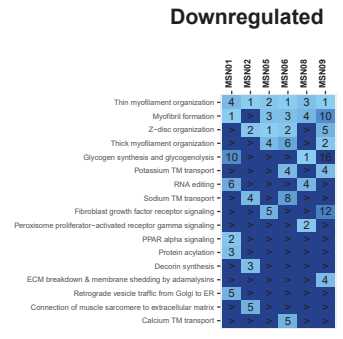
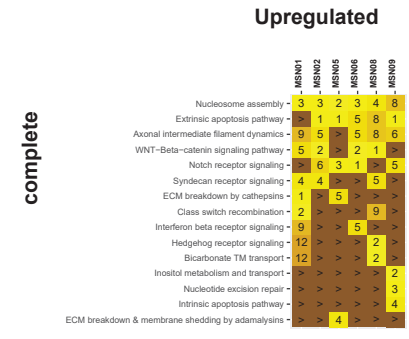
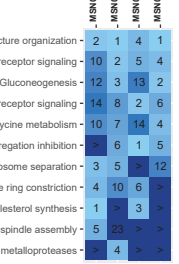
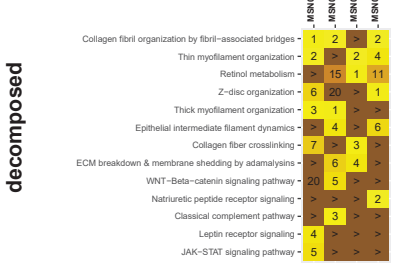
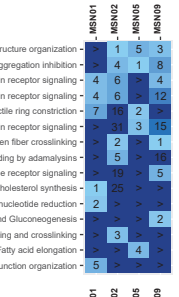
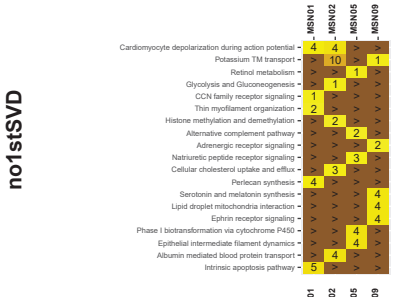
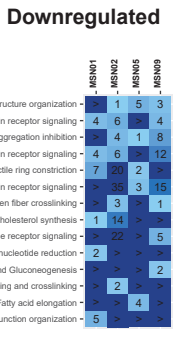
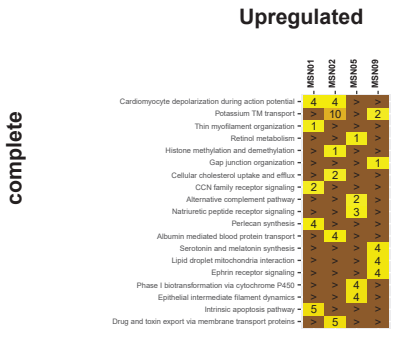
**MBCOL3
cetuximab
(is c.toxic: no)**

**MBCOL3
rituximab
(is c.toxic: no)**



**MBCOL3
trastuzumab
(is c.toxic: yes)**

**MBCOL3
daunorubicin
(is c.toxic: yes)**



**MBCOL3
doxorubicin**
(is c.toxic: yes)

**MBCOL3
epirubicin**
(is c.toxic: yes)

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08
Nucleosome assembly	2	3	1	2
Extrinsic apoptosis pathway	6	6	8	1
Syndecan receptor signaling	4	2	4	
WNT-Beta-catenin signaling pathway	7	1	3	
Axonal intermediate filament dynamics	6	6	2	
Prostaglandin E2 receptor signaling	>	5	6	
Motilin receptor signaling	1	>	>	
Intrinsic apoptosis pathway	>	>	>	3
Cannabinoid receptor signaling	4	>	>	
Hedgehog receptor signaling	>	4	>	
Acetylcholine-mediated control of postsynaptic potential	>	>	>	5
Notch receptor signaling	>	>	>	4
Nodal growth differentiation factor receptor signaling	>	>	5	

	MSN01	MSN05	MSN06	MSN08
Thin myofilament organization	2	>	1	1
Actin polymerization	5	>	3	
Myofibril formation	>	2	>	7
Progesterone synthesis	1	>	>	
Mitochondrial transport	>	2	>	
Potassium TM transport	>	>	>	2
Glycolysis and Gluconeogenesis	>	>	2	
Transamination pathways	2	>	>	
Sulfonation	>	>	>	4
Leukocyte transmigration through endothelium	>	>	>	4
Androgen synthesis	4	>	>	
Natriuretic peptide receptor signaling	>	>	>	5

complete

	MSN01	MSN05	MSN06	MSN08
ECM breakdown by cathepsins	4	1	6	2
Amyloid plaque organization	6	3	2	6
Lysosomal lipid degradation	2	6	4	8
Fibrillar collagen core structure organization	1	21	1	4
Basement membrane attachment to cell surface	2	6	4	21
Syndecan receptor signaling	16	2	8	18
ECM breakdown by matrix metalloproteases	26	19	5	>
Metabolism of branched-chain amino acids	>	14	>	1
Beta-oxidation	18	>	>	3
Lysosomal glycosaminoglycan degradation	>	4	>	
Basement membrane assembly and organization	4	>	>	

	MSN01	MSN05	MSN06	MSN08
Myofibril formation	2	>	>	2
Glycogen synthesis and glycogenolysis	1	3	>	
Macrophage migration inhibitory factor signaling	>	6	2	
GM-CSF receptor signaling	>	4	6	
Protein acylation	4	3	8	
Purinergic P1 receptor signaling	>	5	8	
Thin myofilament organization	>	1	3	
Small ribosomal subunit organization	>	>	1	
Natriuretic peptide receptor signaling	>	>	>	1
Chromatin targeting to lamina	2	>	>	
Sister chromatid cohesion	3	>	>	
Large ribosomal subunit organization	>	>	3	
Insulin receptor signaling	>	>	>	3
Lamellipodium organization	>	>	>	4
Electron transport chain	>	>	>	4
Chromatin organization by insulator proteins	4	>	>	
Cholesterol synthesis	>	>	>	5

no1stSVD

	MSN01	MSN05	MSN06	MSN08
WNT-Beta-catenin signaling pathway	3	1	1	
Natriuretic peptide receptor signaling	1	3	2	
Nucleosome assembly	2	4	5	
Thick myofilament organization	4	5	4	
Extrinsic apoptosis pathway	>	10	>	2
Nucleotide excision repair	>	>	>	1
Syndecan receptor signaling	>	2	>	
Nodal growth differentiation factor receptor signaling	>	>	3	
Inositol metabolism and transport	>	>	>	3
Ribonucleotide reduction	>	>	>	4
Intrinsic apoptosis pathway	>	>	>	5

	MSN01	MSN05	MSN06	MSN08
Chaperone-mediated autophagy	1	2	2	1
Cellular iron storage	6	4	4	
Protein polyubiquitination	2	1	12	
Hepatocyte growth factor receptor signaling	4	>	2	14
Cytosolic protein folding	3	>	>	10
CD44-mediated leukocyte rolling	4	>	>	14
Neurotosis induction	>	1	>	
ECM breakdown & membrane shedding by adamalysins	>	>	>	2
Z-disc organization	>	>	>	3
Heme degradation to bilirubin	>	4	>	
Collagen fiber crosslinking	>	>	>	4
Natriuretic peptide receptor signaling	>	>	>	5

no1stSVD

	MSN01	MSN05	MSN06	MSN08
Fibrillar collagen core structure organization	1	9	1	4
Amyloid plaque organization	6	5	3	6
Lysosomal lipid degradation	2	7	4	8
ECM breakdown by cathepsins	4	1	18	2
Basement membrane attachment to cell surface	2	2	2	21
Basement membrane assembly and organization	4	4	>	
Antigen presentation via MHC class I molecules	>	4	7	
Beta-oxidation	18	>	>	3
Metabolism of branched-chain amino acids	>	26	>	1
Fibulin receptor signaling	>	>	5	

	MSN01	MSN05	MSN06	MSN08
GM-CSF receptor signaling	>	2	>	1
Myofibril formation	>	1	>	4
Macrophage migration inhibitory factor signaling	>	3	>	2
Protein acylation	4	>	6	
Large ribosomal subunit organization	>	>	1	
Glycogen synthesis and glycogenolysis	1	>	>	
Small ribosomal subunit organization	>	>	2	
Chromatin targeting to lamina	2	>	>	
Sister chromatid cohesion	3	>	>	
Neoptosis induction	>	>	3	
Natriuretic peptide receptor signaling	>	>	>	3
Myelin biogenesis and maturation	>	4	>	
Cholesterol synthesis	>	4	>	
Chromatin organization by insulator proteins	4	>	>	
Thin myofilament organization	>	5	>	
Insulin receptor signaling	>	>	>	5

decomposed

	MSN01	MSN05	MSN06	MSN08
WNT-Beta-catenin signaling pathway	3	1	1	
Natriuretic peptide receptor signaling	1	3	2	
Nucleosome assembly	2	4	5	
Thick myofilament organization	4	5	4	
Extrinsic apoptosis pathway	>	10	>	2
Nucleotide excision repair	>	>	>	1
Syndecan receptor signaling	>	2	>	
Nodal growth differentiation factor receptor signaling	>	>	3	
Inositol metabolism and transport	>	>	>	3
Ribonucleotide reduction	>	>	>	4
Intrinsic apoptosis pathway	>	>	>	5

	MSN01	MSN05	MSN06	MSN08
Chaperone-mediated autophagy	1	2	2	1
Cellular iron storage	6	4	4	
Protein polyubiquitination	2	1	12	
Hepatocyte growth factor receptor signaling	4	>	2	14
Cytosolic protein folding	3	>	>	10
CD44-mediated leukocyte rolling	4	>	>	14
Neurotosis induction	>	1	>	
ECM breakdown & membrane shedding by adamalysins	>	>	>	2
Z-disc organization	>	>	>	3
Heme degradation to bilirubin	>	4	>	
Collagen fiber crosslinking	>	>	>	4
Natriuretic peptide receptor signaling	>	>	>	5

decomposed

	MSN01	MSN05	MSN06	MSN08
Fibrillar collagen core structure organization	1	9	1	4
Amyloid plaque organization	6	5	3	6
Lysosomal lipid degradation	2	7	4	8
ECM breakdown by cathepsins	4	1	18	2
Basement membrane attachment to cell surface	2	2	2	21
Basement membrane assembly and organization	4	4	>	
Antigen presentation via MHC class I molecules	>	4	7	
Beta-oxidation	18	>	>	3
Metabolism of branched-chain amino acids	>	26	>	1
Fibulin receptor signaling	>	>	5	

	MSN01	MSN05	MSN06	MSN08
GM-CSF receptor signaling	>	2	>	1
Myofibril formation	>	1	>	4
Macrophage migration inhibitory factor signaling	>	3	>	2
Protein acylation	4	>	6	
Large ribosomal subunit organization	>	>	1	
Glycogen synthesis and glycogenolysis	1	>	>	
Small ribosomal subunit organization	>	>	2	
Chromatin targeting to lamina	2	>	>	
Sister chromatid cohesion	3	>	>	
Neoptosis induction	>	>	3	
Natriuretic peptide receptor signaling	>	>	>	3
Myelin biogenesis and maturation	>	4	>	
Cholesterol synthesis	>	4	>	
Chromatin organization by insulator proteins	4	>	>	
Thin myofilament organization	>	5	>	
Insulin receptor signaling	>	>	>	5

**MBCOL3
idarubicin**
(is c.toxic: yes)

**MBCOL3
amiodarone**
(is c.toxic: nd)

Upregulated

Downregulated

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08
Extrinsic apoptosis pathway	1	1	2	4
Intrinsic apoptosis pathway	4	3	1	12
Cell cycle arrest in response to DNA damage	3	2	4	24
Nucleotide excision repair	2	>	>	3
Coagulation cascade	>	10	>	3
Drug and toxin export via membrane transport proteins	>	4	>	17
Fibrillar collagen core structure organization	>	>	>	1
Amyloid degradation, uptake and aggregation inhibition	>	>	>	2
Syndecan receptor signaling	5	>	>	
Hyaluronan receptor CD44 signaling	>	>	>	5

	MSN01	MSN05	MSN06	MSN08
Z-disc organization	1	3	3	6
Thin myofilament organization	2	4	4	5
Centrosome separation	5	7	2	3
Mitotic spindle assembly	23	11	7	4
Myofibril formation	5	15	20	8
Eukaryotic kinetochore dynamics	>	1	1	1
Metaphase to anaphase checkpoint	>	6	5	2
Focal adhesion organization	3	24	11	>
DNA replication elongation	>	2	6	>
Fibulin receptor signaling	>	5	>	
Connection of muscle sarcomere to plasma membrane	5	>	>	

complete

	MSN01	MSN05	MSN06	MSN08	
Cellular cholesterol uptake and efflux	>	1	10	12	8
Serotonin inactivation	>	12	11	16	11
Fibrillar collagen core structure organization	>	3	1	1	4
Amyloid degradation, uptake and aggregation inhibition	>	3	13	2	4
Semaphorin signaling	>	3	13	7	
ECM breakdown & membrane shedding by adamalysins	>	1	7	4	
Alternative complement pathway	>	8	4	3	
Adenosine receptor signaling	>	8	3	3	
Metaphase to anaphase checkpoint	>	>	>	3	
Sister chromatid segregation	>	>	>	2	
Osteonectin receptor signaling	>	>	2	>	
Lipogenesis	2	>	>	>	
CCN family receptor signaling	>	>	4	>	
Thyroid hormone receptor signaling	>	>	4	>	
Leptin receptor signaling	4	>	>	>	
Centrosome separation	>	>	>	4	
Endogenous control of complement activity	>	>	5	>	

	MSN01	MSN05	MSN06	MSN08
Z-disc organization	6	2	1	2
Natriuretic peptide receptor signaling	6	14	6	3
CCN family receptor signaling	3	12	3	6
Thin myofilament organization	7	10	9	4
Collagen fibril organization by fibril-associated bridges	5	8	6	1
Glycolysis and Gluconeogenesis	>	2	>	1
Glycogen synthesis and glycogenolysis	>	5	>	4
Connection of muscle sarcomere to plasma membrane	10	>	>	10
Restriction point	>	10	>	5
GM-CSF receptor signaling	1	>	15	
Fibrillar collagen core structure organization	>	1	>	
Recycling endosome dynamics	>	2	>	
Lectin complement pathway	>	3	>	
Fibronectin synthesis and extracellular assembly	>	3	>	
Contractile ring constriction	>	3	>	
WNT-Beta-catenin signaling pathway	>	4	>	
Thrombospondin receptor signaling	>	4	>	

no1stSVD

	MSN01	MSN05	MSN06	MSN08
Extrinsic apoptosis pathway	1	7	1	
Amyloid degradation, uptake and aggregation inhibition	4	>	3	
RNA editing	12	3	2	
Cell cycle arrest in response to DNA damage	10	4	5	
Intrinsic apoptosis pathway	5	12	6	
ECM breakdown by matrix metalloproteases	2	2	>	31
Nucleotide excision repair	3	>	4	32
Coagulation cascade	>	9	>	2
Fibrillar collagen core structure organization	12	>	>	1
Drug and toxin export via membrane transport proteins	>	1	>	21
Selectin-mediated Leukocyte rolling	>	>	>	4
Microfibril scaffold organization	>	>	>	5

	MSN01	MSN05	MSN06	MSN08
Mitotic spindle assembly	10	7	5	3
Contractile ring constriction	2	9	9	6
Centrosome separation	>	4	1	2
Eukaryotic kinetochore dynamics	>	3	2	4
Metaphase to anaphase checkpoint	>	8	3	1
ECM breakdown & membrane shedding by adamalysins	5	1	13	>
DNA replication elongation	>	2	4	22
DNA replication initiation	>	5	6	>
Thin myofilament organization	1	>	>	16
Z-disc organization	3	>	>	22
Focal adhesion organization	4	>	>	

no1stSVD

	MSN01	MSN05	MSN06	MSN08	
Cellular cholesterol uptake and efflux	>	1	11	12	10
Serotonin inactivation	>	12	11	16	12
Fibrillar collagen core structure organization	>	5	1	1	6
Alternative complement pathway	>	5	4	3	
Amyloid degradation, uptake and aggregation inhibition	>	2	>	4	
ECM breakdown & membrane shedding by adamalysins	>	1	>	4	
Adenosine receptor signaling	>				

MBCOL3
dobutamine
(is c.toxic: nd)

MBCOL3
flecainide
(is c.toxic: nd)

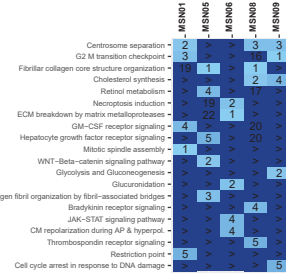
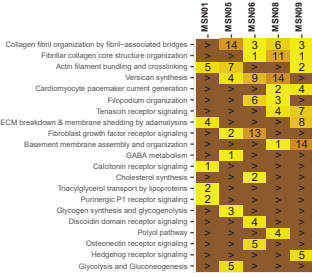
Upregulated

Downregulated

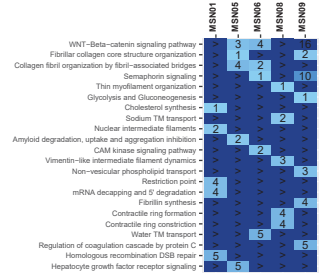
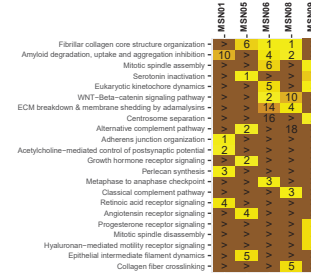
Upregulated

Downregulated

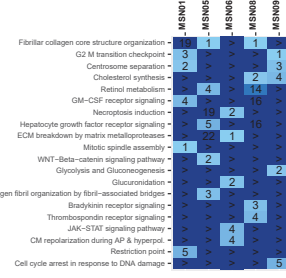
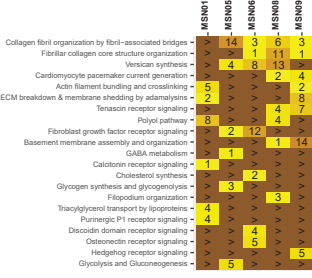
complete



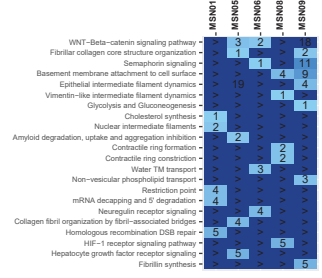
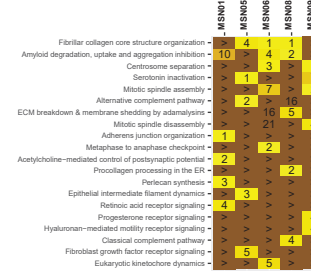
complete



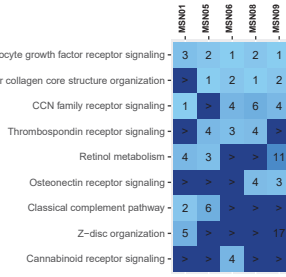
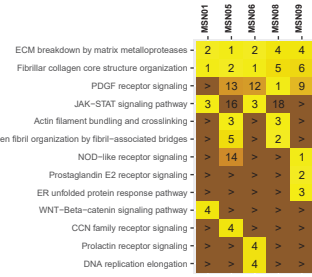
no1stSD



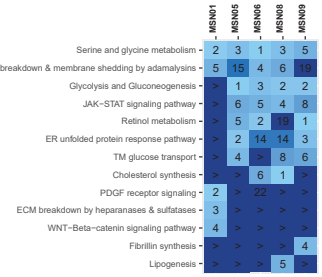
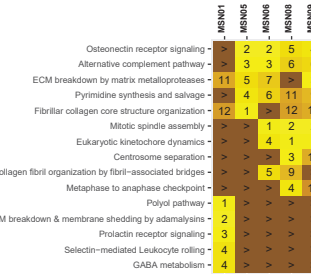
no1stSD



decomposed



decomposed



MBCOL3
isoprenaline
(is c.toxic: nd)

MBCOL3
milrinone
(is c.toxic: nd)

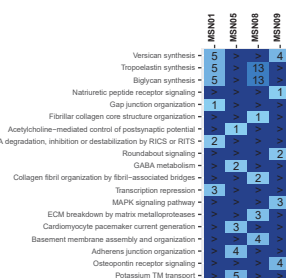
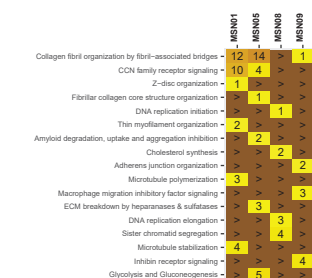
Upregulated

Downregulated

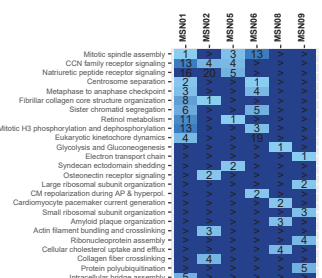
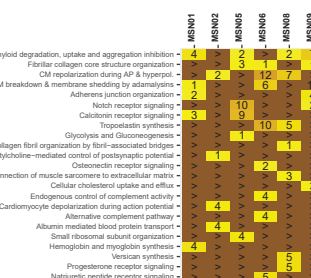
Upregulated

Downregulated

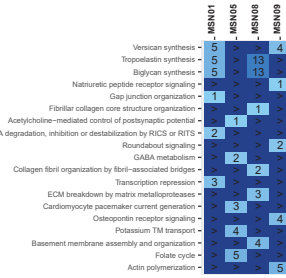
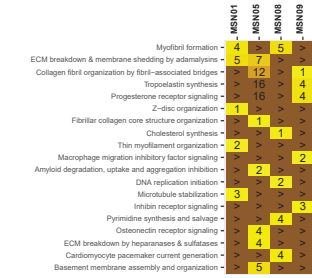
complete



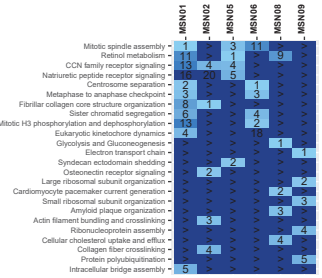
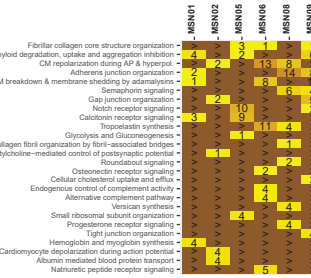
complete



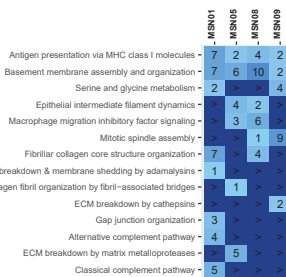
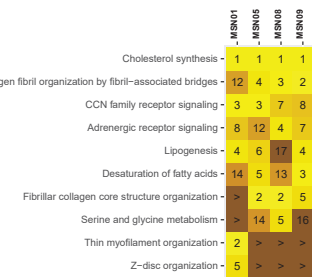
no1stSD



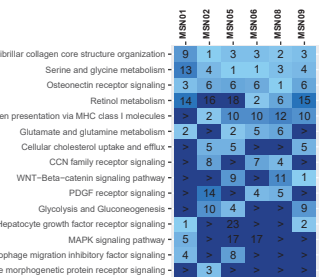
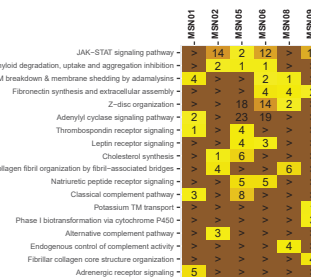
no1stSD



decomposed



decomposed



**MBCOL3
phenylephrine
(is c.toxic: nd)**

**MBCOL3
verapamil
(is c.toxic: nd)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

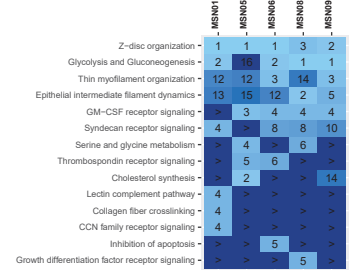
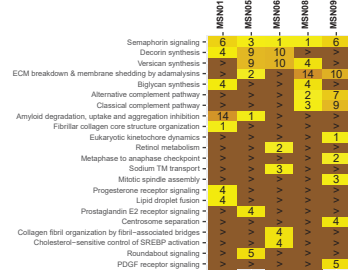
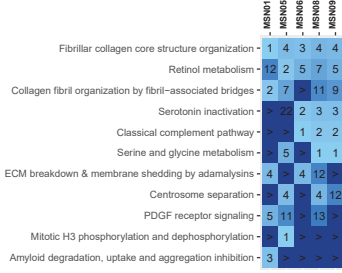
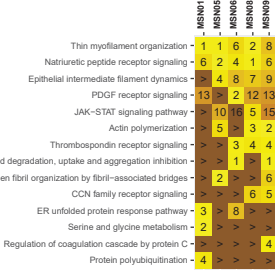
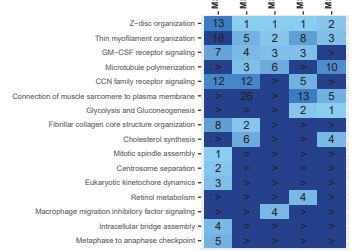
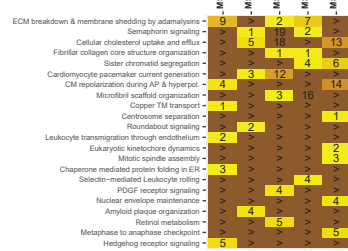
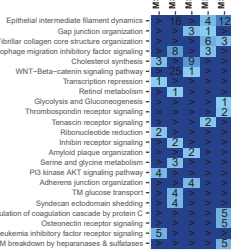
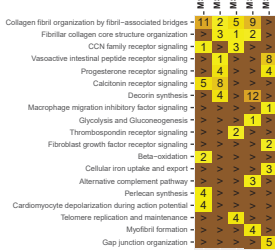
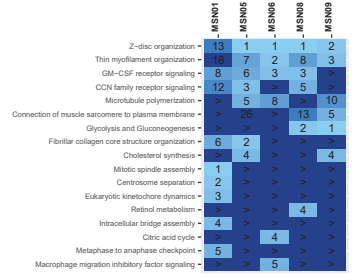
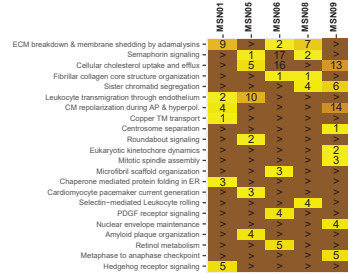
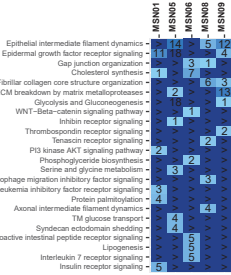
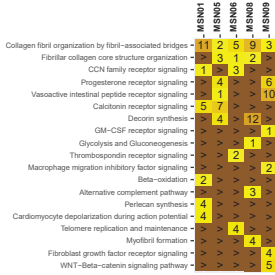
complete

no1stSVD

no1stSVD

decomposed

decomposed



**MBCOL3
azacitidine
(is c.toxic: nd)**

**MBCOL3
bortezomib
(is c.toxic: yes)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

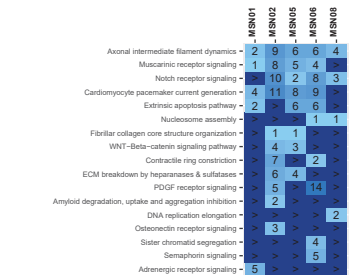
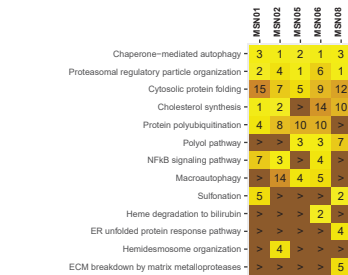
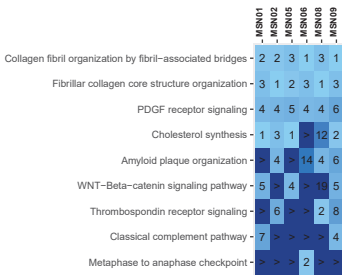
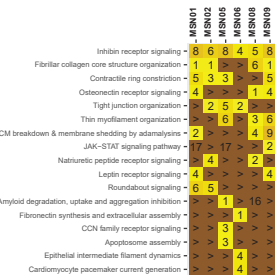
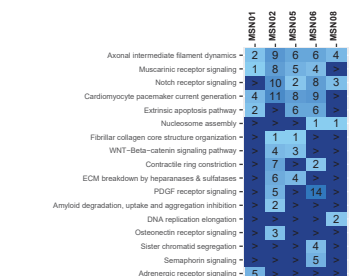
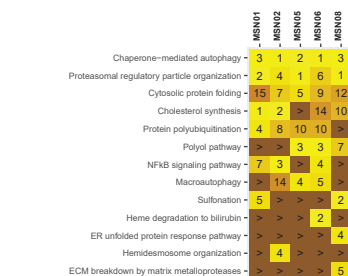
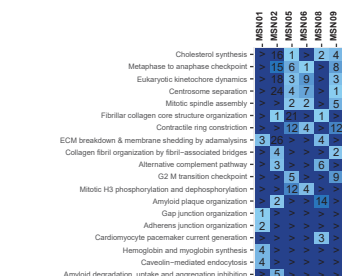
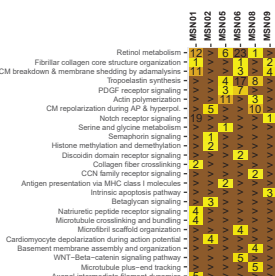
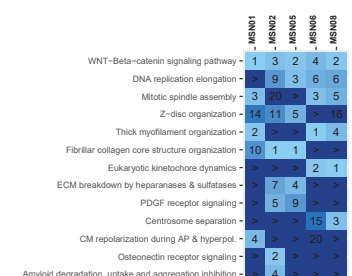
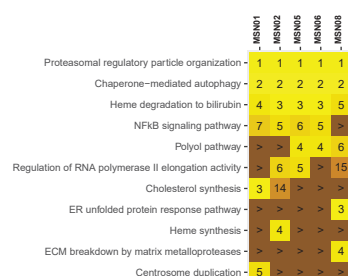
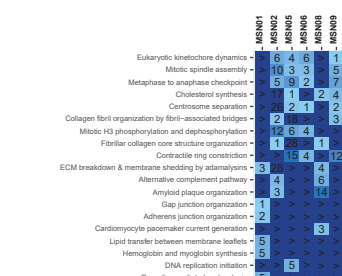
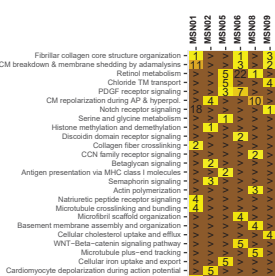
complete

no1stSVD

no1stSVD

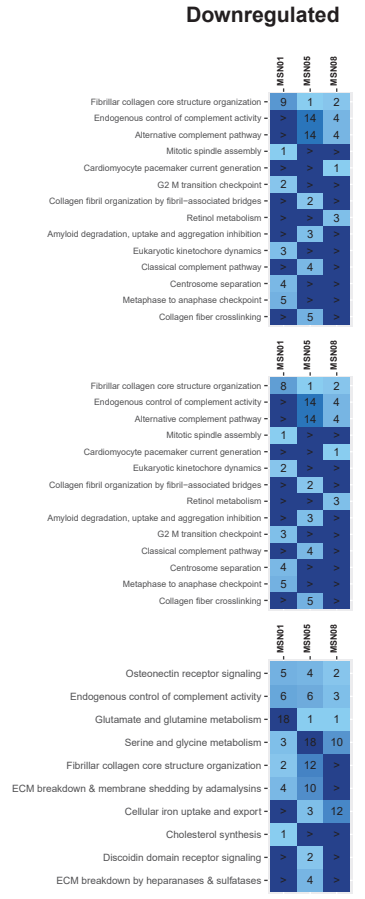
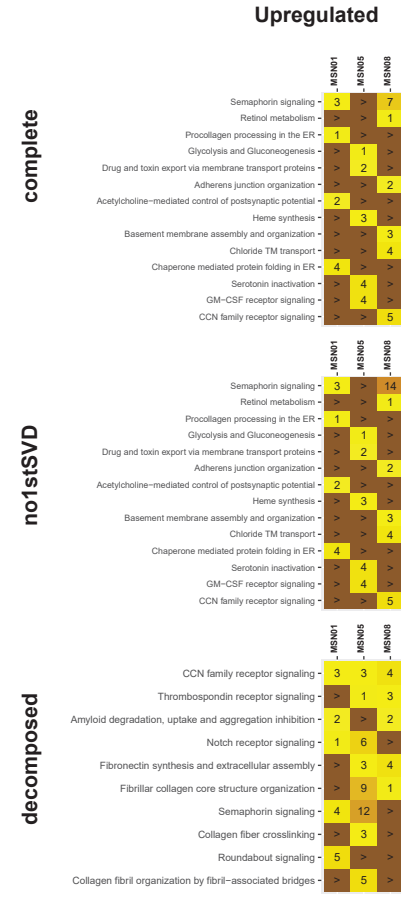
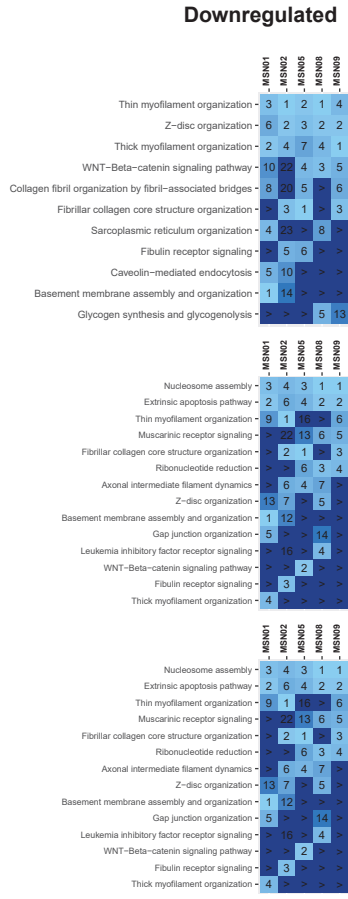
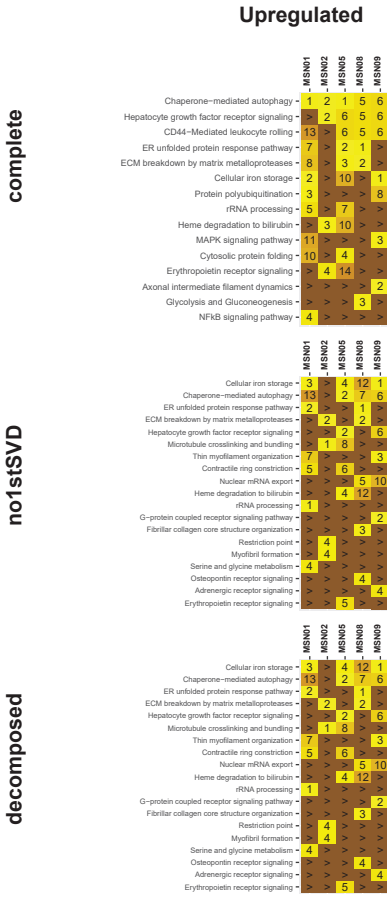
decomposed

decomposed



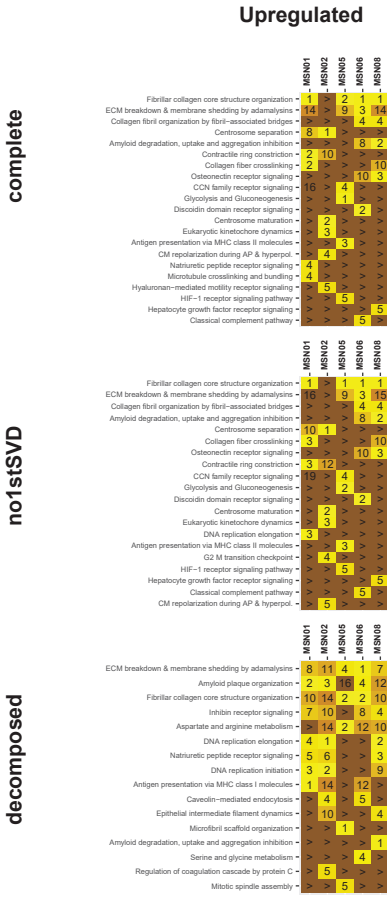
**MBCOL3
carfilzomib
(is c.toxic: yes)**

**MBCOL3
cyclosporine
(is c.toxic: nd)**



**MBCOL3
decitabine
(is c.toxic: nd)**

**MBCOL3
delavirdine
(is c.toxic: nd)**



**MBCOL3
diclofenac
(is c.toxic: nd)**

**MBCOL3
endothelin-1
(is c.toxic: nd)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

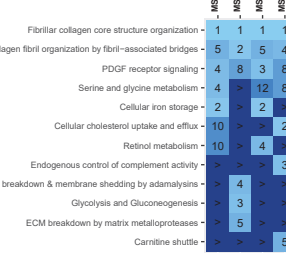
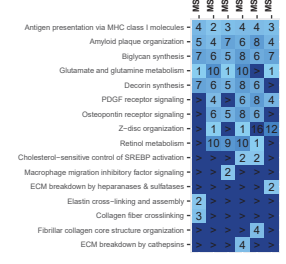
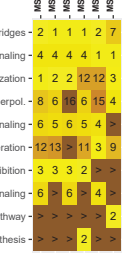
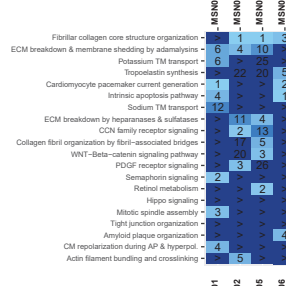
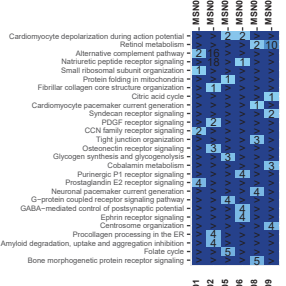
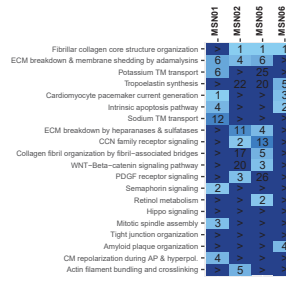
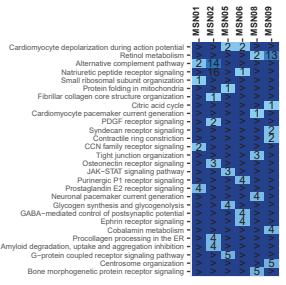
complete

no1stSD

decomposed

no1stSD

decomposed



**MBCOL3
estradiol
(is c.toxic: nd)**

**MBCOL3
insulin-like growth factor 1
(is c.toxic: nd)**

Upregulated

Downregulated

Upregulated

Downregulated

complete

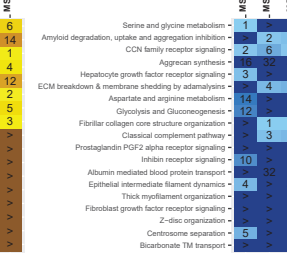
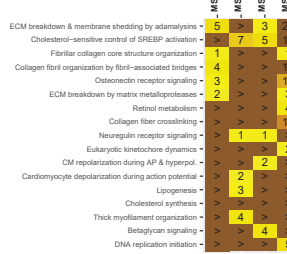
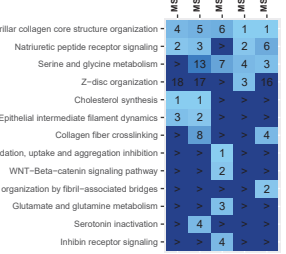
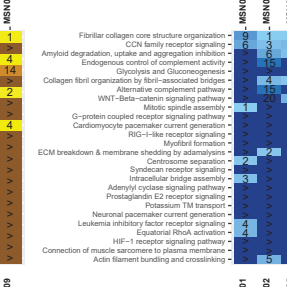
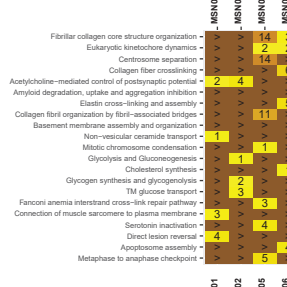
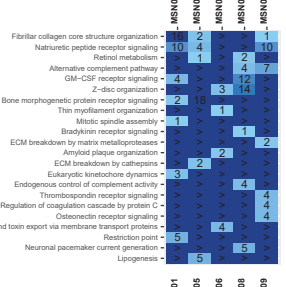
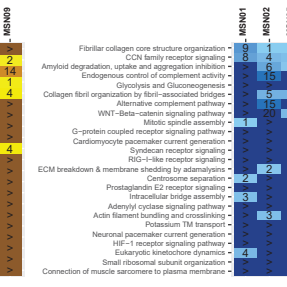
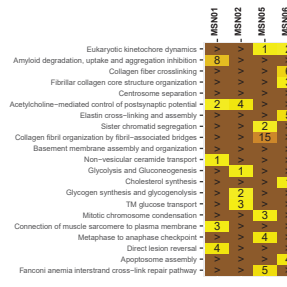
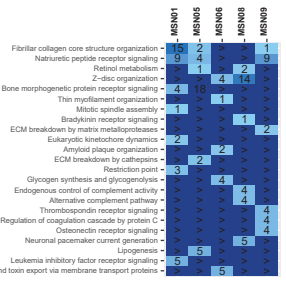
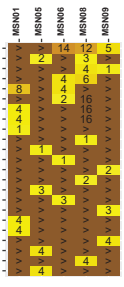
complete

no1stSD

decomposed

no1stSD

decomposed



MBCOL3
olmesartan
(is c.toxic: nd)

MBCOL3
pioglitazone
(is c.toxic: nd)

Upregulated

Downregulated

Upregulated

Downregulated

complete

complete

no1stSVD

no1stSVD

decomposed

decomposed

complete

complete

no1stSVD

no1stSVD

decomposed

decomposed

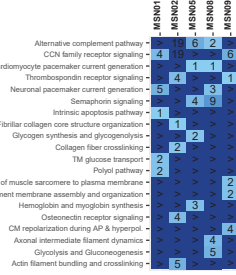
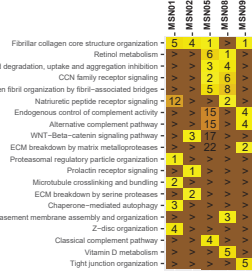
Upregulated

Downregulated

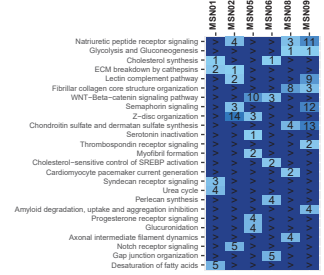
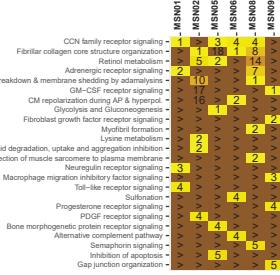
Upregulated

Downregulated

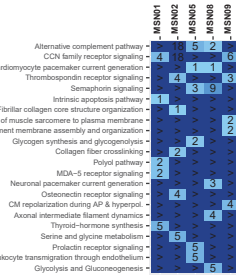
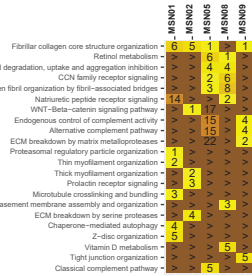
complete



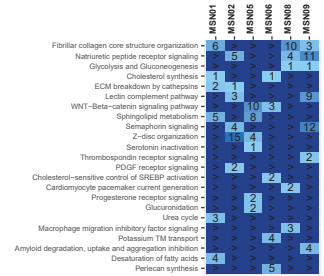
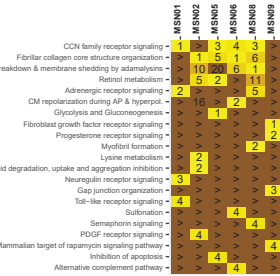
complete



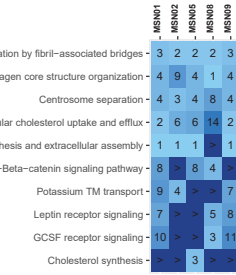
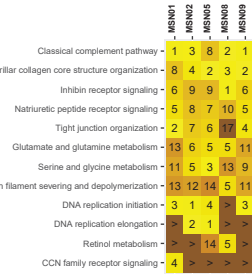
no1stSVD



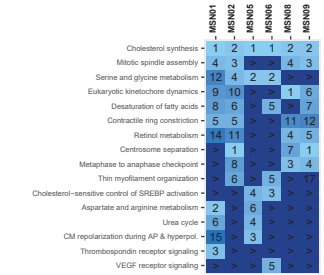
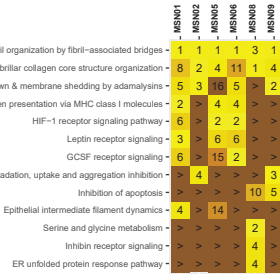
no1stSVD



decomposed

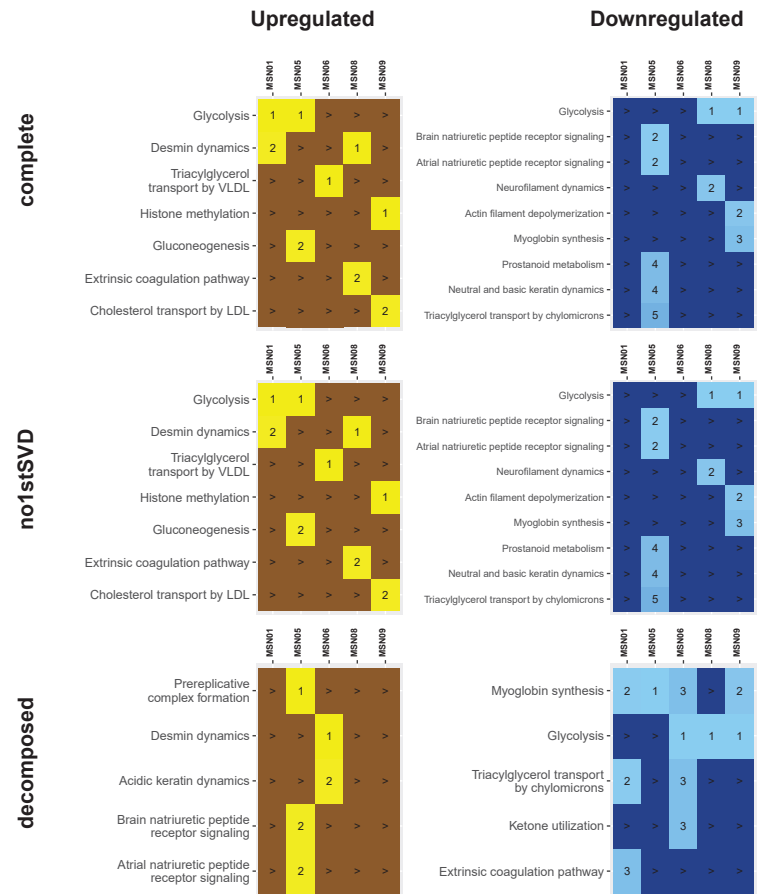
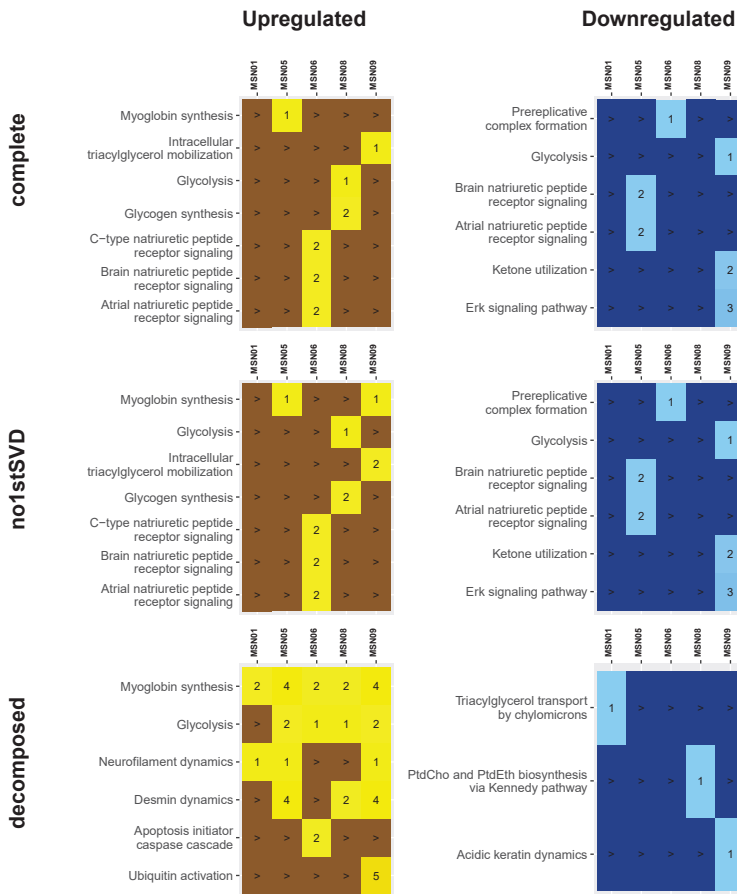


decomposed



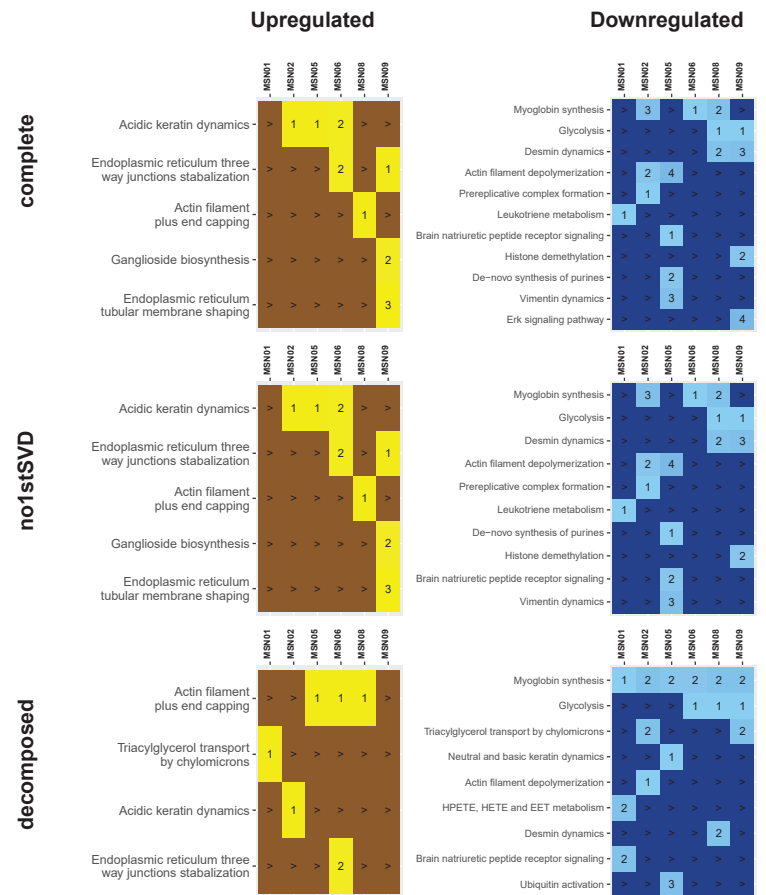
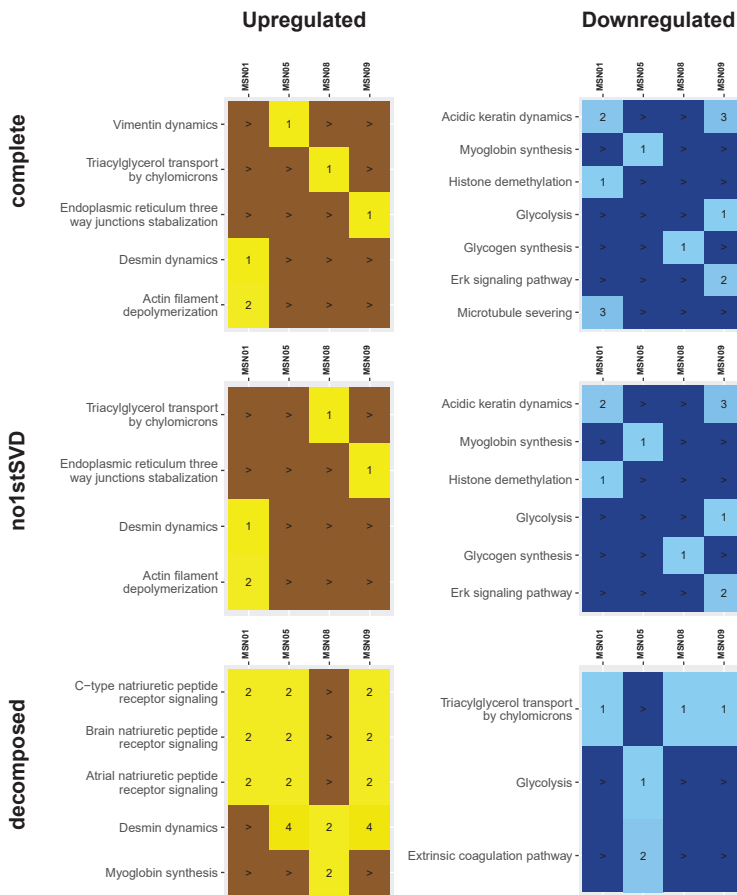
**MBCOL4
afatinib**
(is c.toxic: no)

**MBCOL4
axitinib**
(is c.toxic: no)



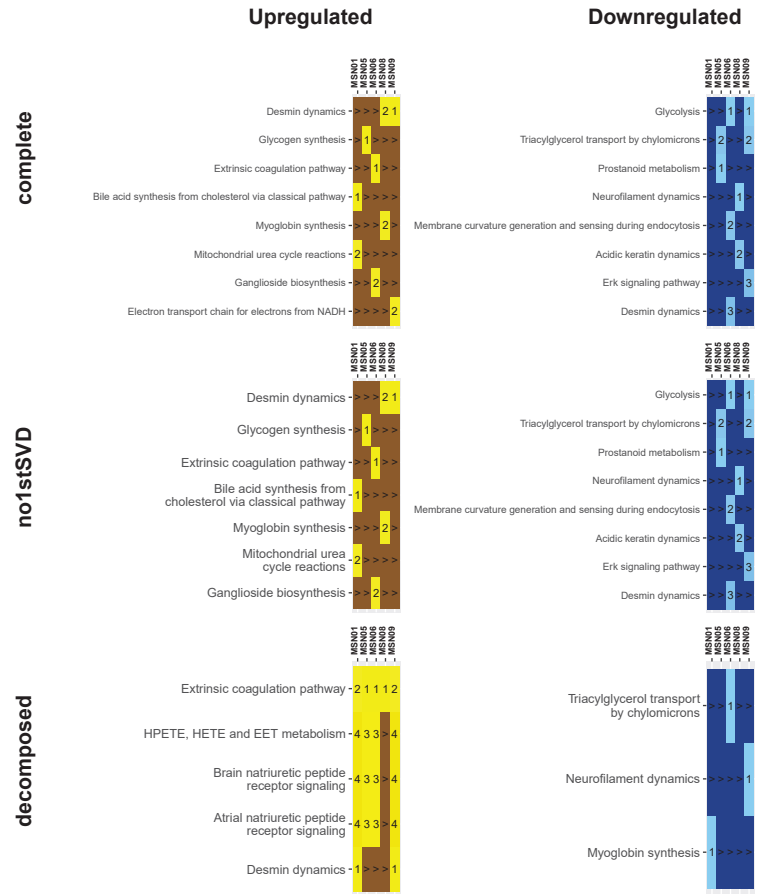
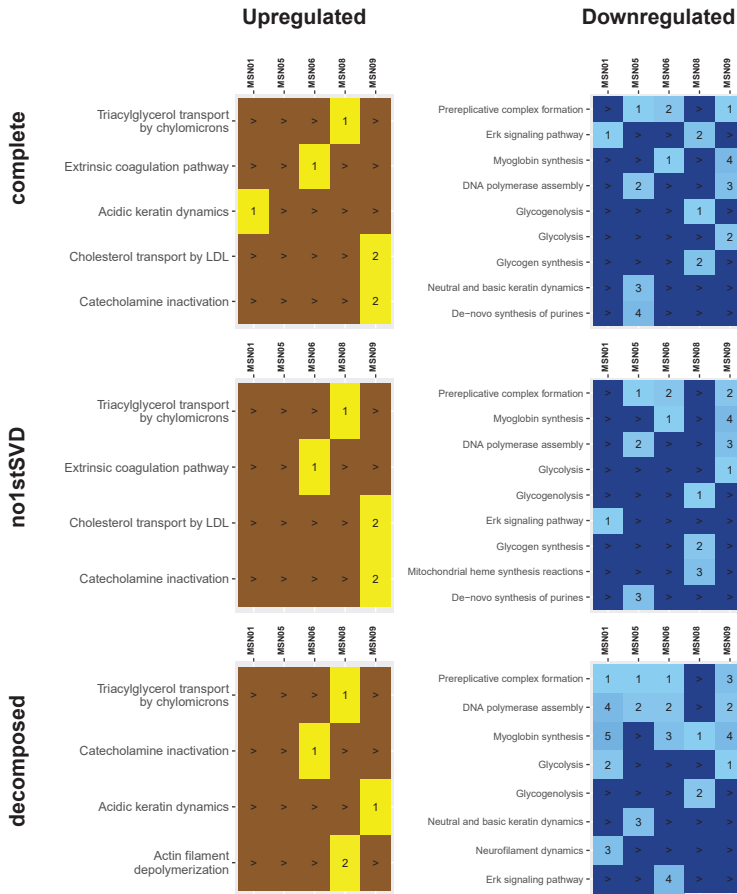
**MBCOL4
bosutinib**
(is c.toxic: no)

**MBCOL4
cabozantinib**
(is c.toxic: no)



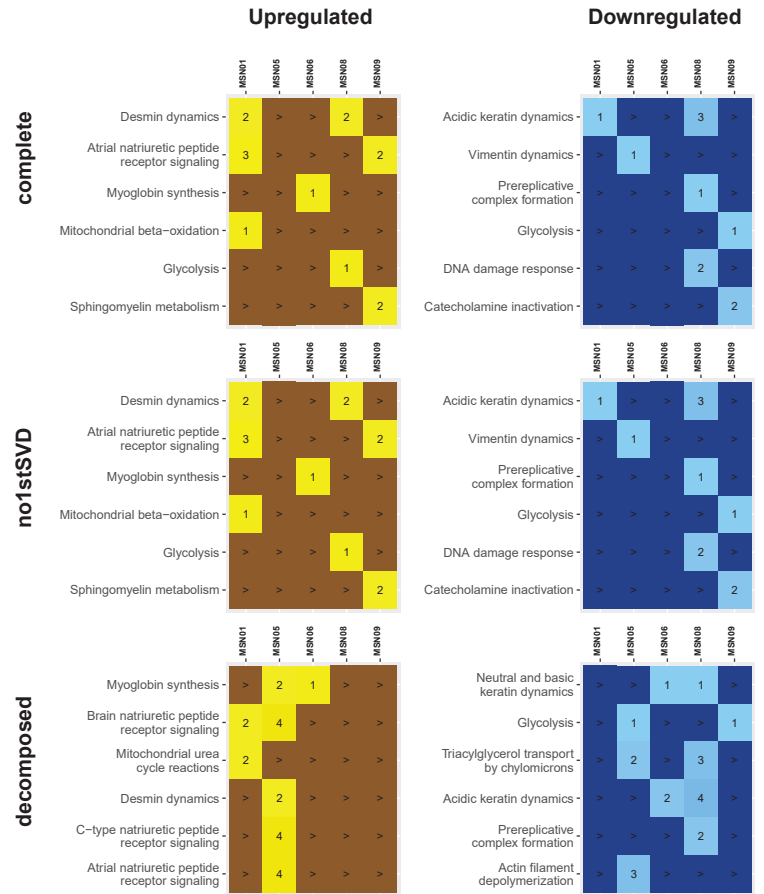
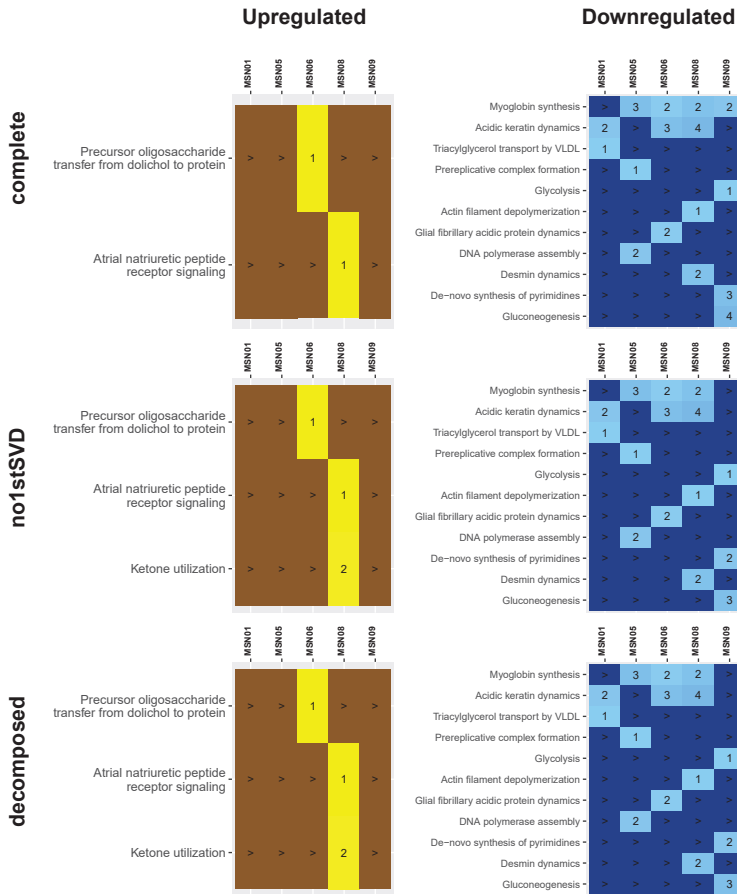
**MBCOL4
ceritinib**
(is c.toxic: no)

**MBCOL4
crizotinib**
(is c.toxic: no)



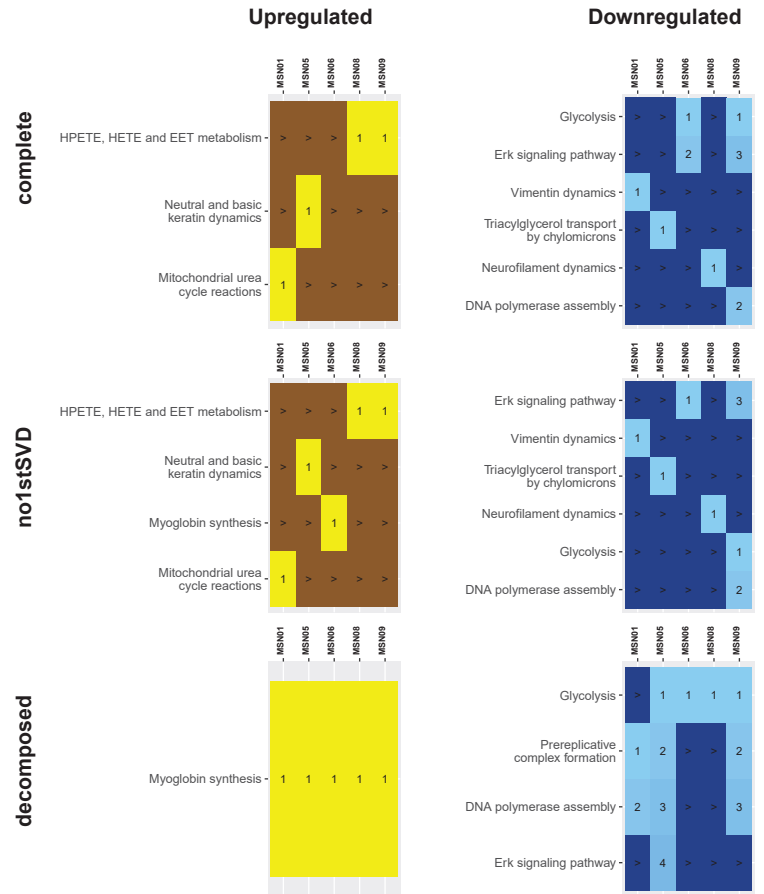
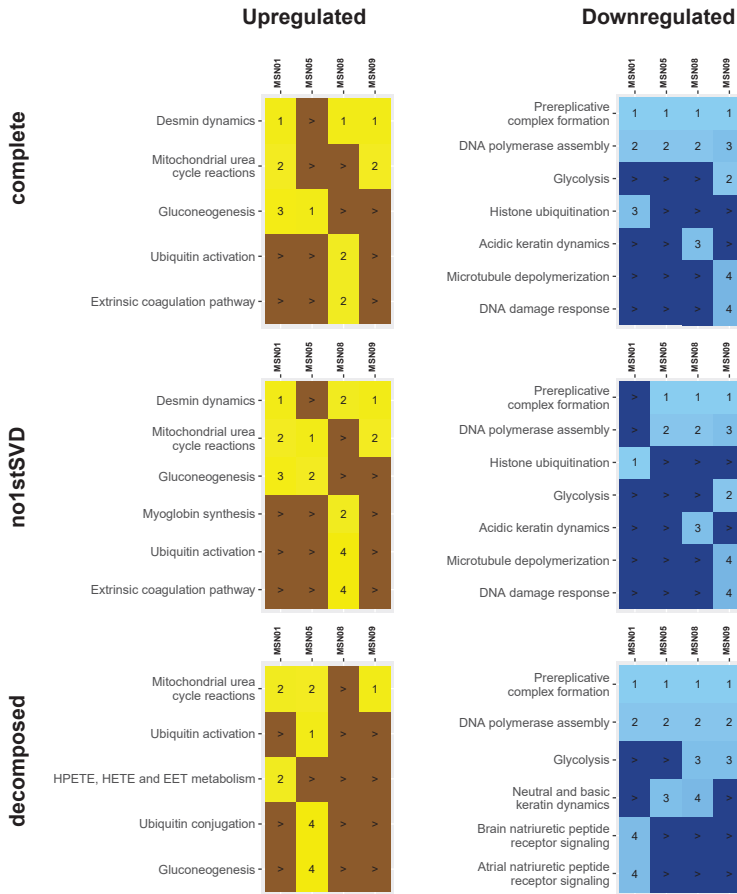
**MBCOL4
dabrafenib**
(is c.toxic: yes)

**MBCOL4
dasatinib**
(is c.toxic: no)



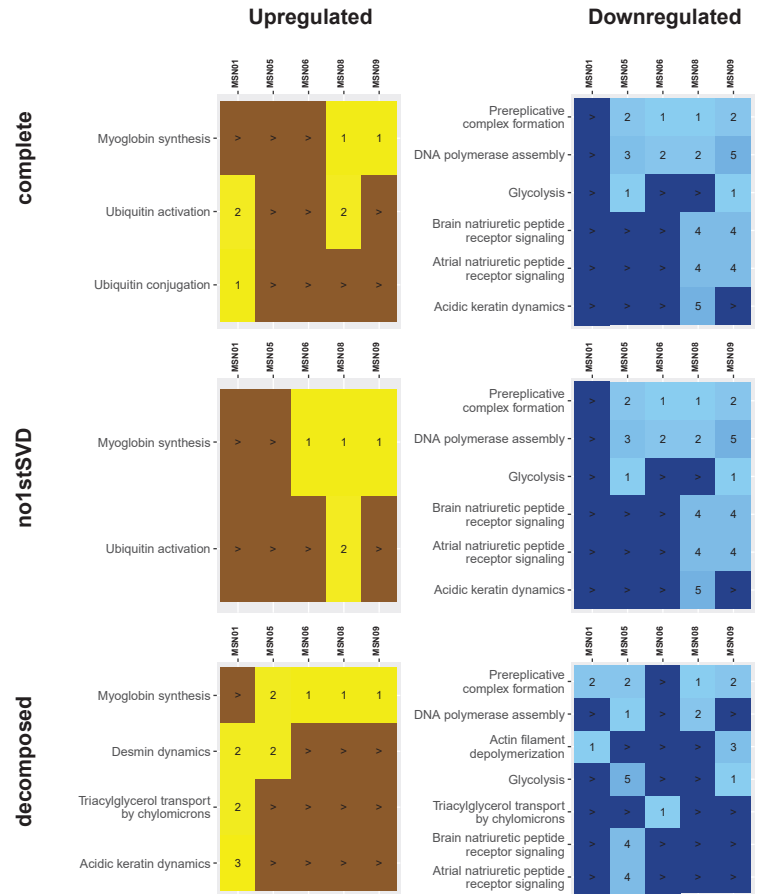
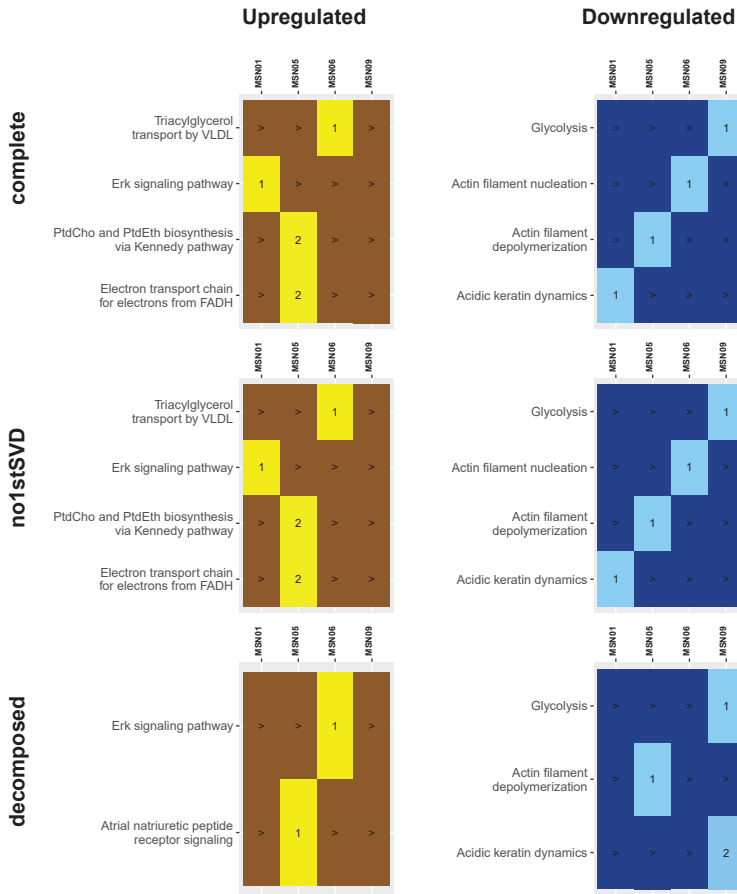
**MBCOL4
erlotinib**
(is c.toxic: no)

**MBCOL4
gefitinib**
(is c.toxic: no)



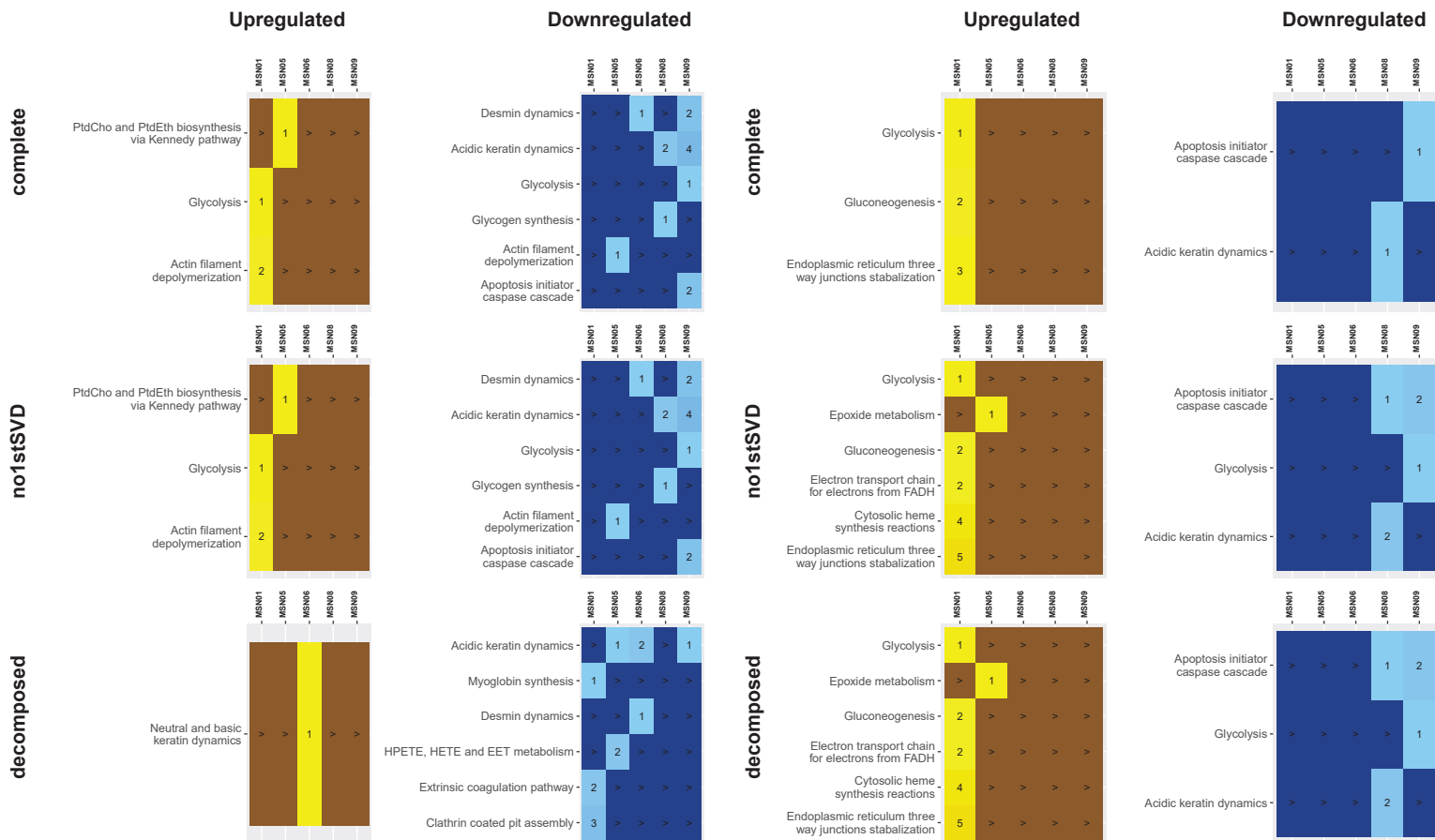
**MBCOL4
imatinib**
(is c.toxic: no)

**MBCOL4
lapatinib**
(is c.toxic: yes)



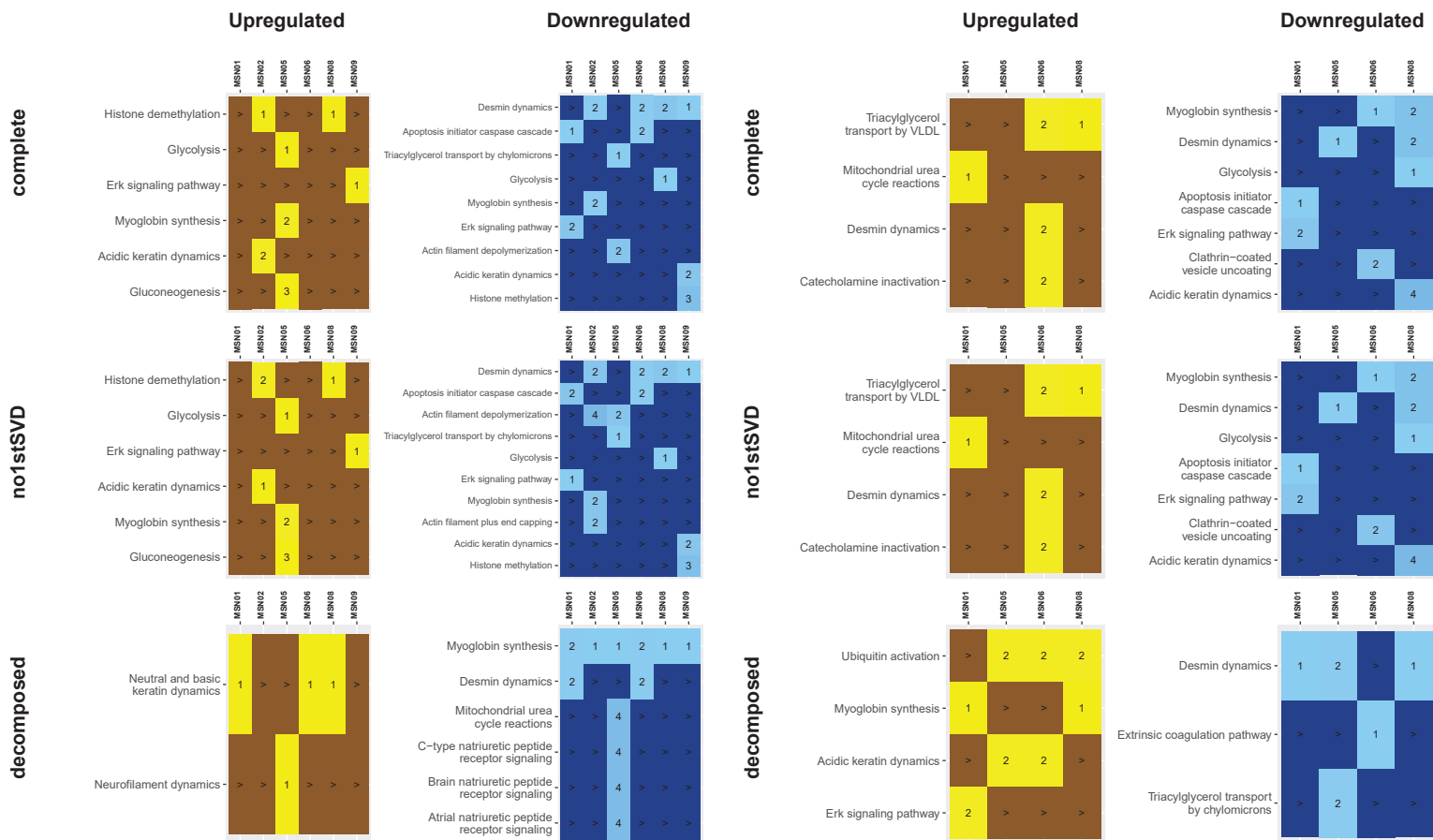
**MBCOL4
nilotinib**
(is c.toxic: no)

**MBCOL4
pazopanib**
(is c.toxic: yes)

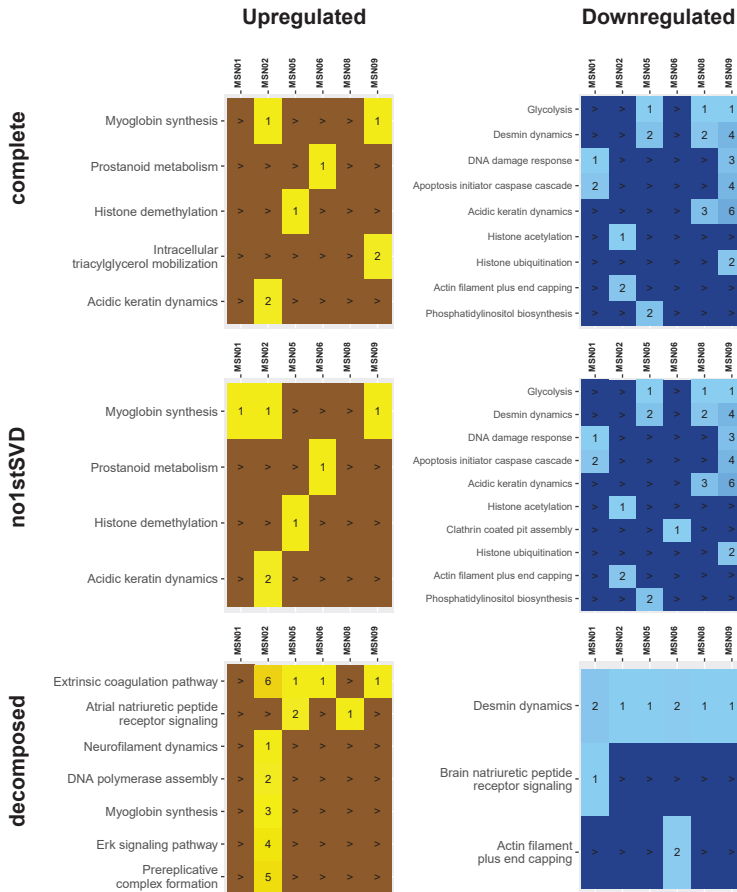


**MBCOL4
ponatinib**
(is c.toxic: yes)

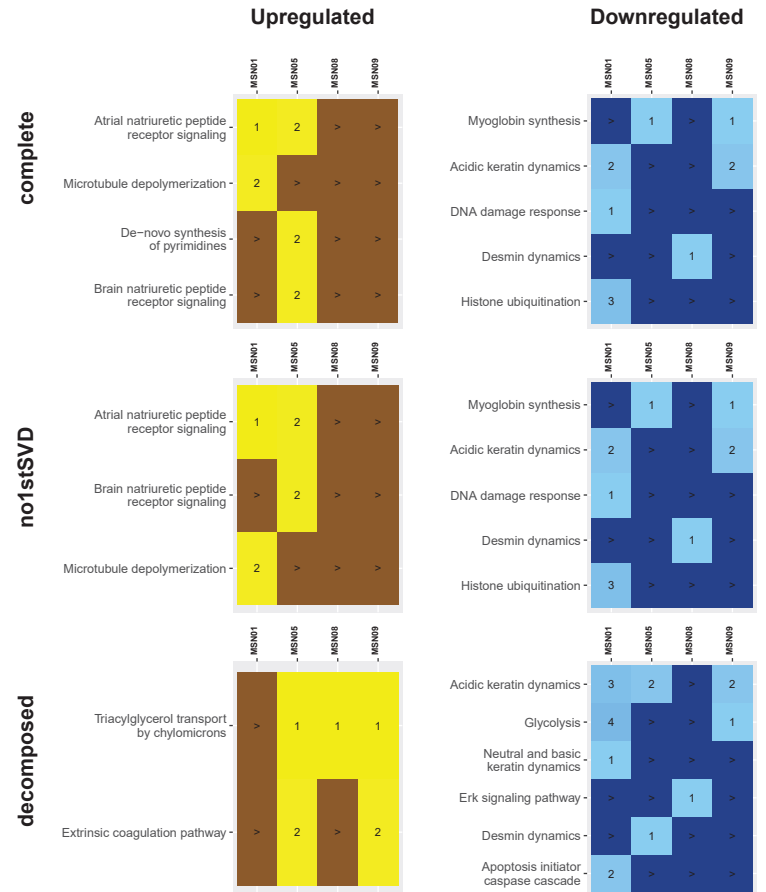
**MBCOL4
regorafenib**
(is c.toxic: no)



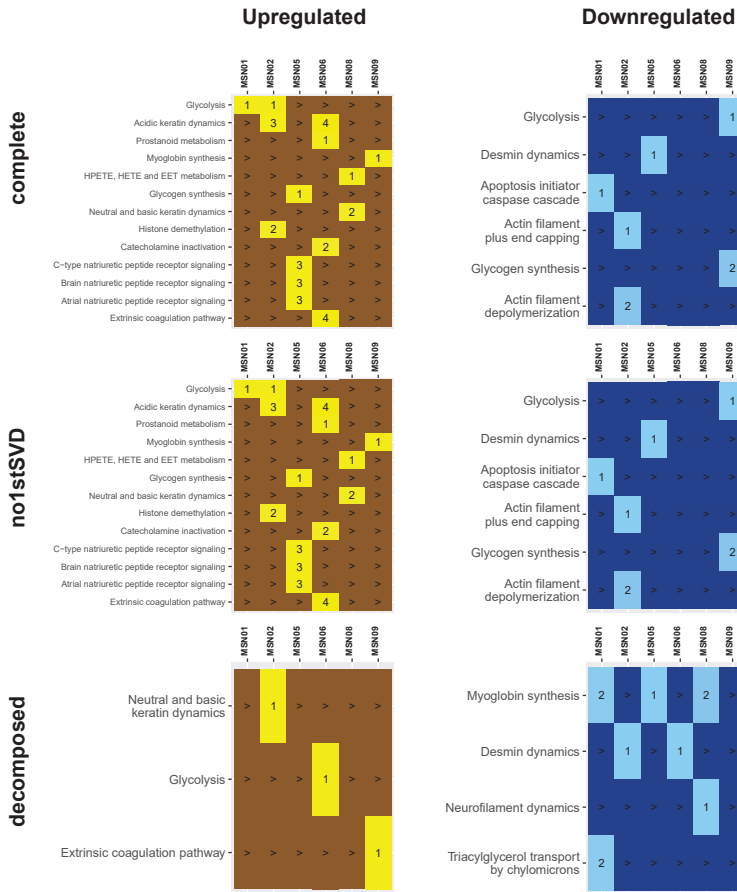
**MBCOL4
ruxolitinib**
(is c.toxic: no)



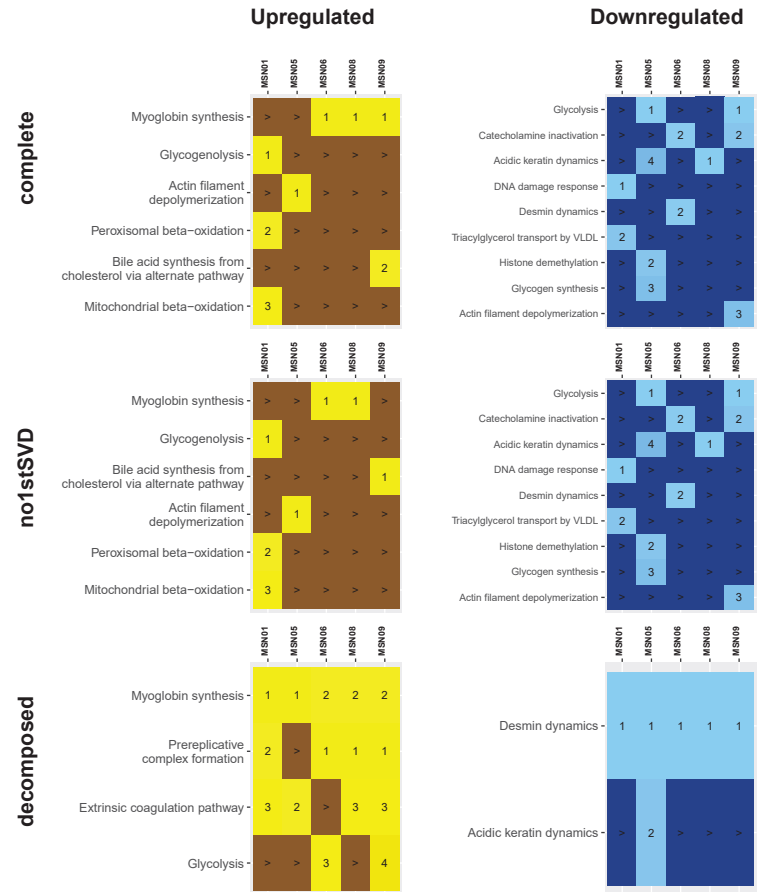
**MBCOL4
sorafenib**
(is c.toxic: yes)



**MBCOL4
sunitinib**
(is c.toxic: yes)

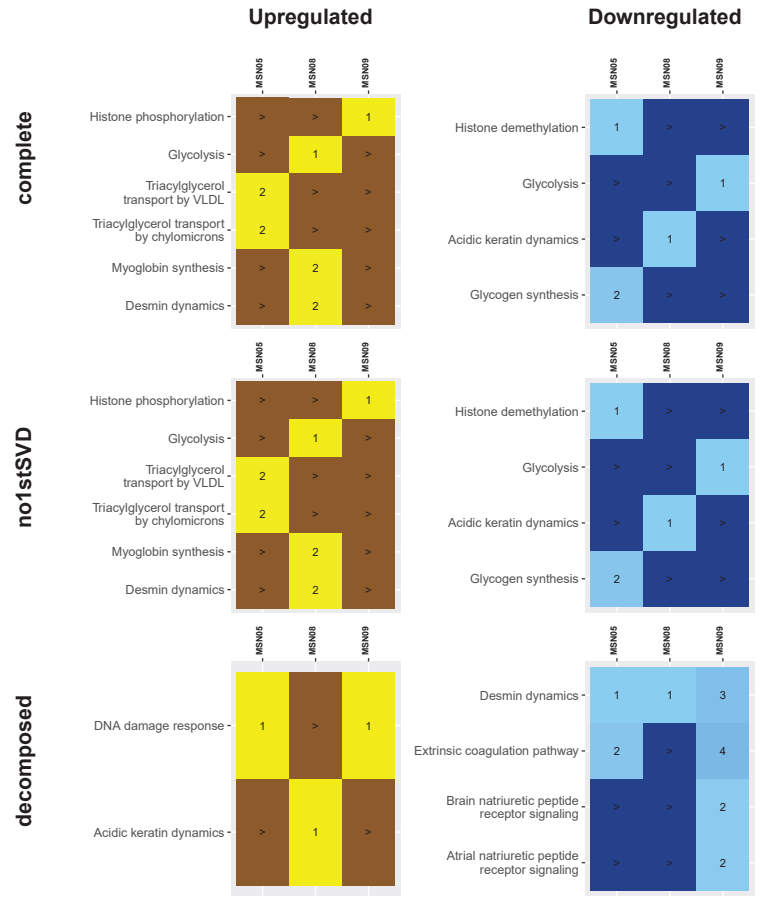
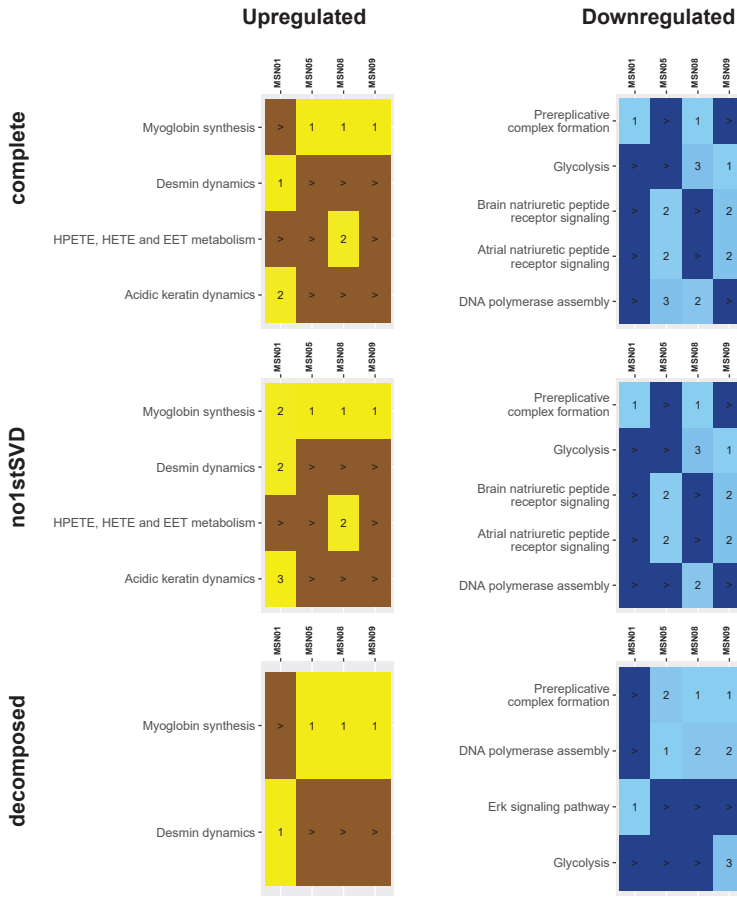


**MBCOL4
tofacitinib**
(is c.toxic: no)



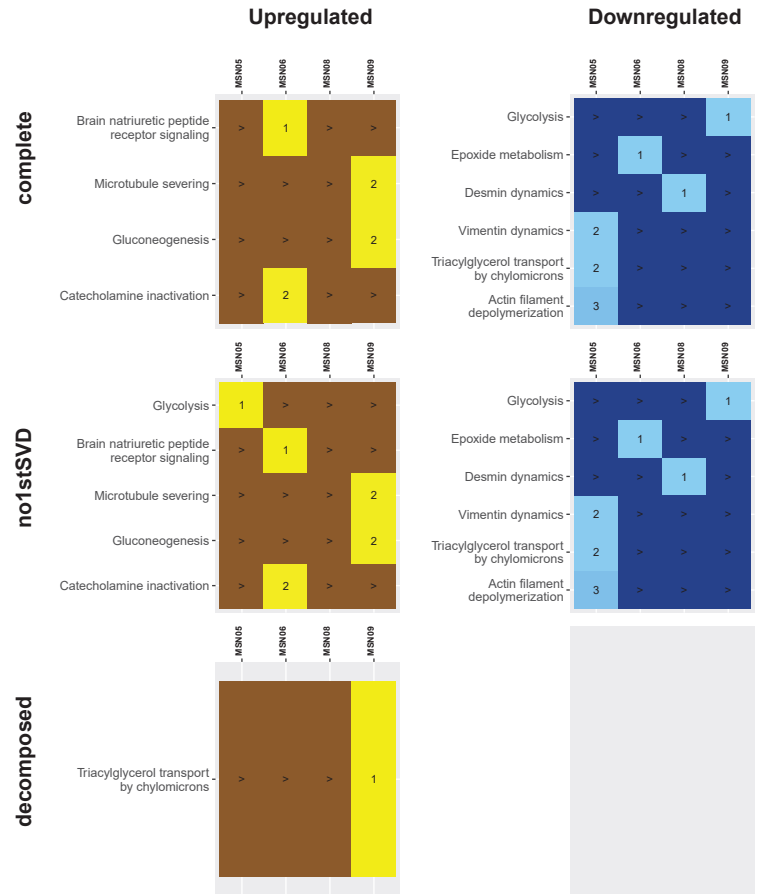
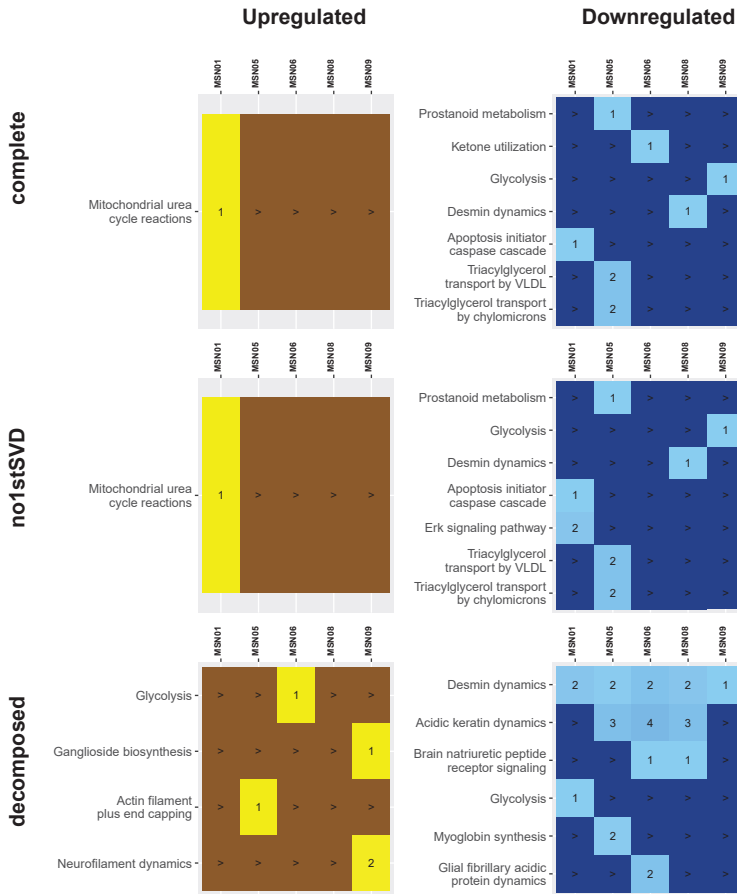
**MBCOL4
trametinib**
(is c.toxic: yes)

**MBCOL4
vandetanib**
(is c.toxic: yes)



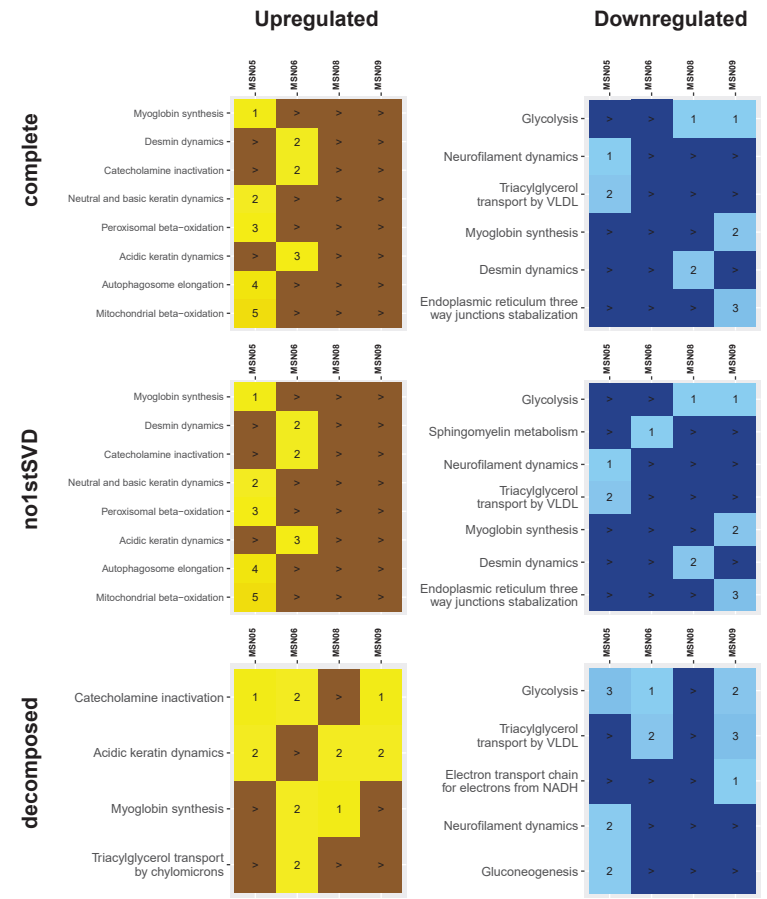
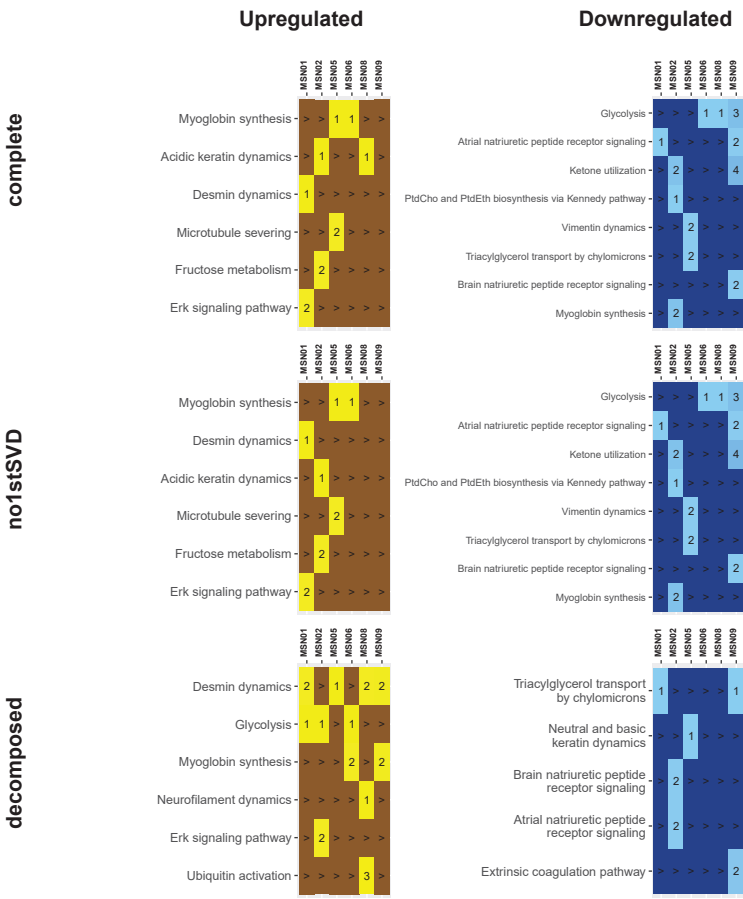
**MBCOL4
vemurafenib**
(is c.toxic: no)

**MBCOL4
bevacizumab**
(is c.toxic: yes)



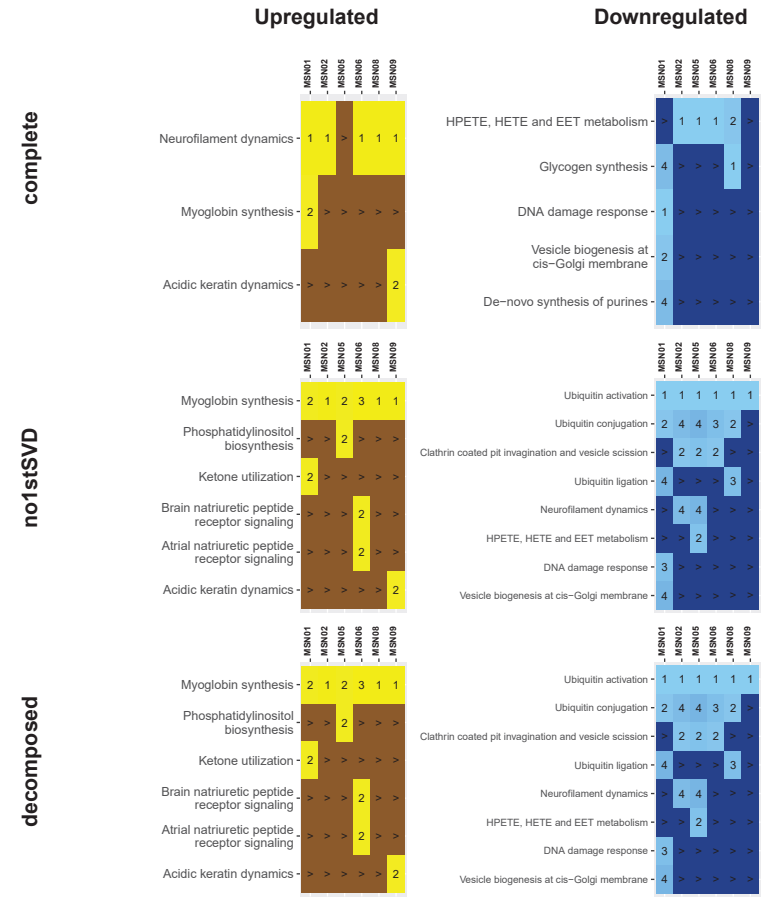
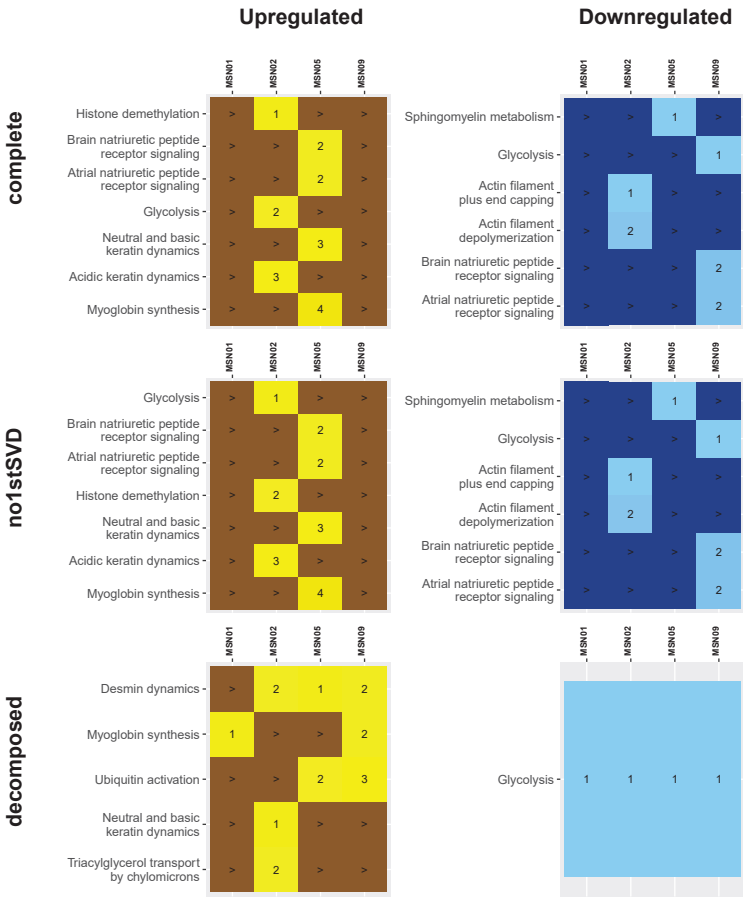
**MBCOL4
cetuximab
(is c.toxic: no)**

**MBCOL4
rituximab
(is c.toxic: no)**



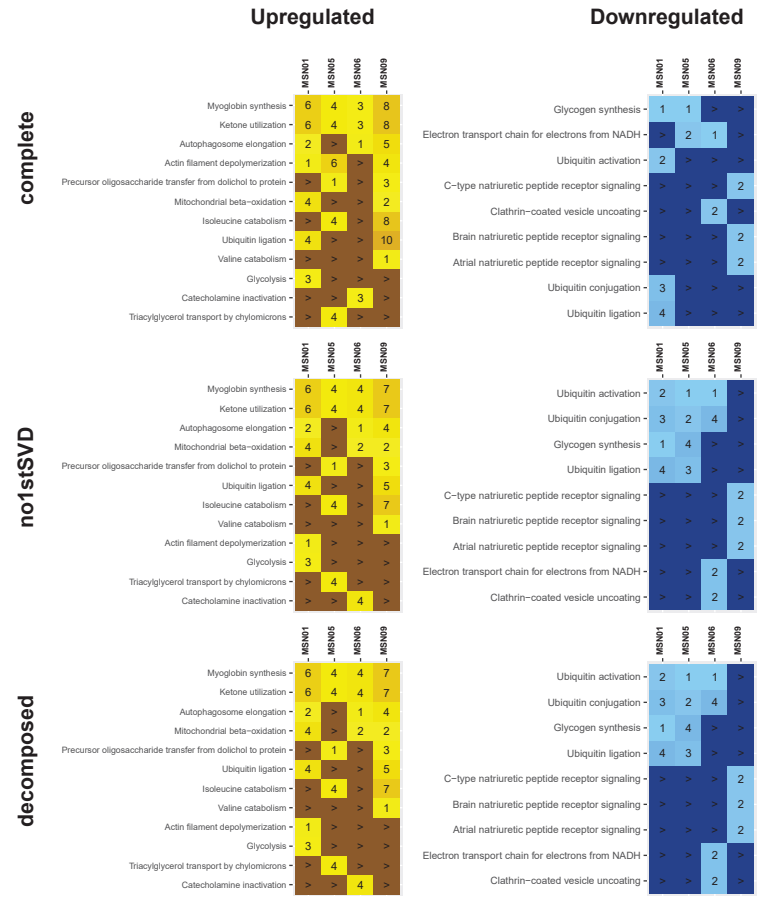
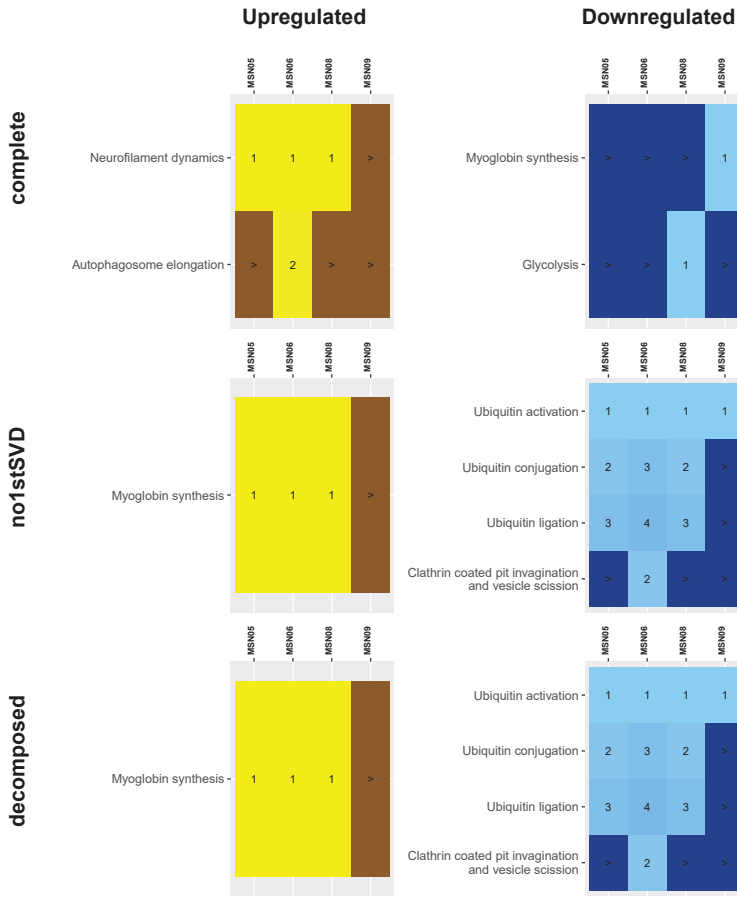
**MBCOL4
trastuzumab
(is c.toxic: yes)**

**MBCOL4
daunorubicin
(is c.toxic: yes)**



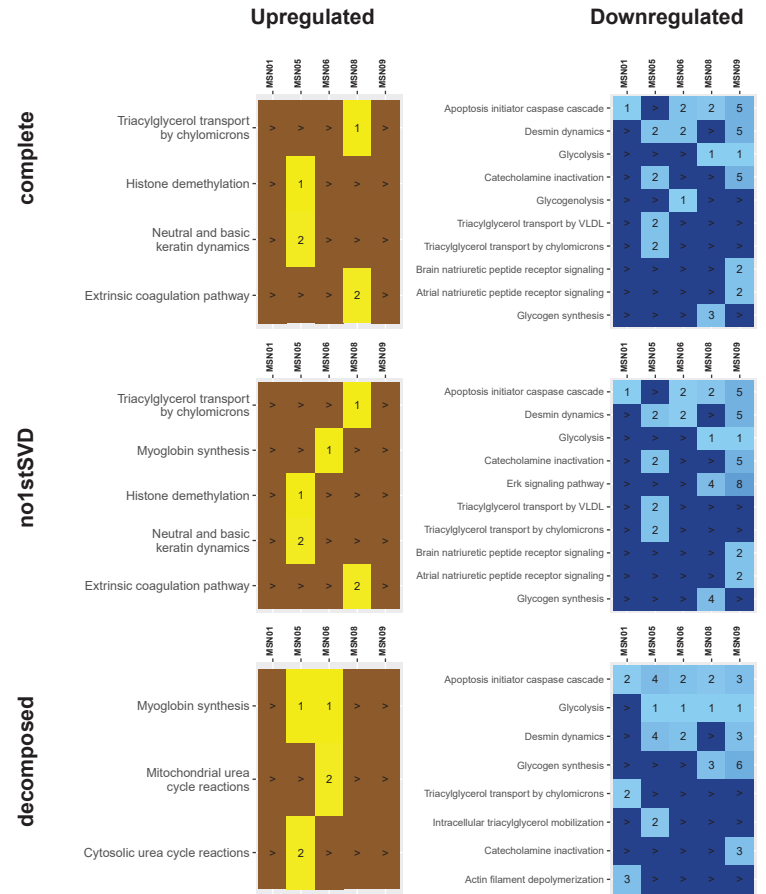
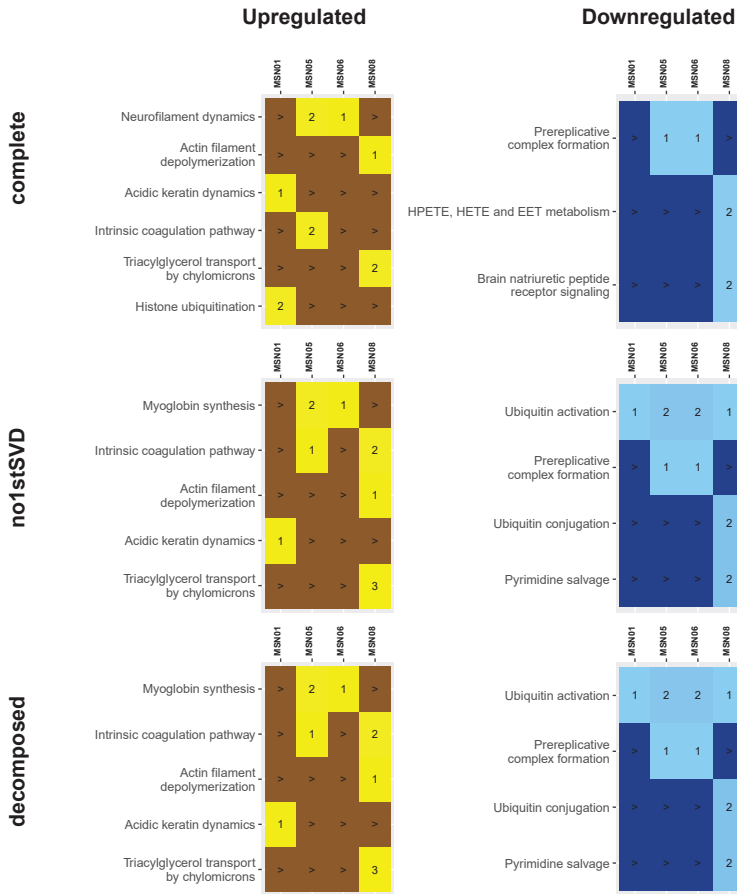
**MBCOL4
doxorubicin**
(is c.toxic: yes)

**MBCOL4
epirubicin**
(is c.toxic: yes)



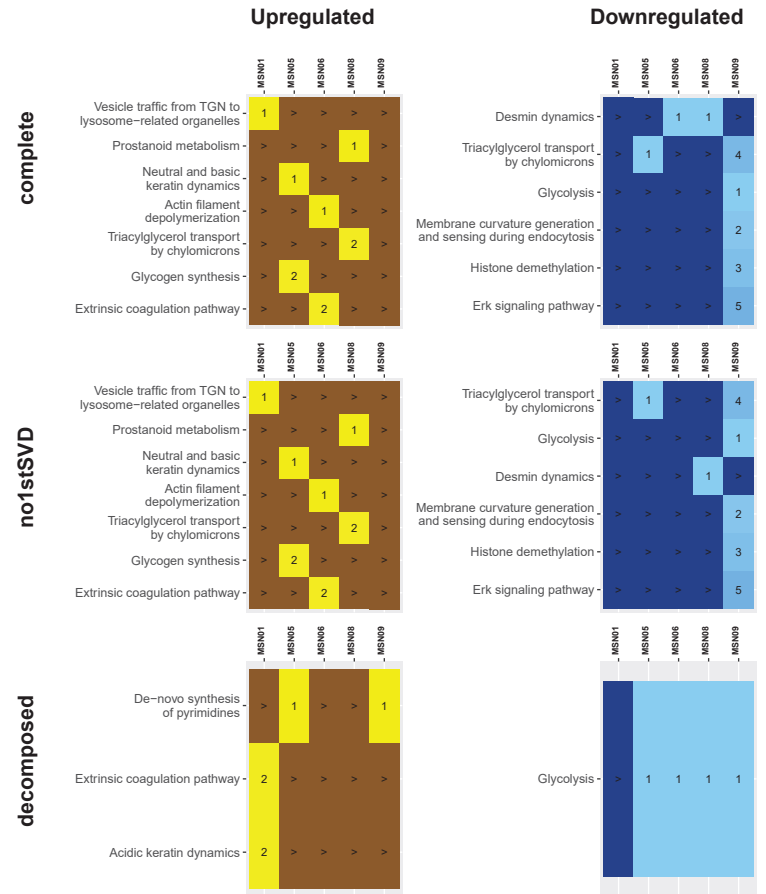
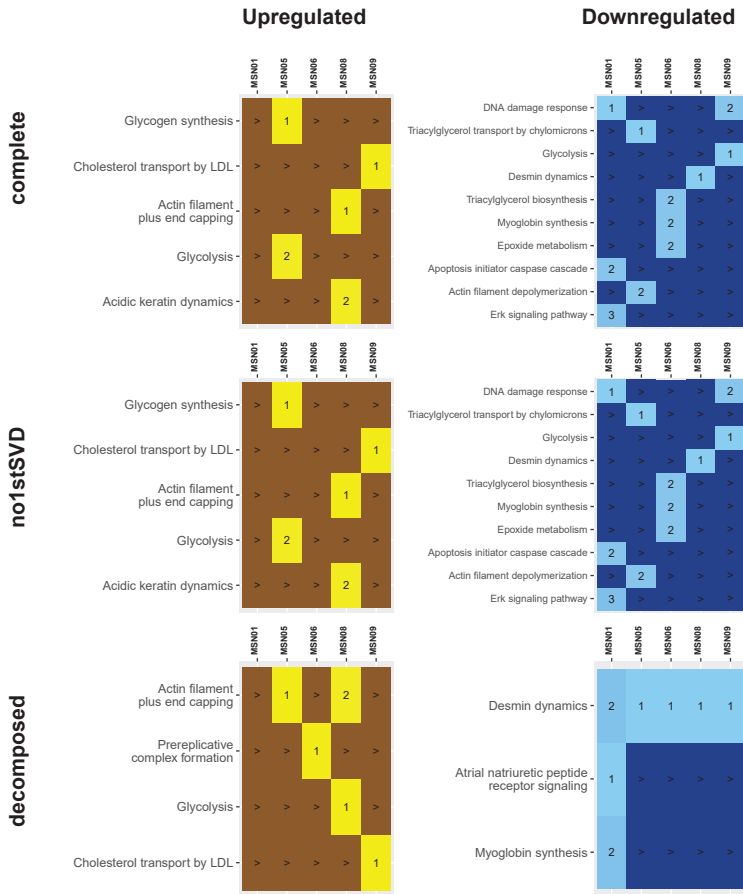
**MBCOL4
idarubicin**
(is c.toxic: yes)

**MBCOL4
amiodarone**
(is c.toxic: nd)



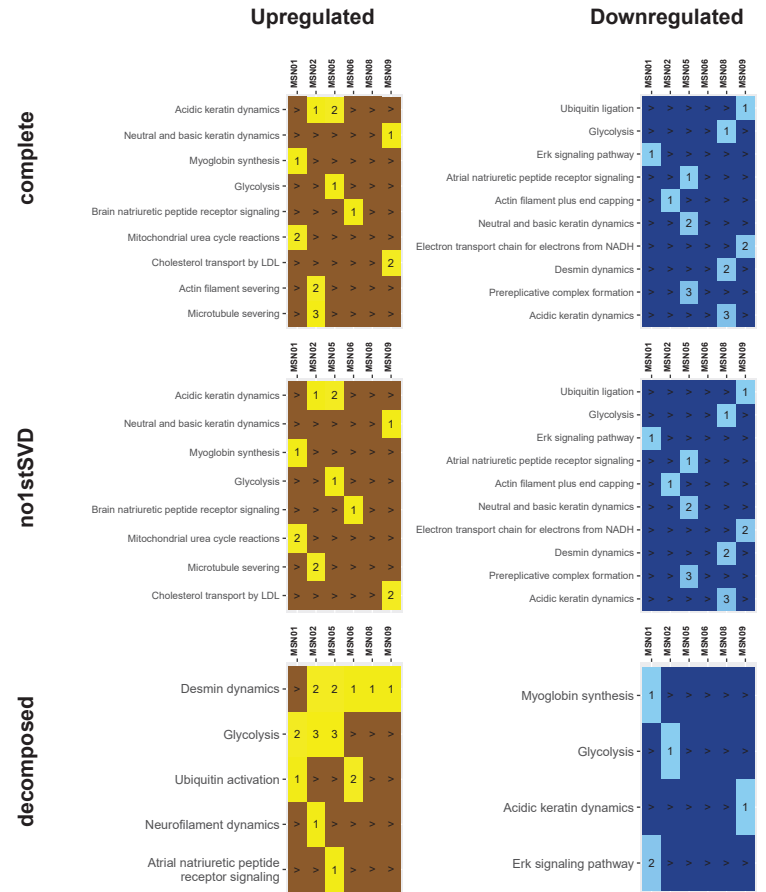
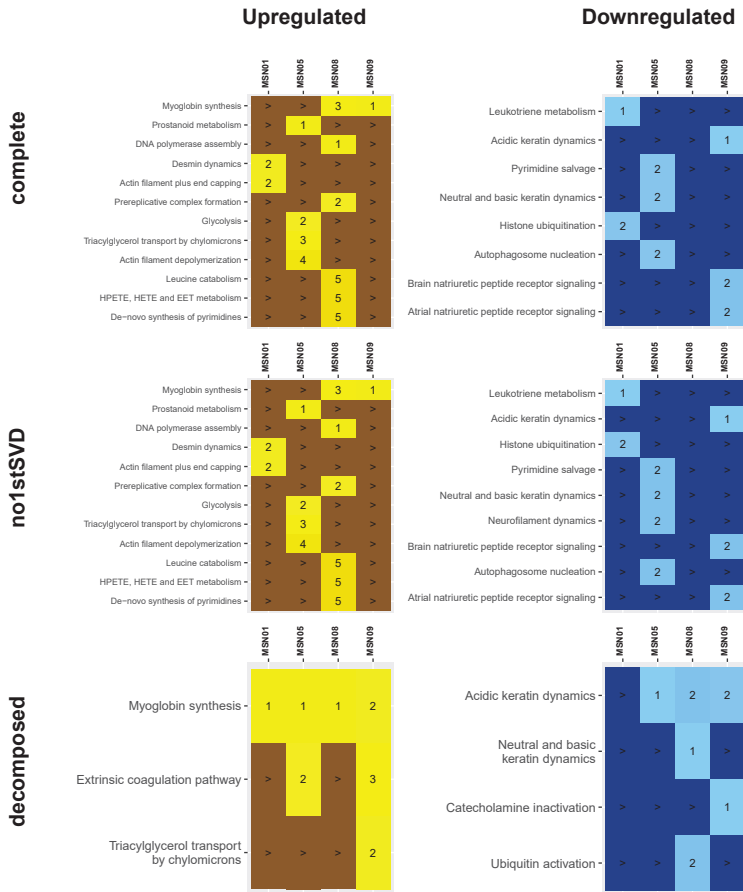
MBCOL4
dobutamine
(is c.toxic: nd)

MBCOL4
flecainide
(is c.toxic: nd)



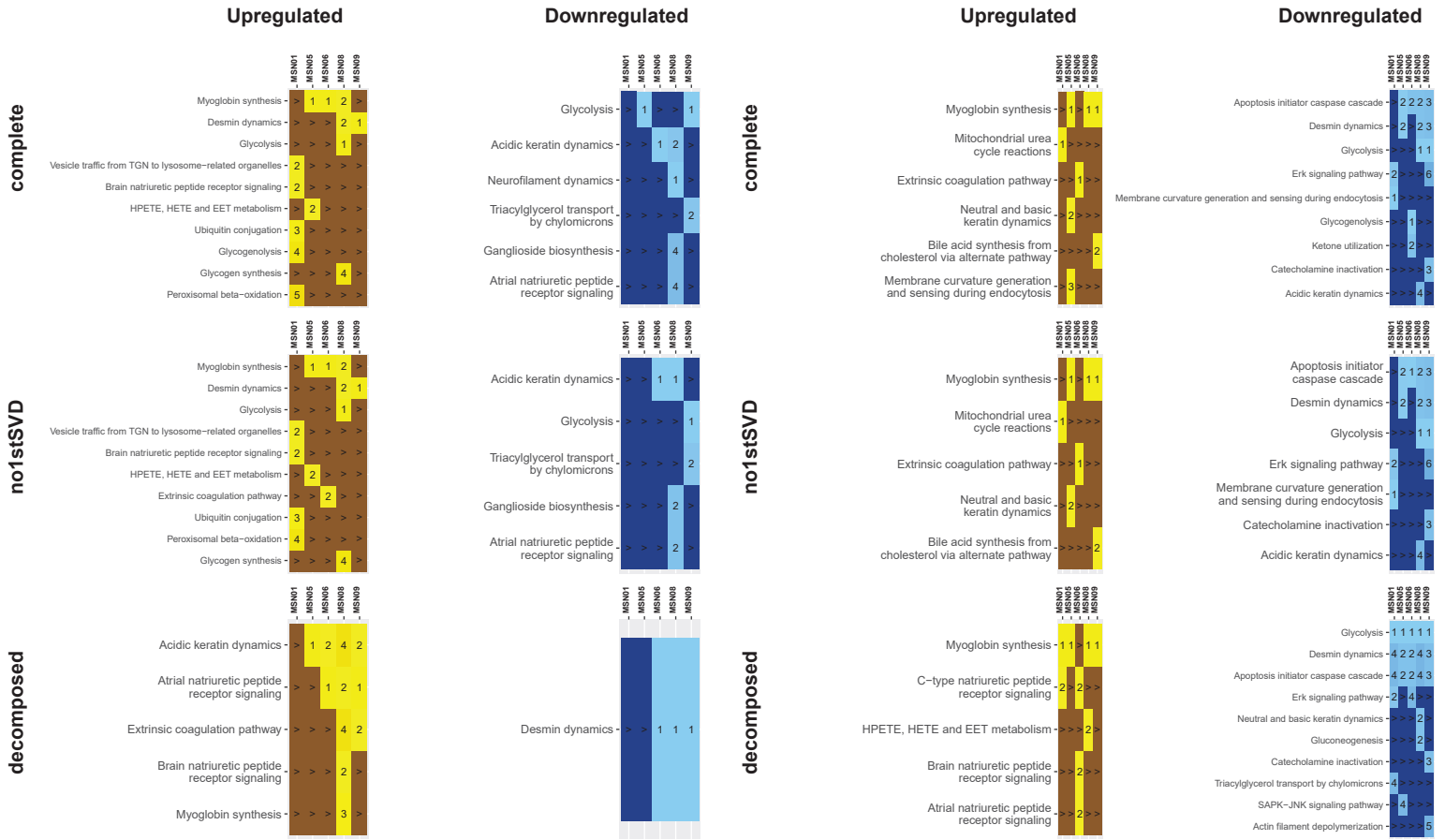
MBCOL4
isoprenaline
(is c.toxic: nd)

MBCOL4
milrinone
(is c.toxic: nd)



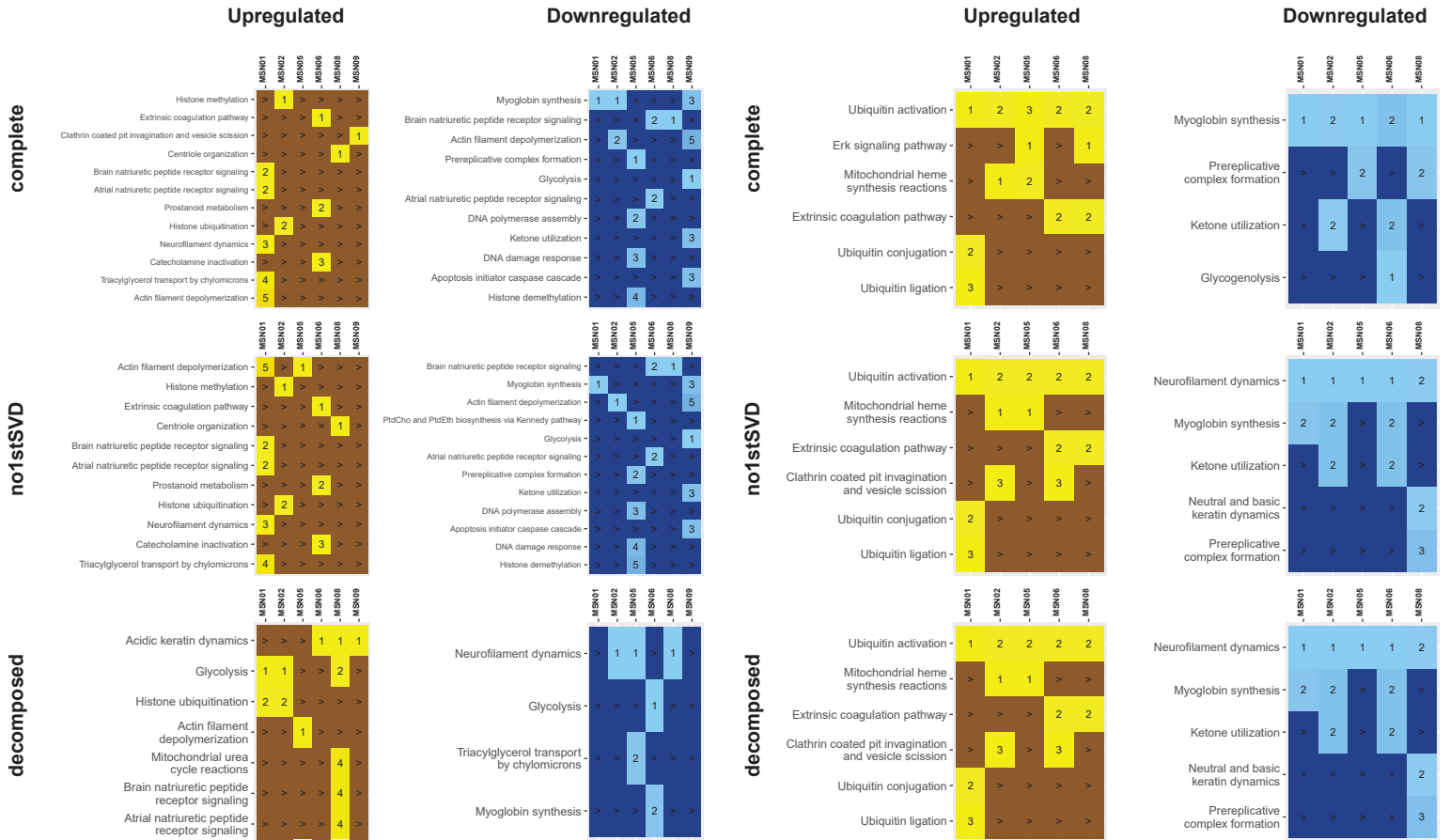
**MBCOL4
phenylephrine**
(is c.toxic: nd)

**MBCOL4
verapamil**
(is c.toxic: nd)



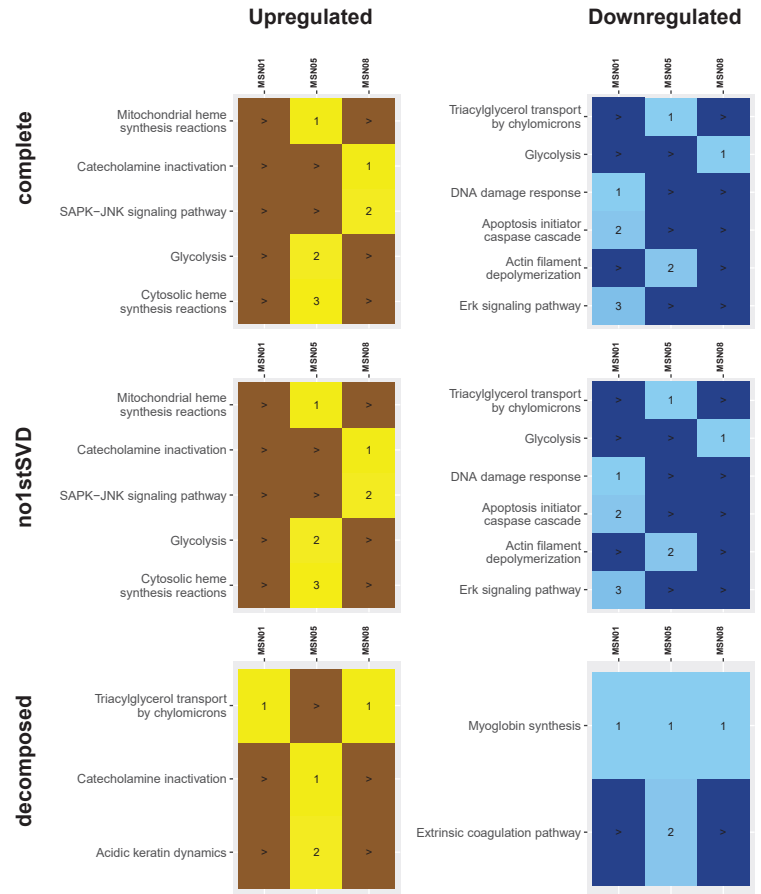
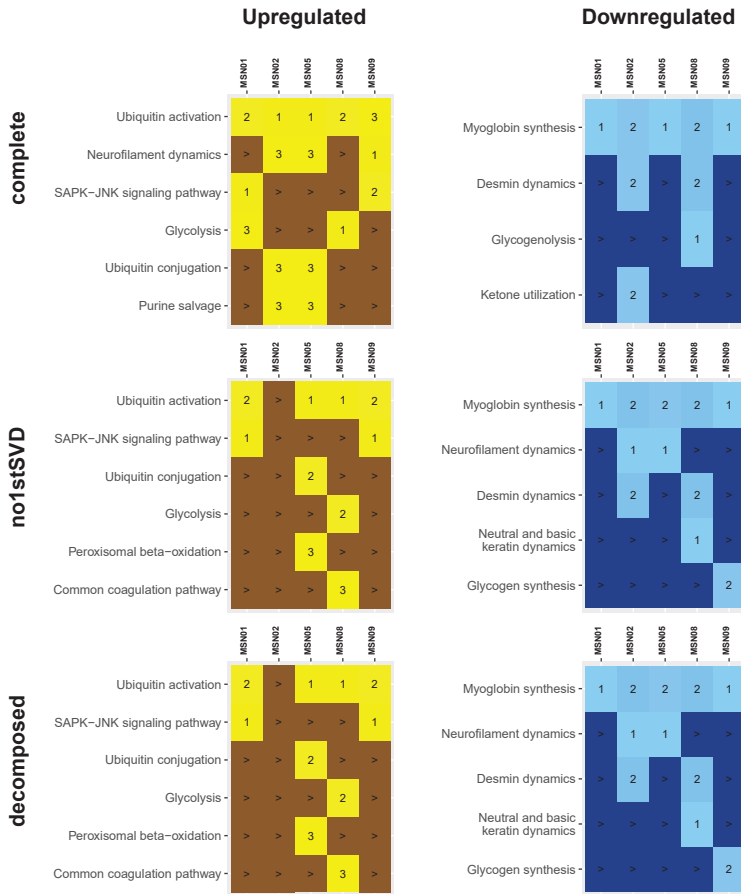
**MBCOL4
azacitidine**
(is c.toxic: nd)

**MBCOL4
bortezomib**
(is c.toxic: yes)



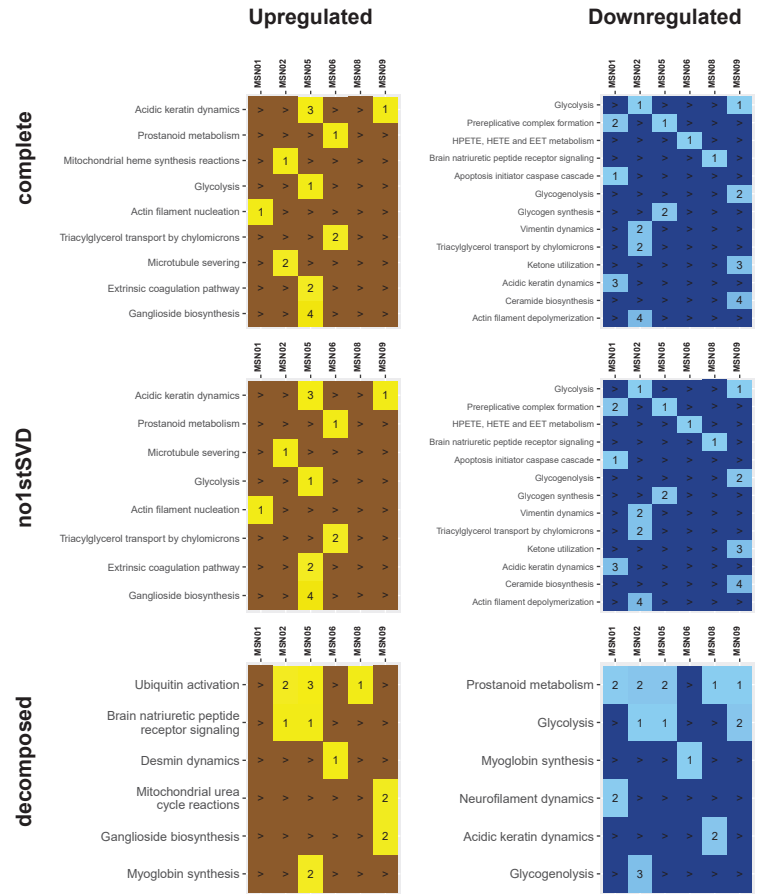
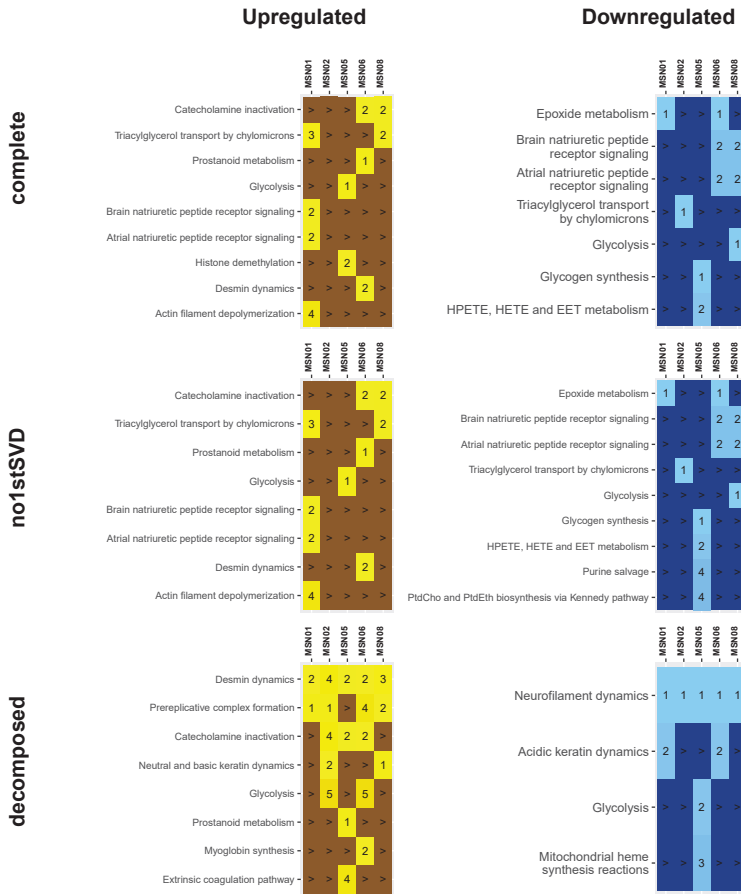
**MBCOL4
carfilzomib
(is c.toxic: yes)**

**MBCOL4
cyclosporine
(is c.toxic: nd)**



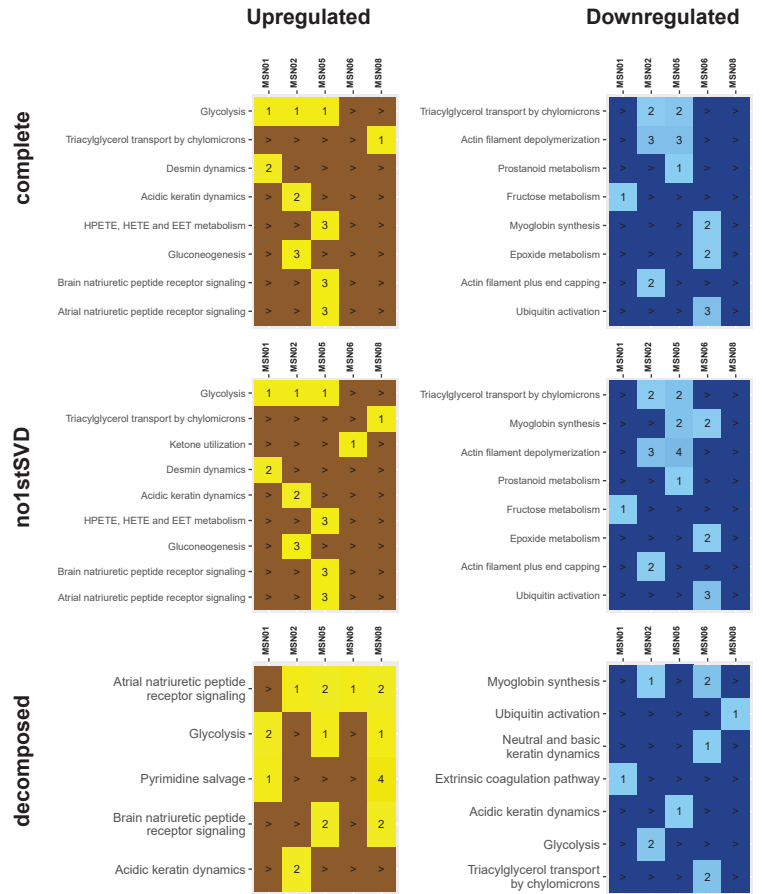
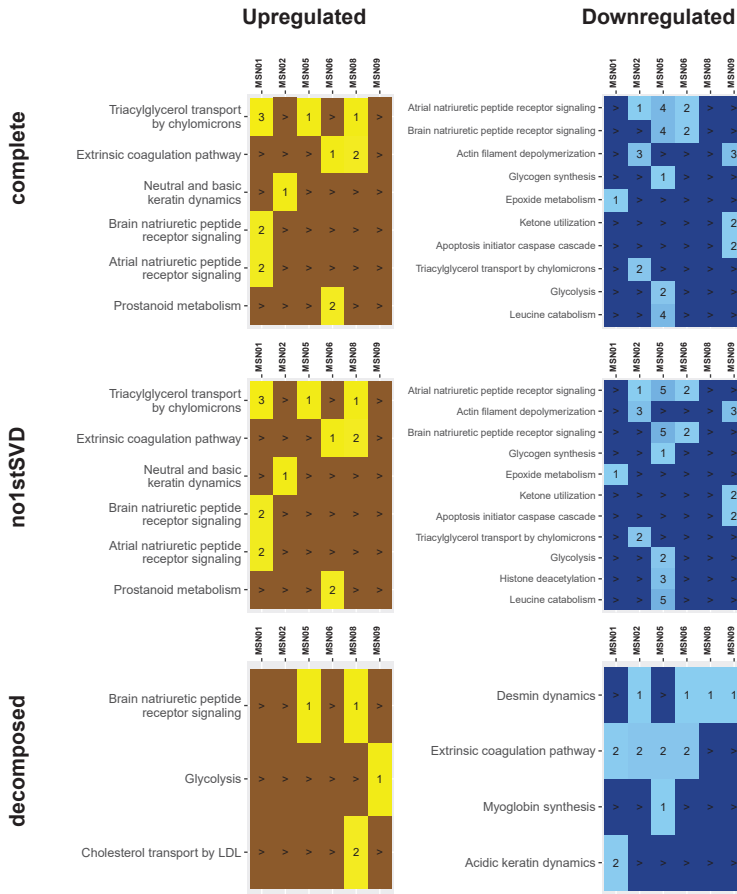
**MBCOL4
decitabine
(is c.toxic: nd)**

**MBCOL4
delavirdine
(is c.toxic: nd)**



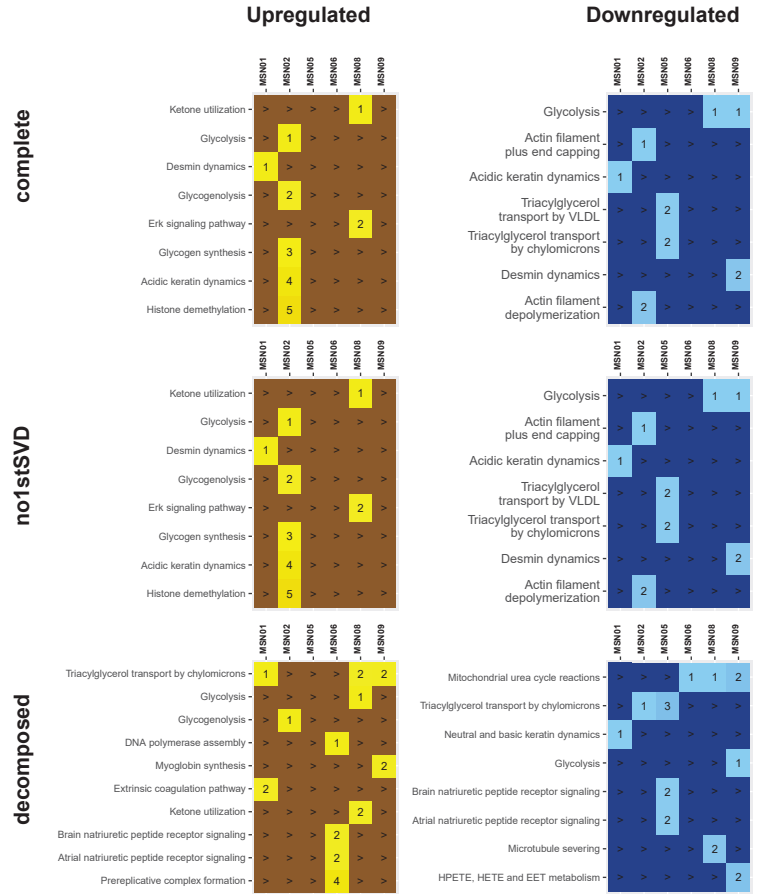
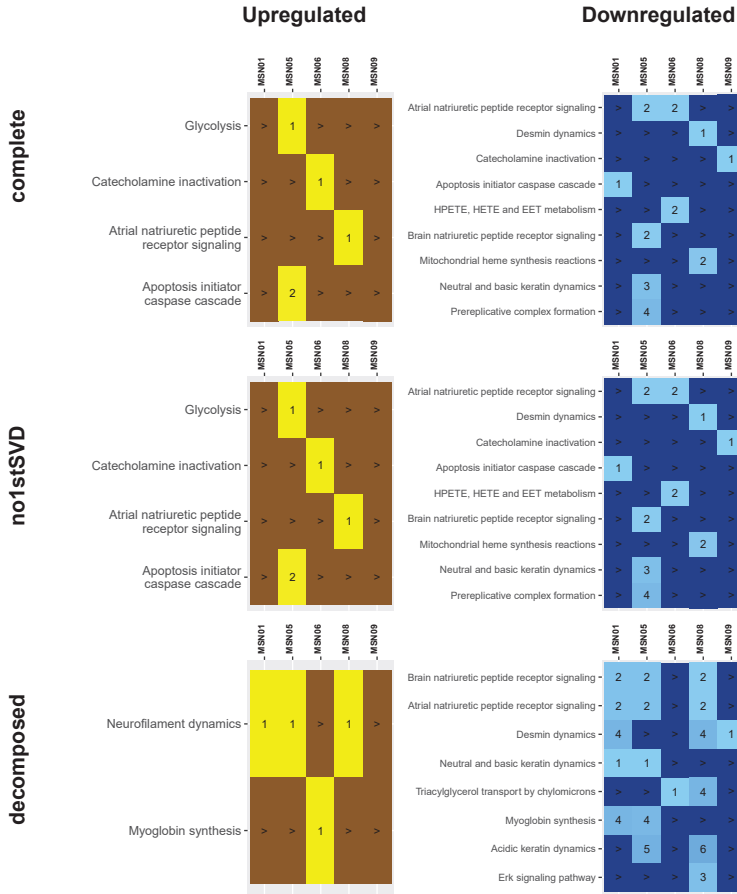
**MBCOL4
diclofenac
(is c.toxic: nd)**

**MBCOL4
endothelin-1
(is c.toxic: nd)**



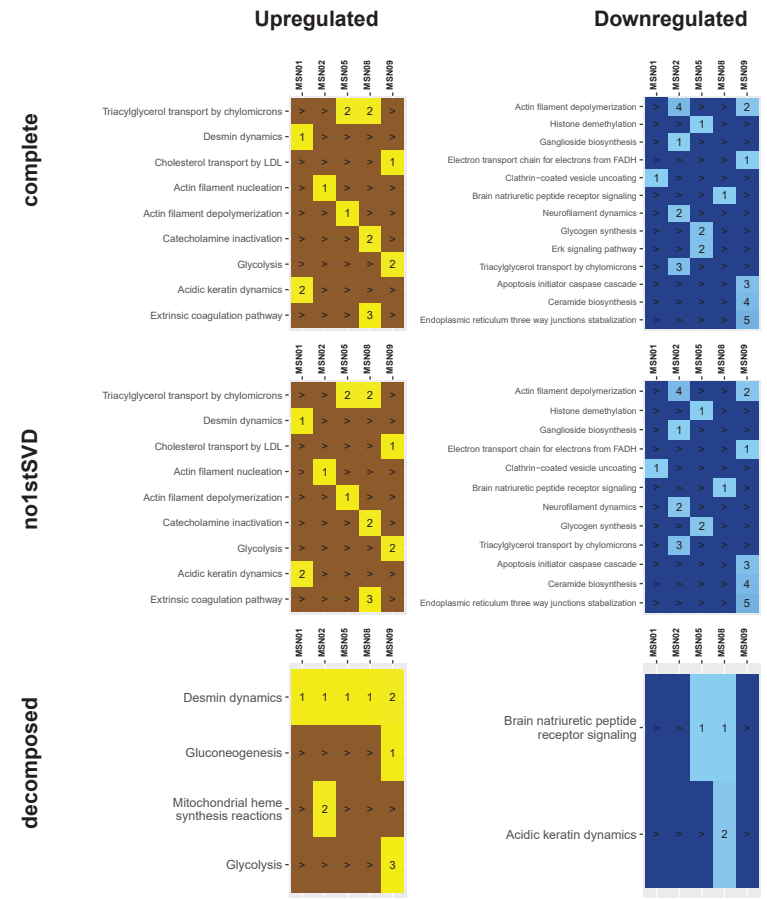
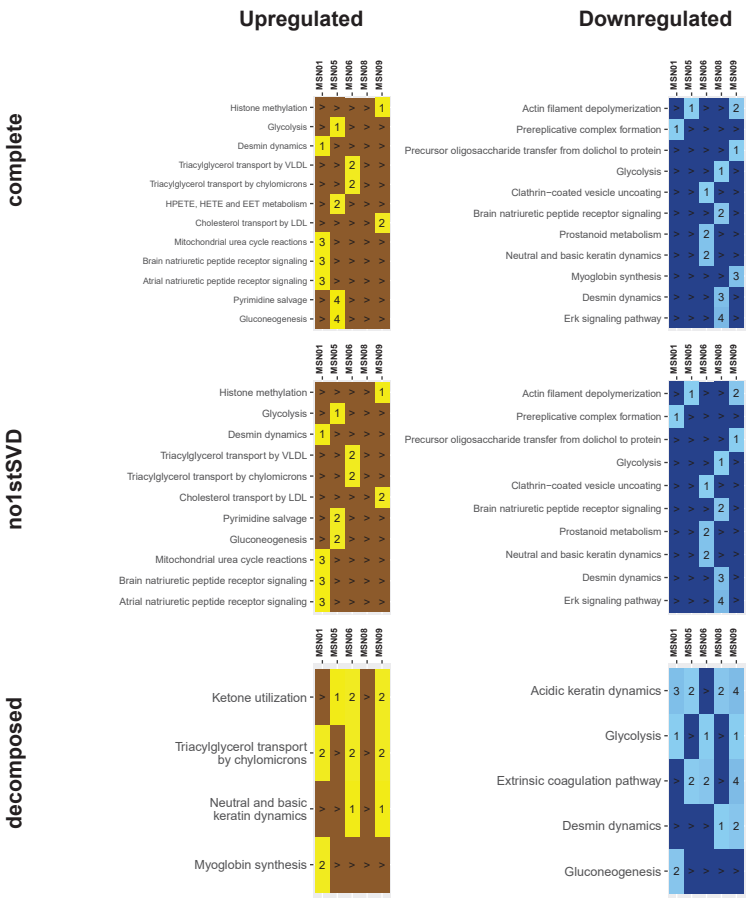
**MBCOL4
estradiol
(is c.toxic: nd)**

**MBCOL4
insulin-like growth factor 1
(is c.toxic: nd)**



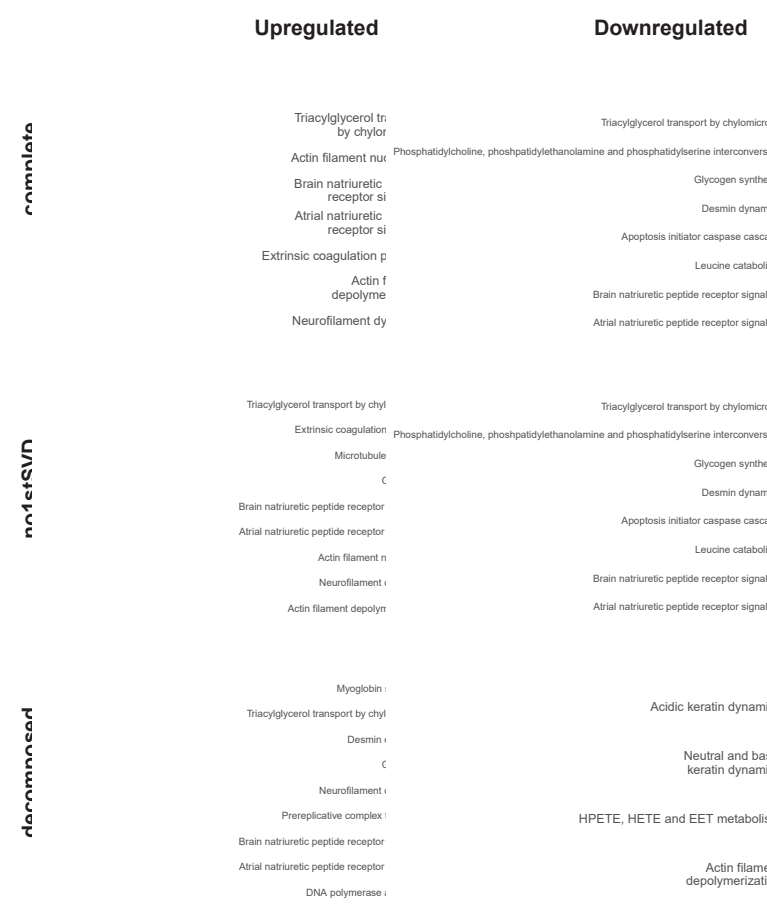
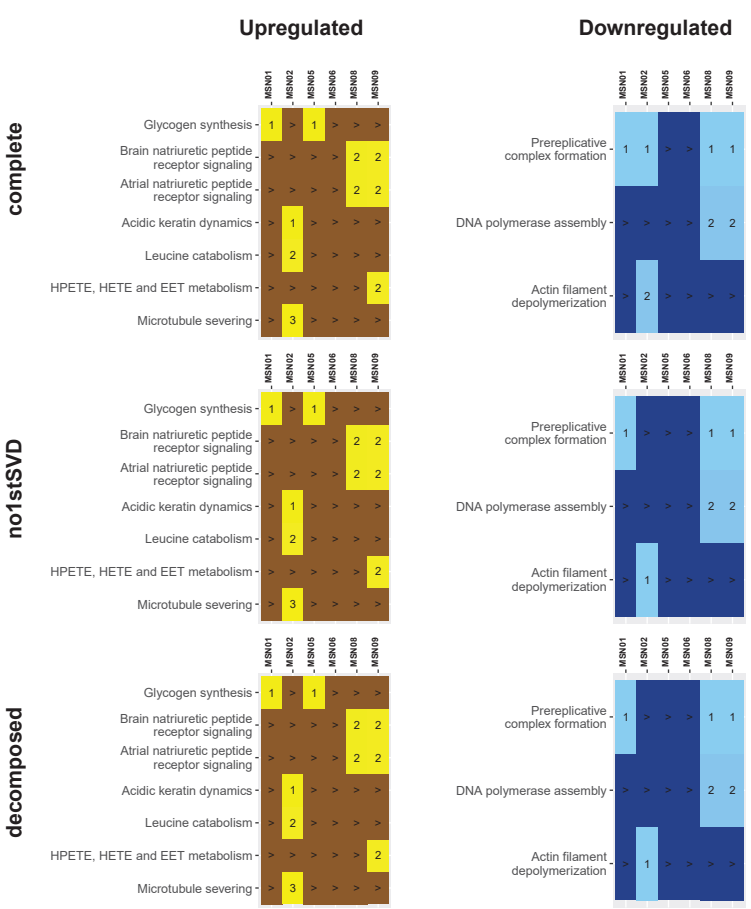
**MBCOL4
olmesartan
(is c.toxic: nd)**

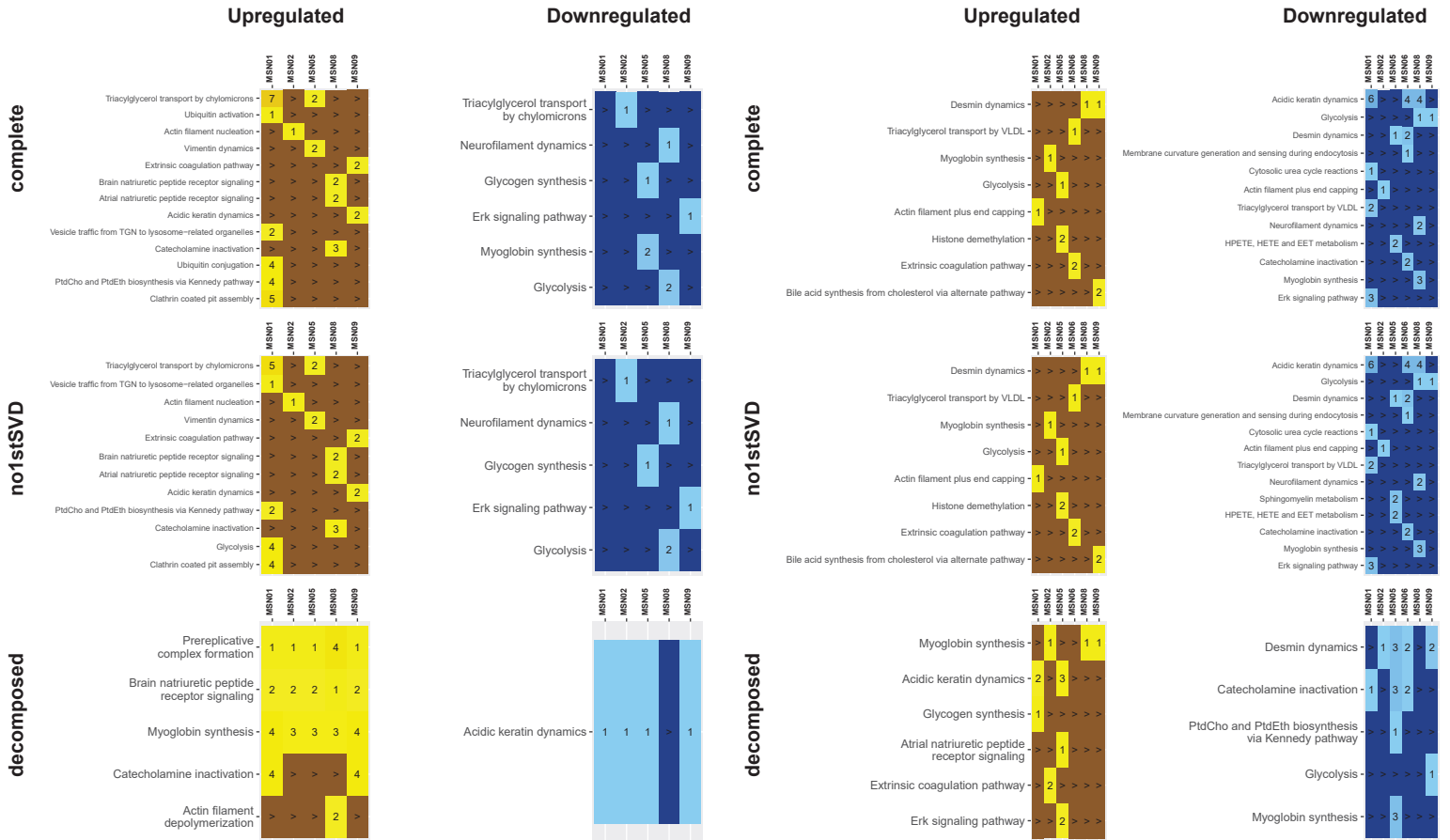
**MBCOL4
pioglitazone
(is c.toxic: nd)**



**MBCOL4
prednisolone
(is c.toxic: nd)**

**MBCOL4
rosiglitazone
(is c.toxic: nd)**



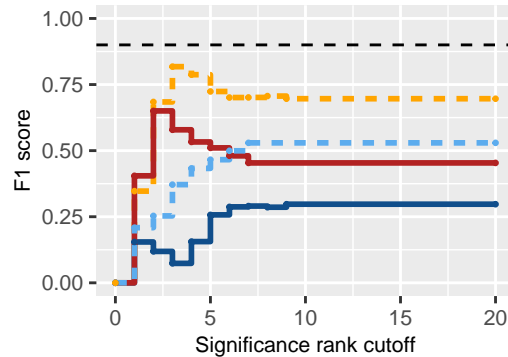
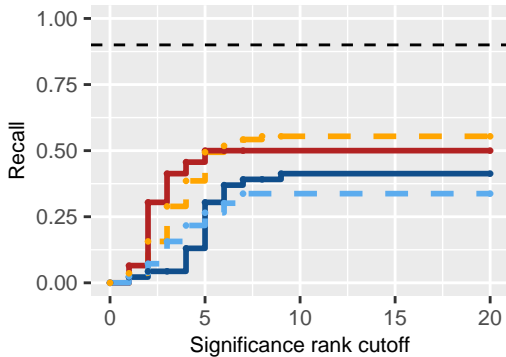
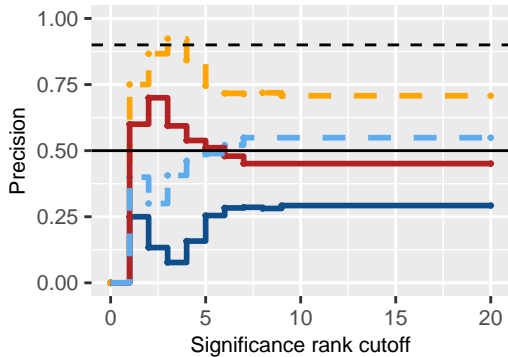


Supplementary Figure 14. Top Subcellular Processes predicted from complete gene expression profiles, after removal of first eigenarray and from drug-selective gene expression profiles. **(A)** Complete, decomposed gene expression profiles and gene expression profiles after removal of the first eigenarray were subjected to pathway enrichment analysis using the Molecular Biology of the Cell Ontology and Fisher's Exact Test to identify up- and downregulated subcellular processes (SCPs). Significant up- or downregulated **(B)** level-1, **(C)** -2, **(D)** -3 and **(E)** -4 SCPs ($p\text{-value} \leq 0.05$) were separately ranked by significance for each cell line/drug combination. SCPs predicted for each drug are shown if they are among the top five ranked SCPs for at least one cell line. Numbers indicate ranks, '>' indicates that an SCP was not predicted or predicted with a rank above 99. Cell lines with identified outlier responses to treatment with a drug of interest are colored purple.

MBCOL1 – Cardiotoxicity
Amino acid metabolism

MBCOL1 – Cardiotoxicity
Amino acid metabolism

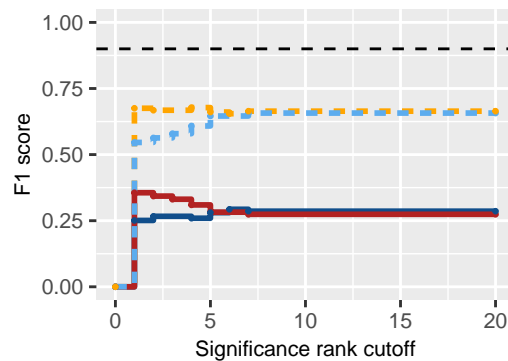
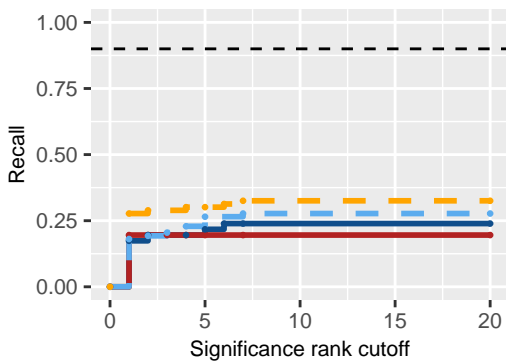
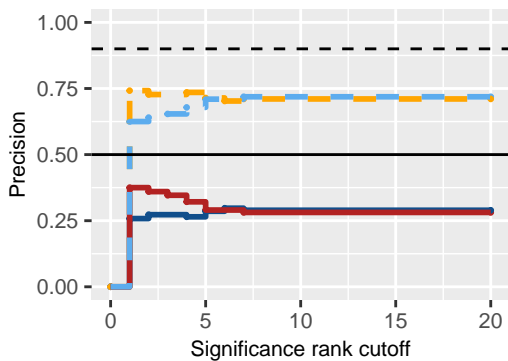
MBCOL1 – Cardiotoxicity
Amino acid metabolism



MBCOL1 – Cardiotoxicity
Cell cycle and cell division

MBCOL1 – Cardiotoxicity
Cell cycle and cell division

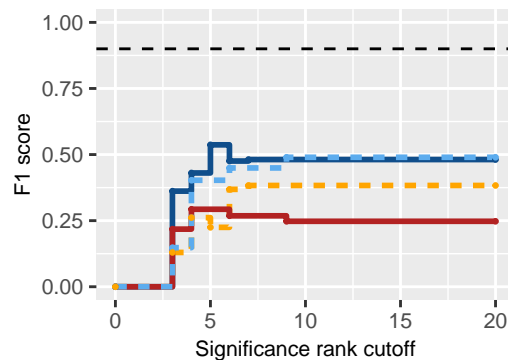
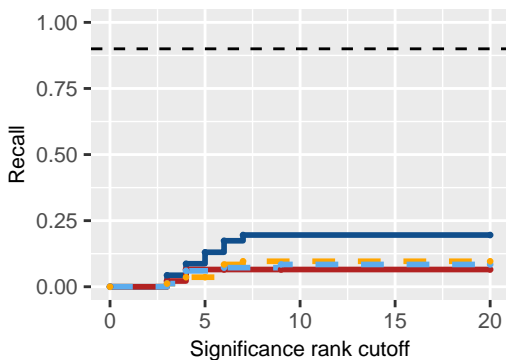
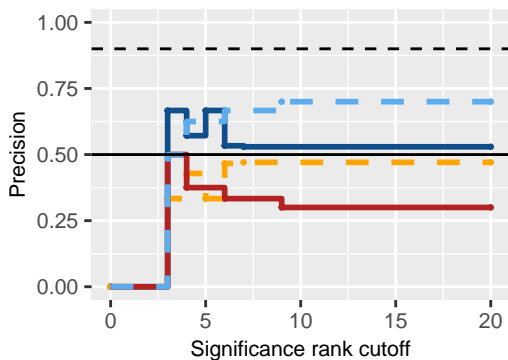
MBCOL1 – Cardiotoxicity
Cell cycle and cell division



MBCOL1 – Cardiotoxicity
Cellular adhesion

MBCOL1 – Cardiotoxicity
Cellular adhesion

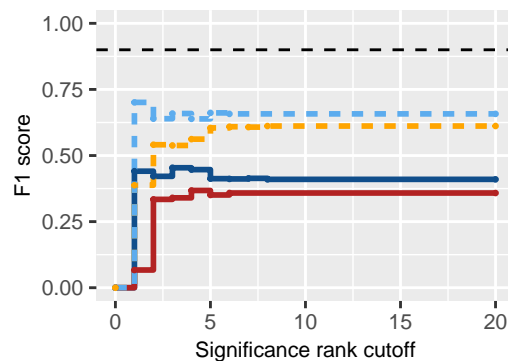
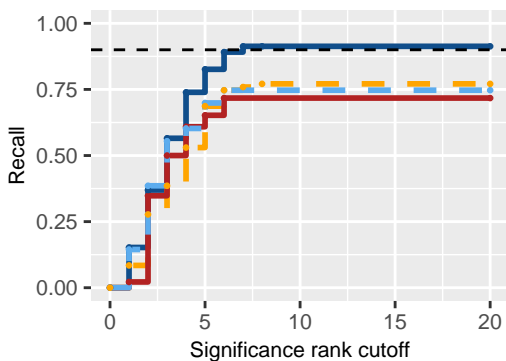
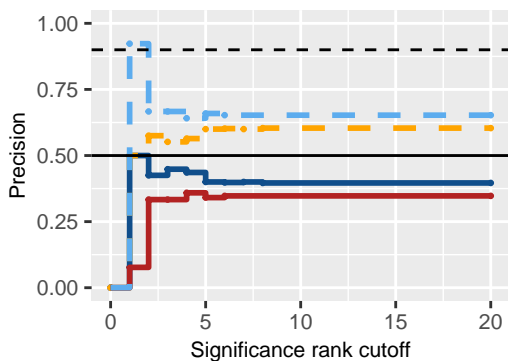
MBCOL1 – Cardiotoxicity
Cellular adhesion



MBCOL1 – Cardiotoxicity
Cellular communication

MBCOL1 – Cardiotoxicity
Cellular communication

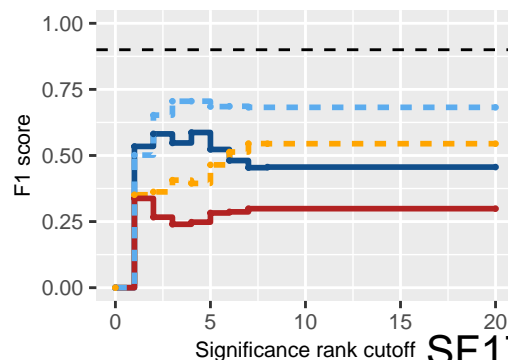
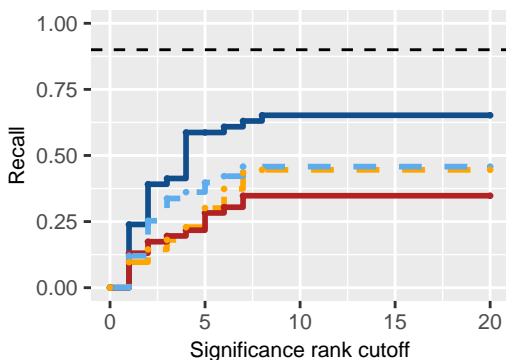
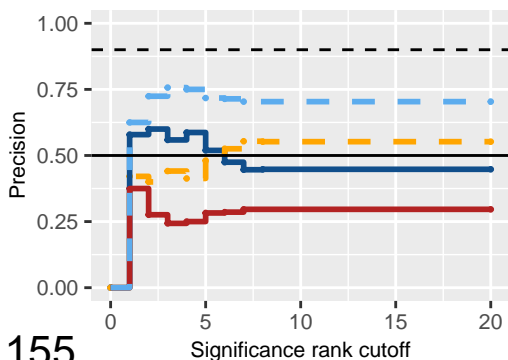
MBCOL1 – Cardiotoxicity
Cellular communication



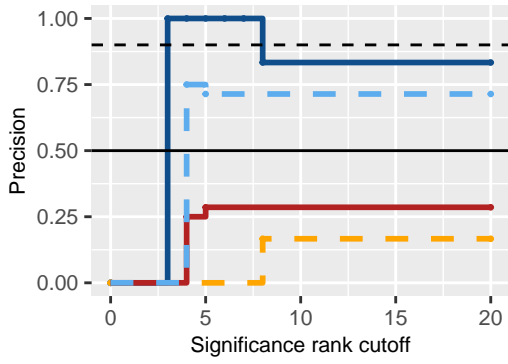
MBCOL1 – Cardiotoxicity
Cellular contraction

MBCOL1 – Cardiotoxicity
Cellular contraction

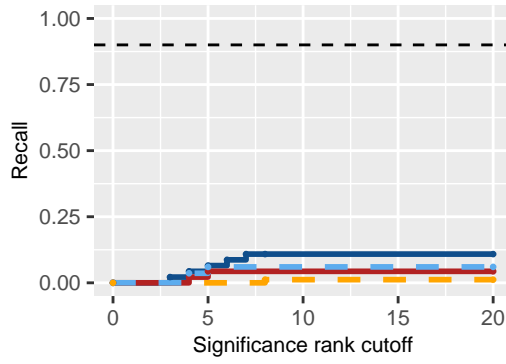
MBCOL1 – Cardiotoxicity
Cellular contraction



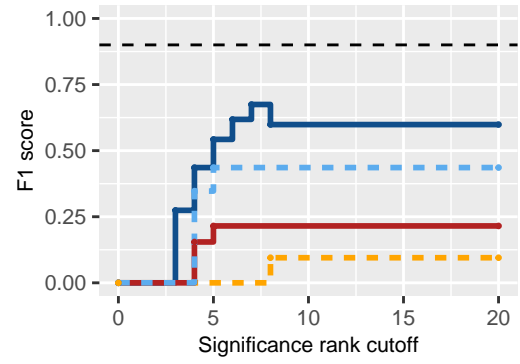
MBCOL1 – Cardiotoxicity
Cellular redox homeostasis



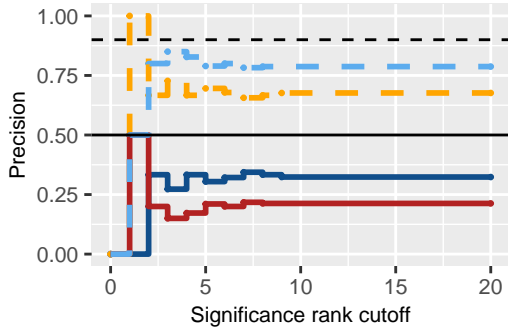
MBCOL1 – Cardiotoxicity
Cellular redox homeostasis



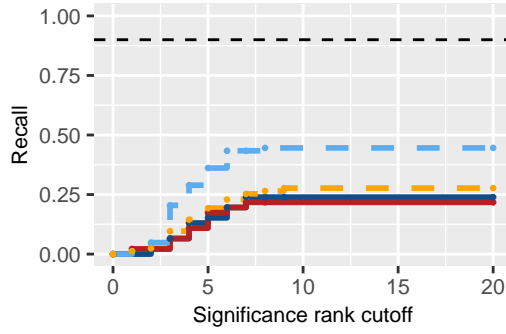
MBCOL1 – Cardiotoxicity
Cellular redox homeostasis



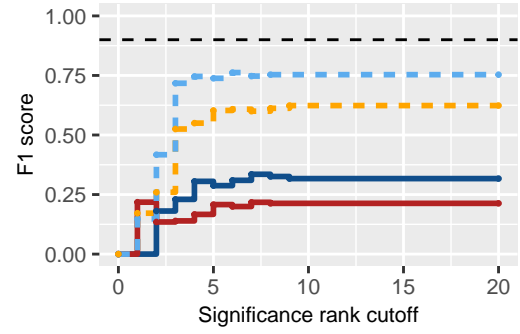
MBCOL1 – Cardiotoxicity
Coag., fib., compl. system
and blood protein dynamics



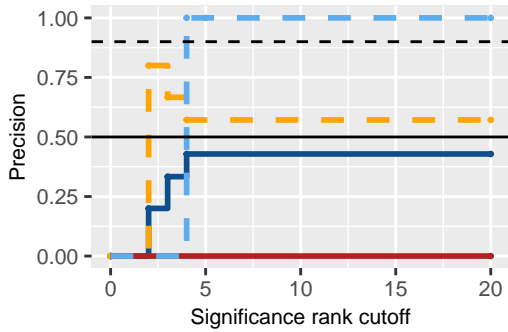
MBCOL1 – Cardiotoxicity
Coag., fib., compl. system
and blood protein dynamics



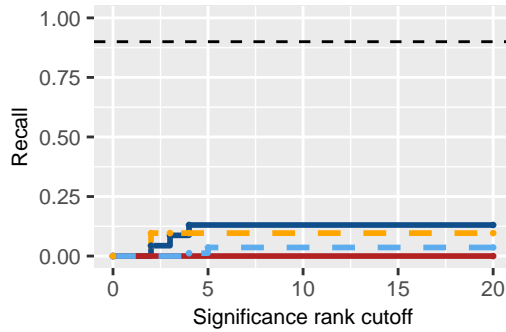
MBCOL1 – Cardiotoxicity
Coag., fib., compl. system
and blood protein dynamics



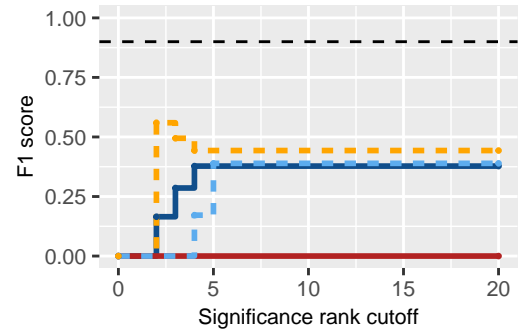
MBCOL1 – Cardiotoxicity
DNA replication,
recombination and repair



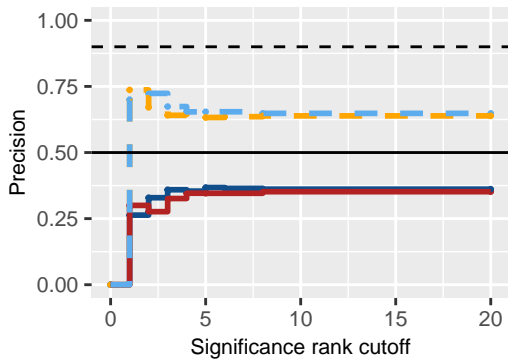
MBCOL1 – Cardiotoxicity
DNA replication,
recombination and repair



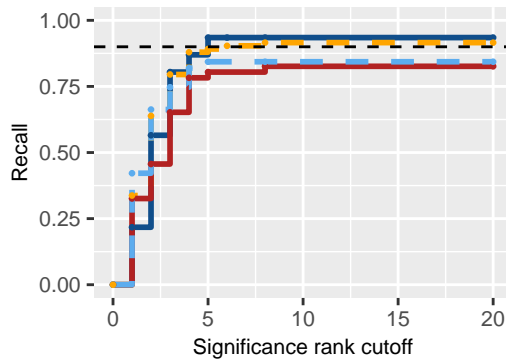
MBCOL1 – Cardiotoxicity
DNA replication,
recombination and repair



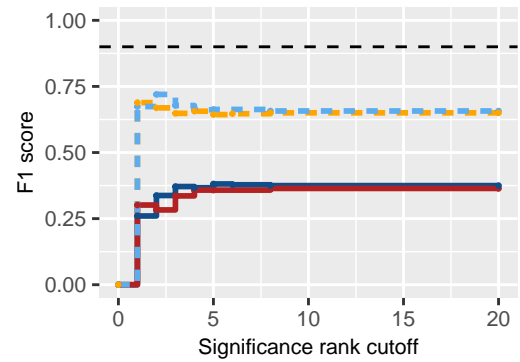
MBCOL1 – Cardiotoxicity
ECM homeostasis



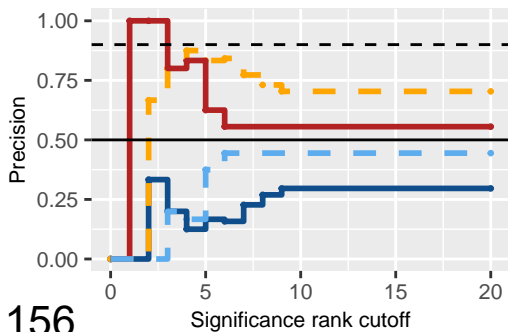
MBCOL1 – Cardiotoxicity
ECM homeostasis



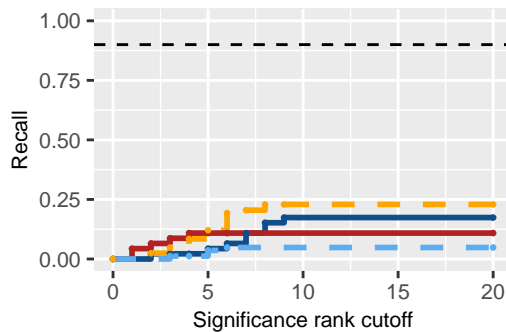
MBCOL1 – Cardiotoxicity
ECM homeostasis



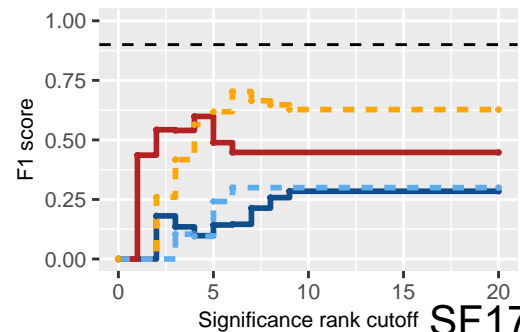
MBCOL1 – Cardiotoxicity
Energy generation and
metabolism of cellular monomers



MBCOL1 – Cardiotoxicity
Energy generation and
metabolism of cellular monomers



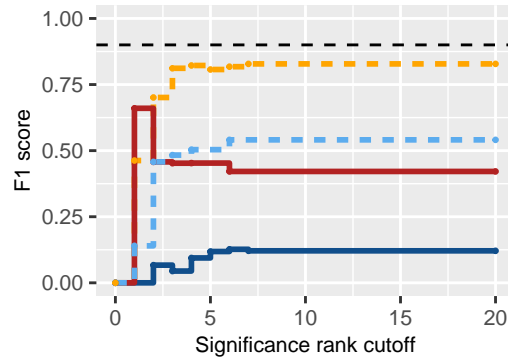
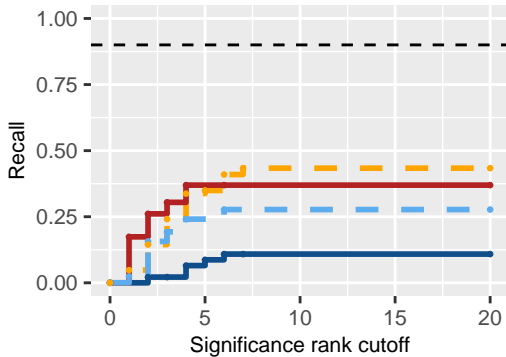
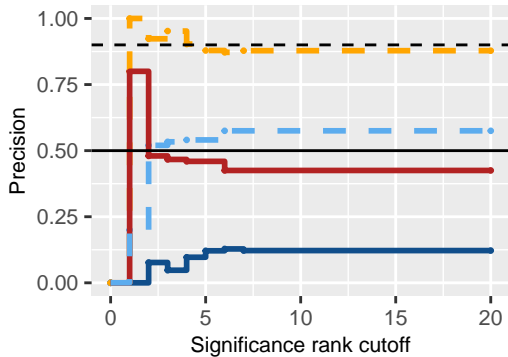
MBCOL1 – Cardiotoxicity
Energy generation and
metabolism of cellular monomers



MBCOL1 – Cardiotoxicity
Lipid metabolism

MBCOL1 – Cardiotoxicity
Lipid metabolism

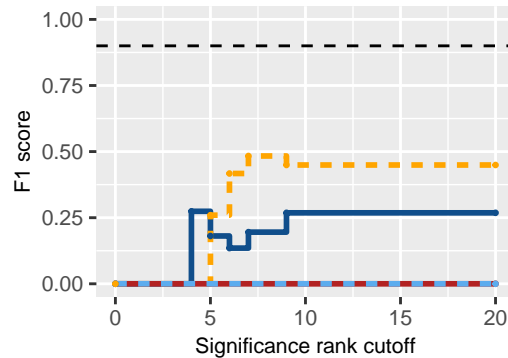
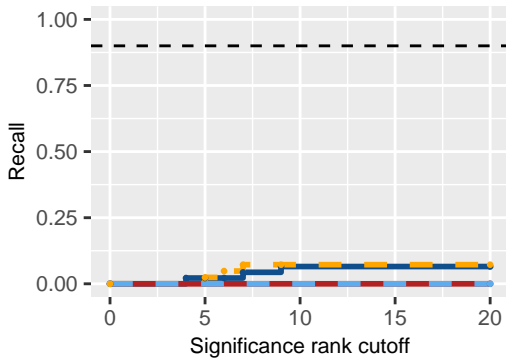
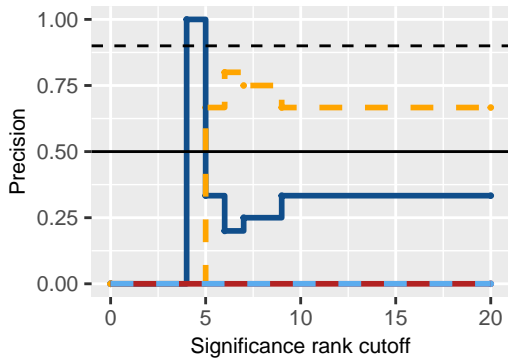
MBCOL1 – Cardiotoxicity
Lipid metabolism



MBCOL1 – Cardiotoxicity
Nucleotide metabolism

MBCOL1 – Cardiotoxicity
Nucleotide metabolism

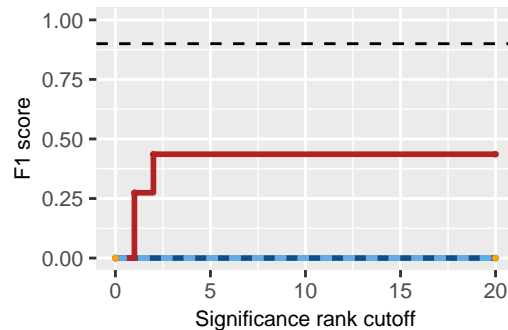
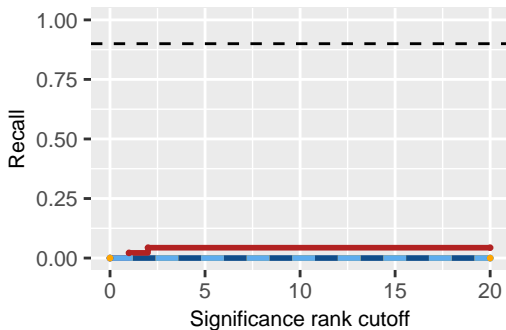
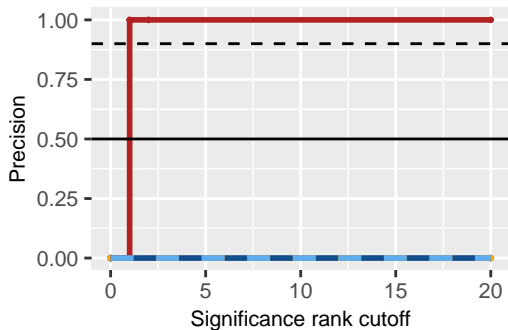
MBCOL1 – Cardiotoxicity
Nucleotide metabolism



MBCOL1 – Cardiotoxicity
Posttranslational
protein modification

MBCOL1 – Cardiotoxicity
Posttranslational
protein modification

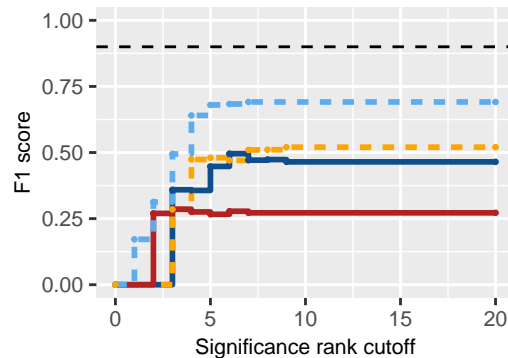
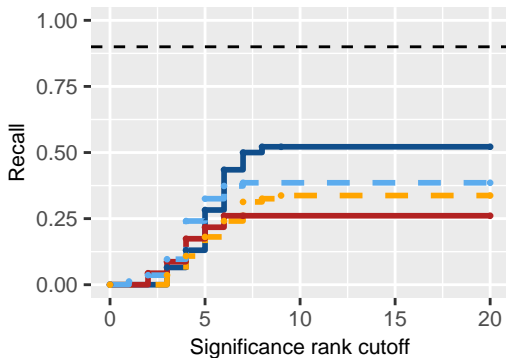
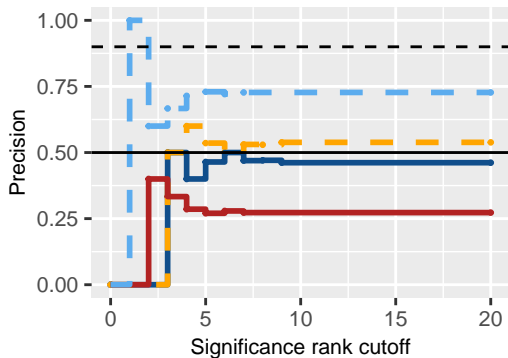
MBCOL1 – Cardiotoxicity
Posttranslational
protein modification



MBCOL1 – Cardiotoxicity
Regulated cell death

MBCOL1 – Cardiotoxicity
Regulated cell death

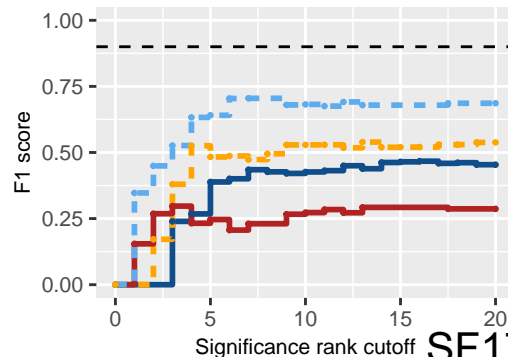
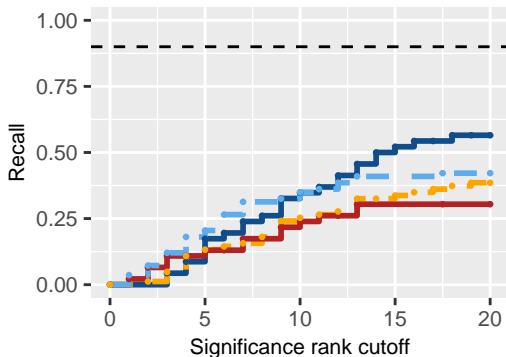
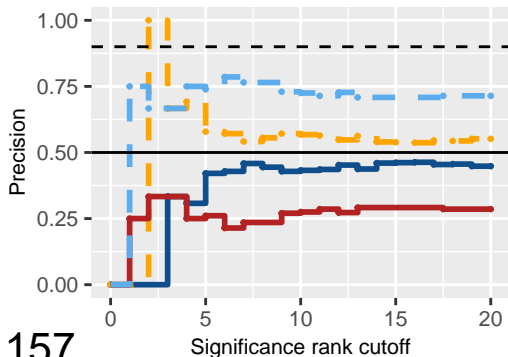
MBCOL1 – Cardiotoxicity
Regulated cell death



MBCOL2 – Cardiotoxicity
Apoptosis

MBCOL2 – Cardiotoxicity
Apoptosis

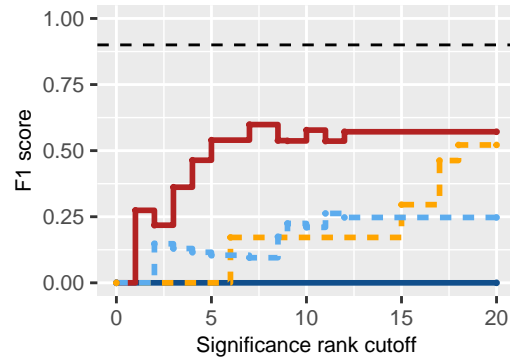
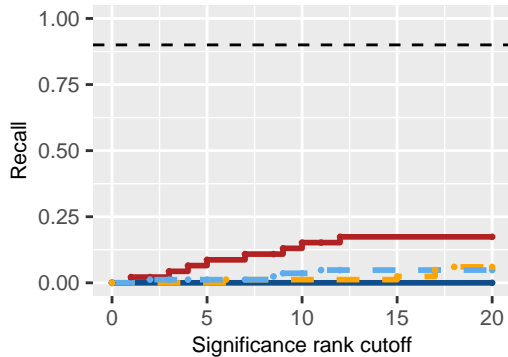
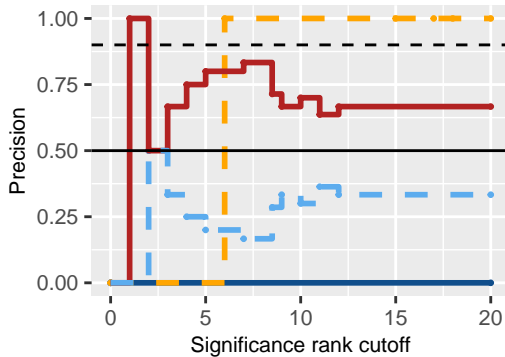
MBCOL2 – Cardiotoxicity
Apoptosis



MBCOL2 – Cardiotoxicity
Fatty acid metabolism

MBCOL2 – Cardiotoxicity
Fatty acid metabolism

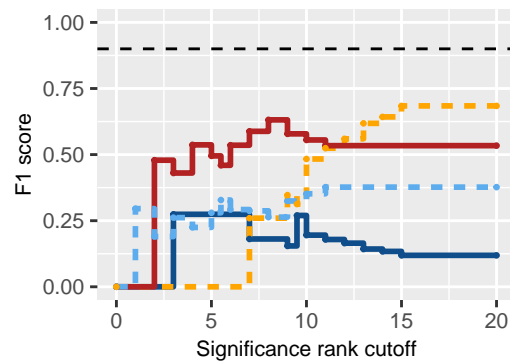
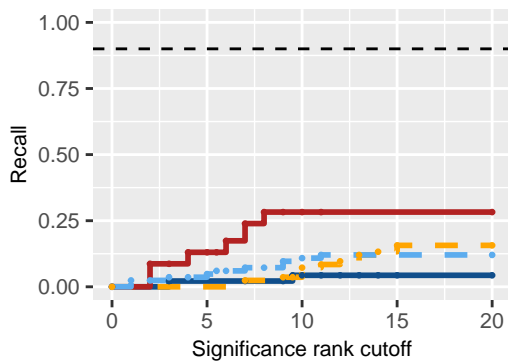
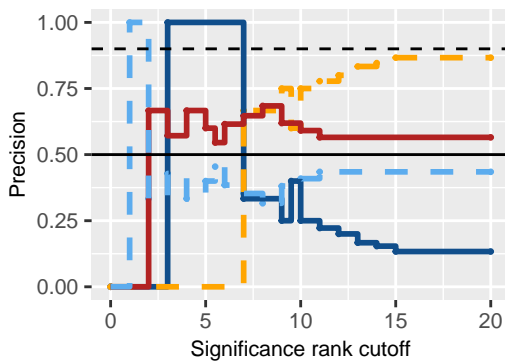
MBCOL2 – Cardiotoxicity
Fatty acid metabolism



MBCOL2 – Cardiotoxicity
Interferon signaling

MBCOL2 – Cardiotoxicity
Interferon signaling

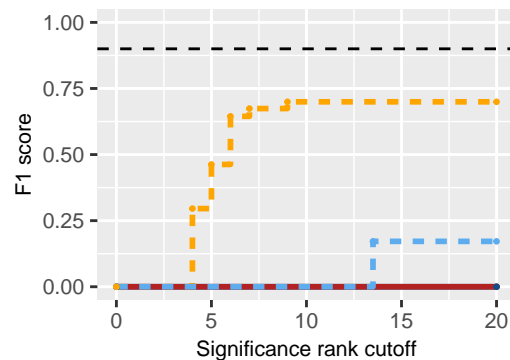
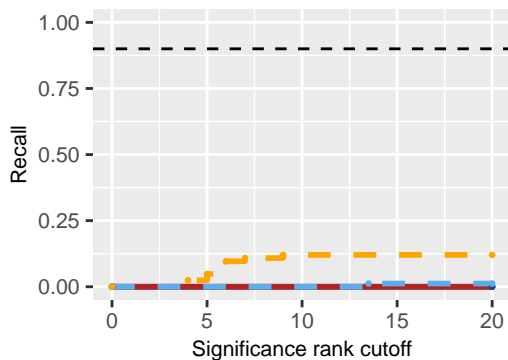
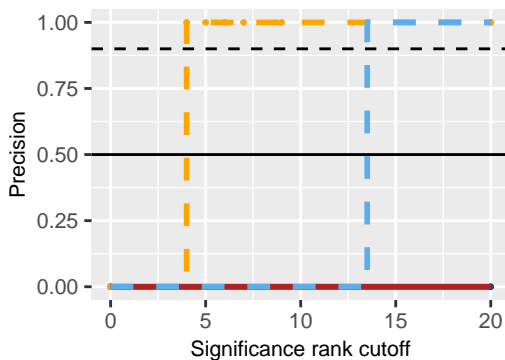
MBCOL2 – Cardiotoxicity
Interferon signaling



MBCOL2 – Cardiotoxicity
Interleukin receptor signaling

MBCOL2 – Cardiotoxicity
Interleukin receptor signaling

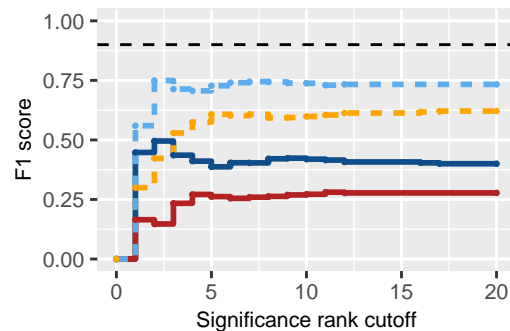
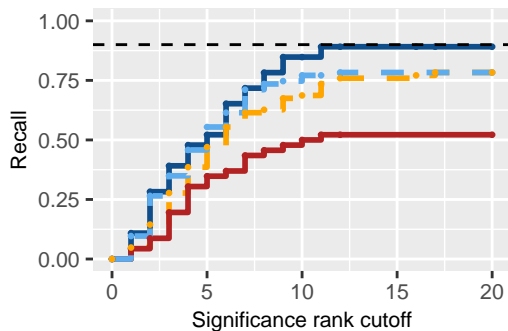
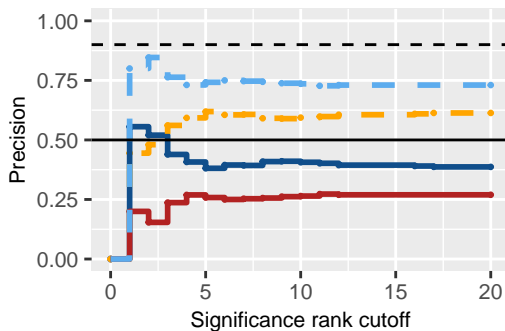
MBCOL2 – Cardiotoxicity
Interleukin receptor signaling



MBCOL2 – Cardiotoxicity
Matricellular protein signaling

MBCOL2 – Cardiotoxicity
Matricellular protein signaling

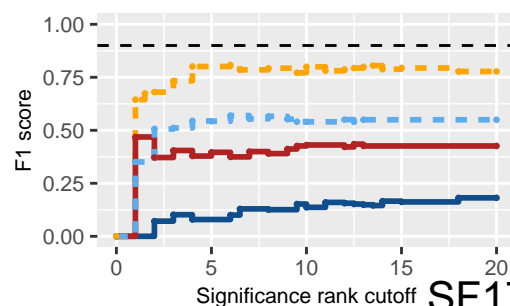
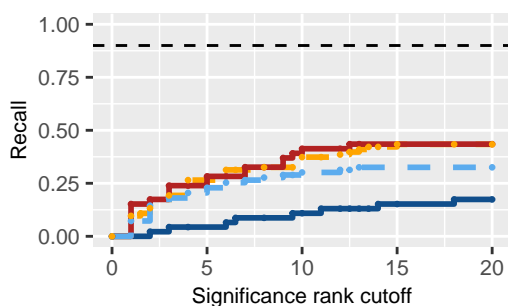
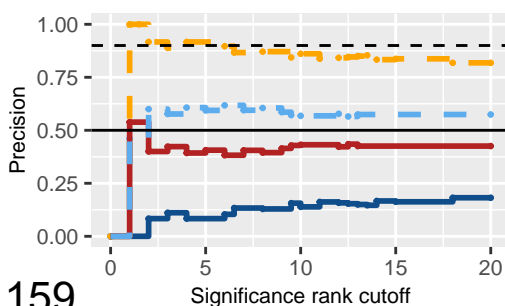
MBCOL2 – Cardiotoxicity
Matricellular protein signaling



MBCOL2 – Cardiotoxicity
Metabolism and transport
of cholesterol, steroids
and bile acids

MBCOL2 – Cardiotoxicity
Metabolism and transport
of cholesterol, steroids
and bile acids

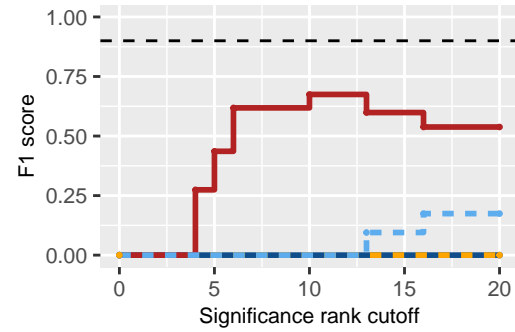
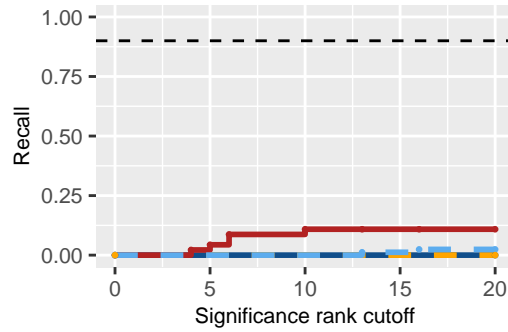
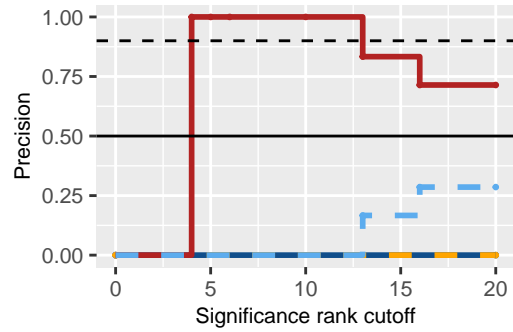
MBCOL2 – Cardiotoxicity
Metabolism and transport
of cholesterol, steroids
and bile acids



MBCOL2 – Cardiotoxicity
PT protein modification
in mitochondria

MBCOL2 – Cardiotoxicity
PT protein modification
in mitochondria

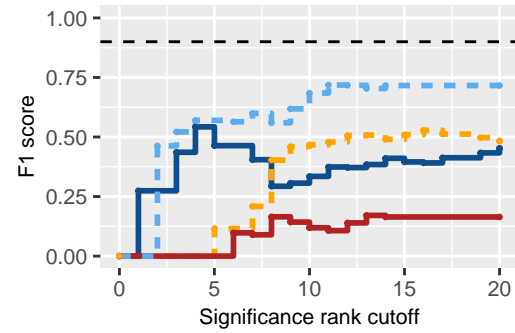
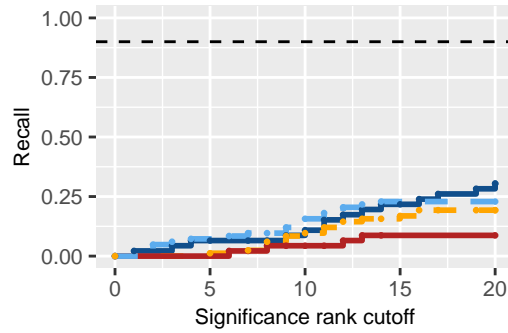
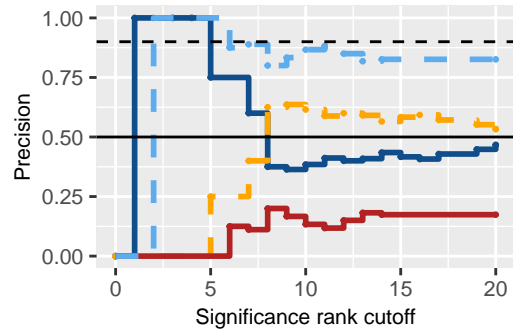
MBCOL2 – Cardiotoxicity
PT protein modification
in mitochondria



MBCOL2 – Cardiotoxicity
Signaling pathways
regulating water homeostasis

MBCOL2 – Cardiotoxicity
Signaling pathways
regulating water homeostasis

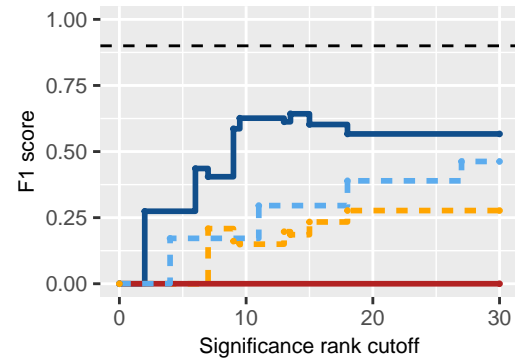
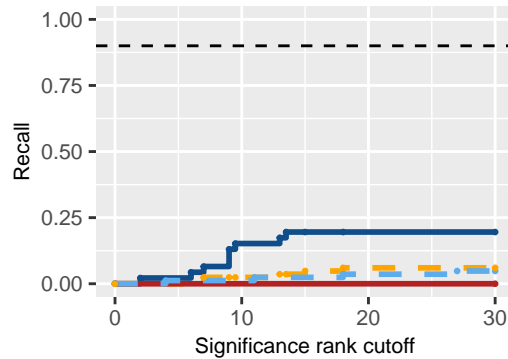
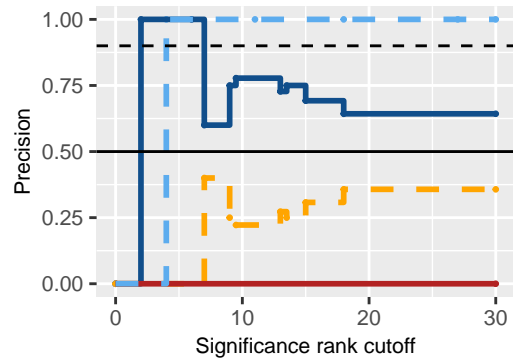
MBCOL2 – Cardiotoxicity
Signaling pathways
regulating water homeostasis



MBCOL3 – Cardiotoxicity
Adrenergic receptor signaling

MBCOL3 – Cardiotoxicity
Adrenergic receptor signaling

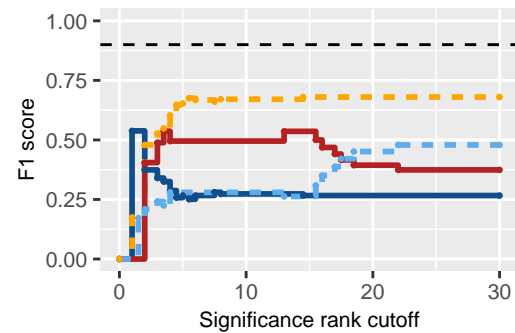
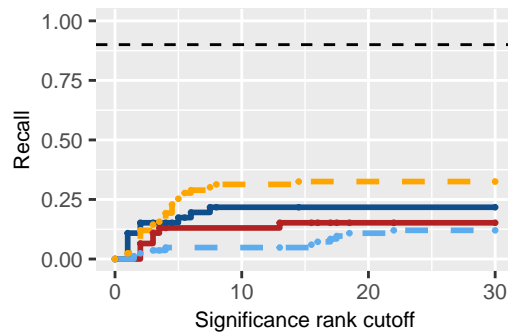
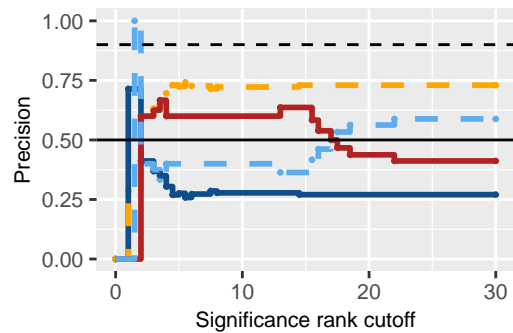
MBCOL3 – Cardiotoxicity
Adrenergic receptor signaling



MBCOL3 – Cardiotoxicity
Amyloid degradation, uptake
and aggregation inhibition

MBCOL3 – Cardiotoxicity
Amyloid degradation, uptake
and aggregation inhibition

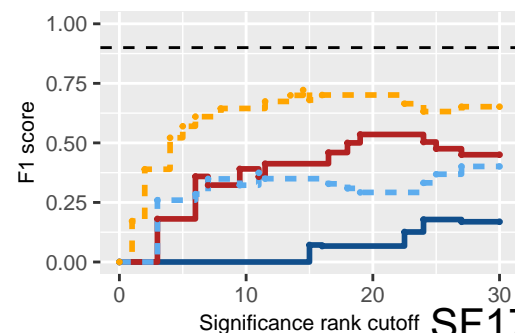
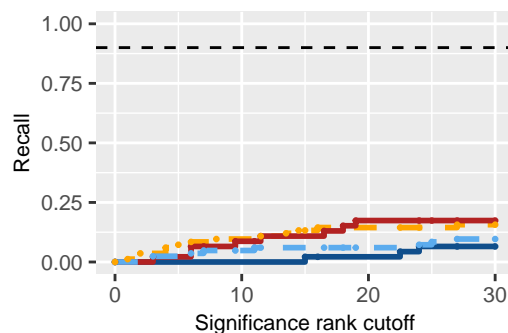
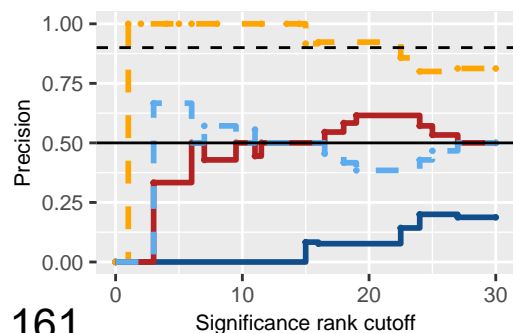
MBCOL3 – Cardiotoxicity
Amyloid degradation, uptake
and aggregation inhibition



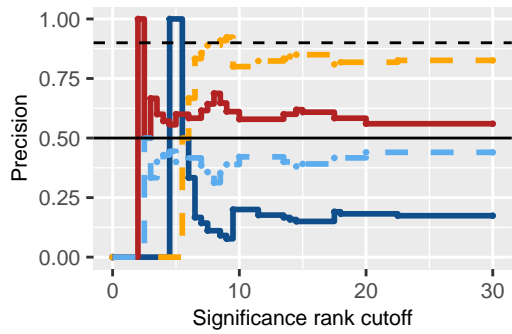
MBCOL3 – Cardiotoxicity
Aspartate and
arginine metabolism

MBCOL3 – Cardiotoxicity
Aspartate and
arginine metabolism

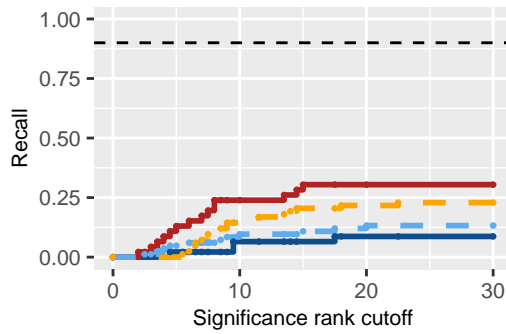
MBCOL3 – Cardiotoxicity
Aspartate and
arginine metabolism



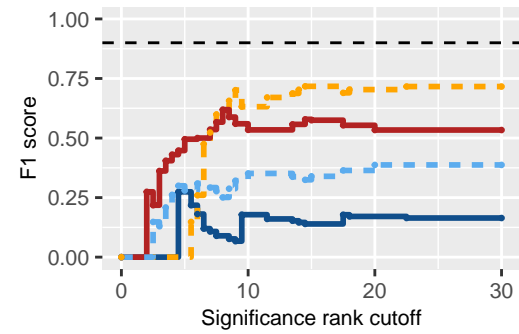
MBCOL3 – Cardiotoxicity
Cholesterol-sensitive
control of SREBP activation



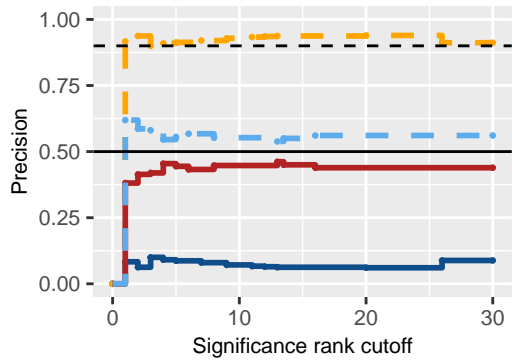
MBCOL3 – Cardiotoxicity
Cholesterol-sensitive
control of SREBP activation



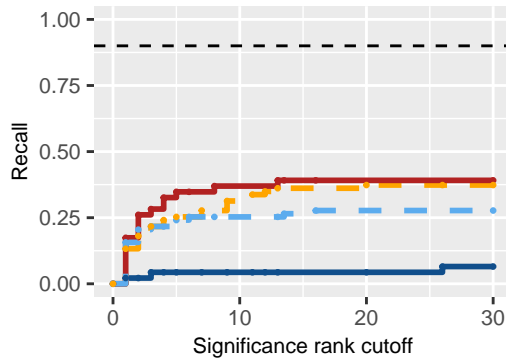
MBCOL3 – Cardiotoxicity
Cholesterol-sensitive
control of SREBP activation



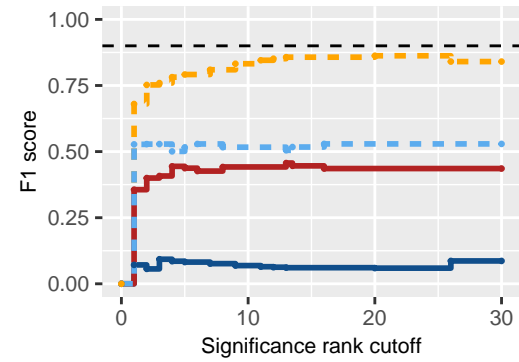
MBCOL3 – Cardiotoxicity
Cholesterol synthesis



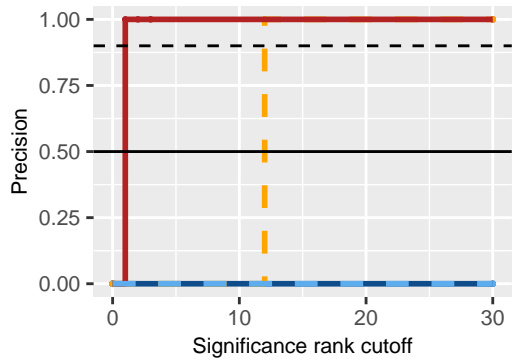
MBCOL3 – Cardiotoxicity
Cholesterol synthesis



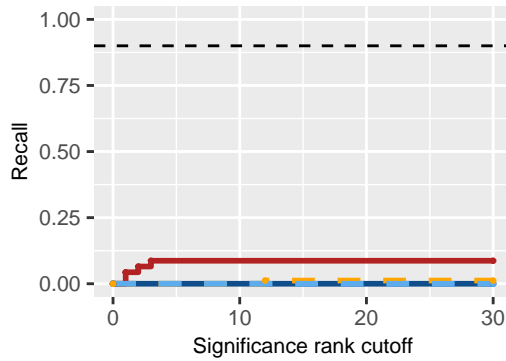
MBCOL3 – Cardiotoxicity
Cholesterol synthesis



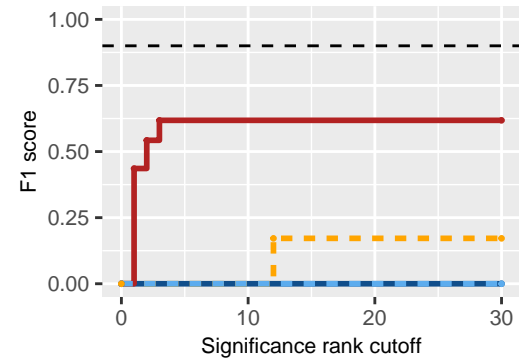
MBCOL3 – Cardiotoxicity
Citric acid cycle



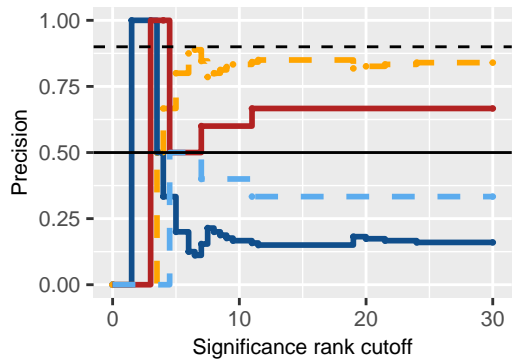
MBCOL3 – Cardiotoxicity
Citric acid cycle



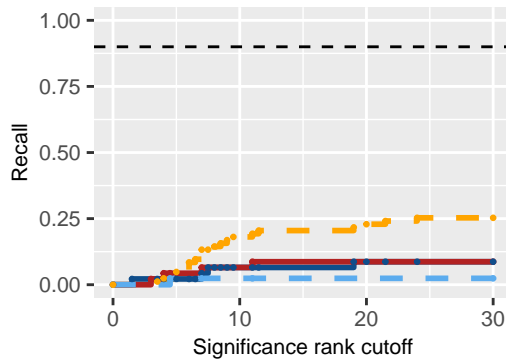
MBCOL3 – Cardiotoxicity
Citric acid cycle



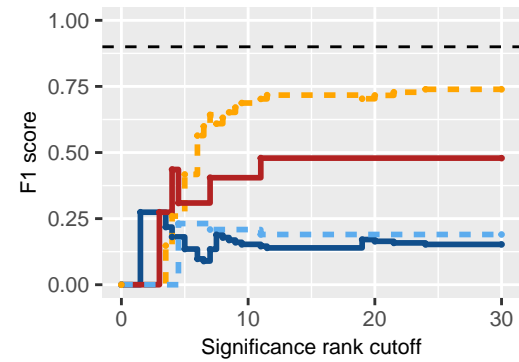
MBCOL3 – Cardiotoxicity
Collagen fiber crosslinking



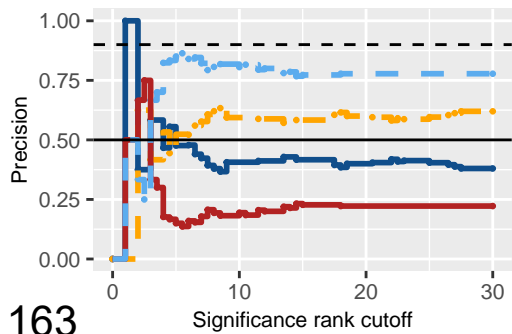
MBCOL3 – Cardiotoxicity
Collagen fiber crosslinking



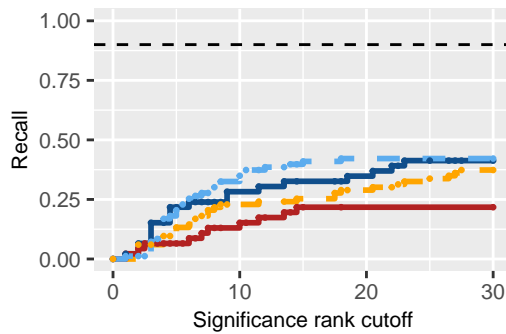
MBCOL3 – Cardiotoxicity
Collagen fiber crosslinking



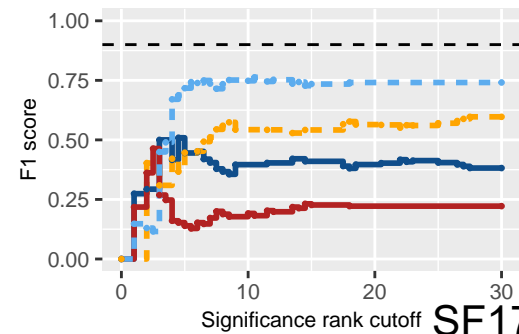
MBCOL3 – Cardiotoxicity
Collagen fibril organization
by fibril-associated bridges



MBCOL3 – Cardiotoxicity
Collagen fibril organization
by fibril-associated bridges



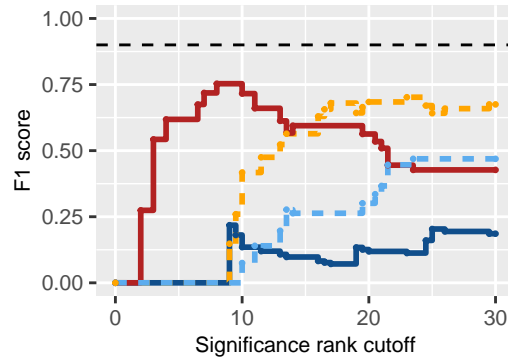
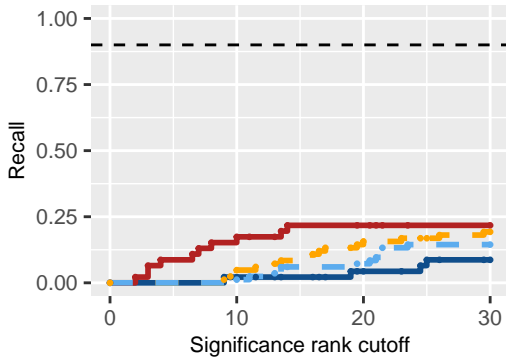
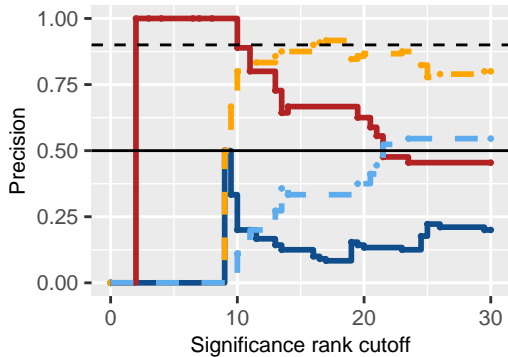
MBCOL3 – Cardiotoxicity
Collagen fibril organization
by fibril-associated bridges



MBCOL3 – Cardiotoxicity
Desaturation of fatty acids

MBCOL3 – Cardiotoxicity
Desaturation of fatty acids

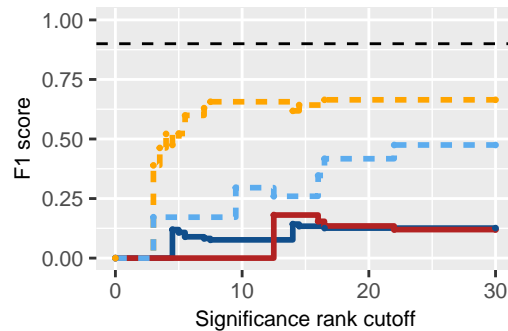
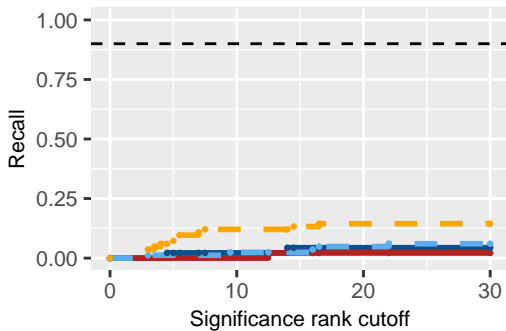
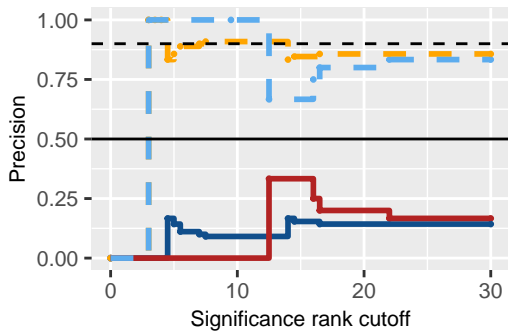
MBCOL3 – Cardiotoxicity
Desaturation of fatty acids



MBCOL3 – Cardiotoxicity
Elastin cross-linking
and assembly

MBCOL3 – Cardiotoxicity
Elastin cross-linking
and assembly

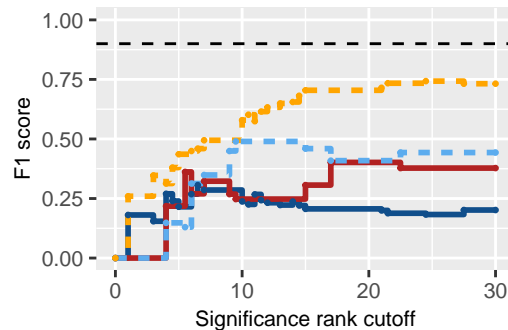
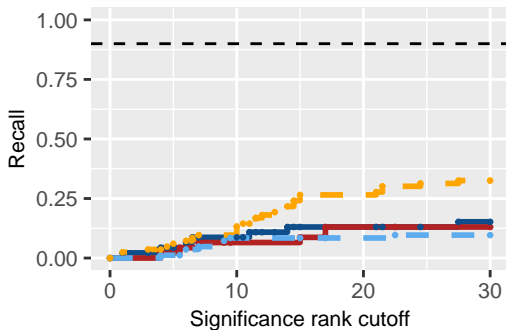
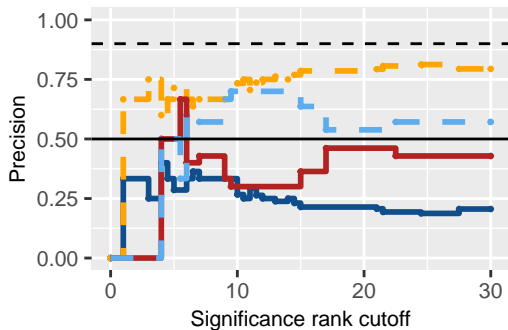
MBCOL3 – Cardiotoxicity
Elastin cross-linking
and assembly



MBCOL3 – Cardiotoxicity
Epithelial intermediate
filament dynamics

MBCOL3 – Cardiotoxicity
Epithelial intermediate
filament dynamics

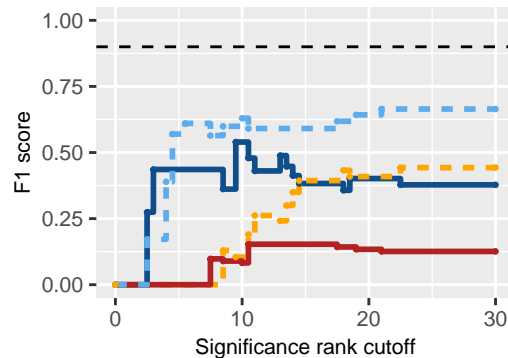
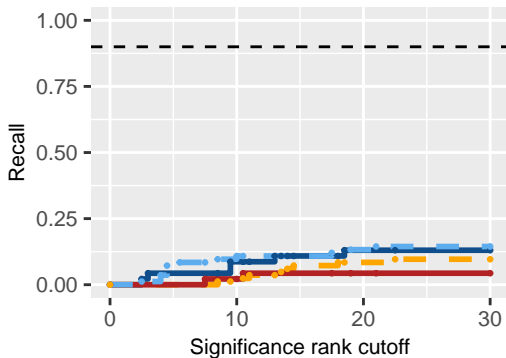
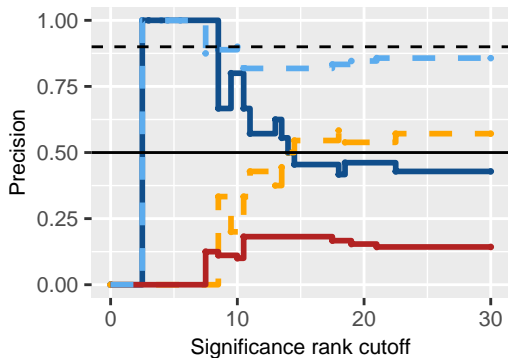
MBCOL3 – Cardiotoxicity
Epithelial intermediate
filament dynamics



MBCOL3 – Cardiotoxicity
GABA metabolism

MBCOL3 – Cardiotoxicity
GABA metabolism

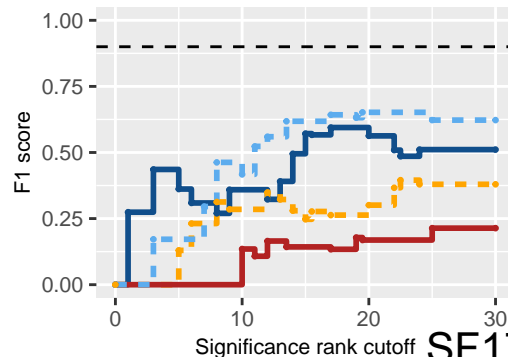
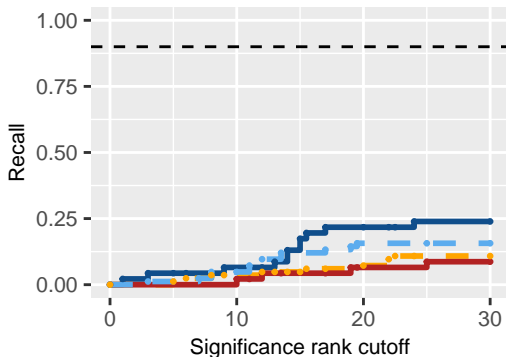
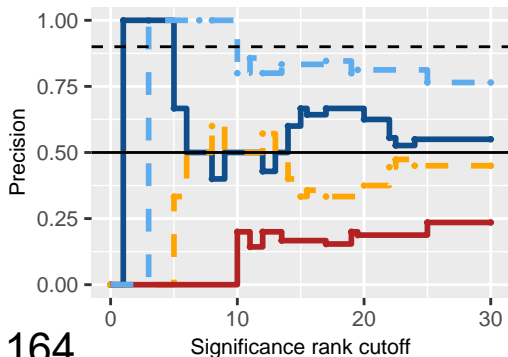
MBCOL3 – Cardiotoxicity
GABA metabolism

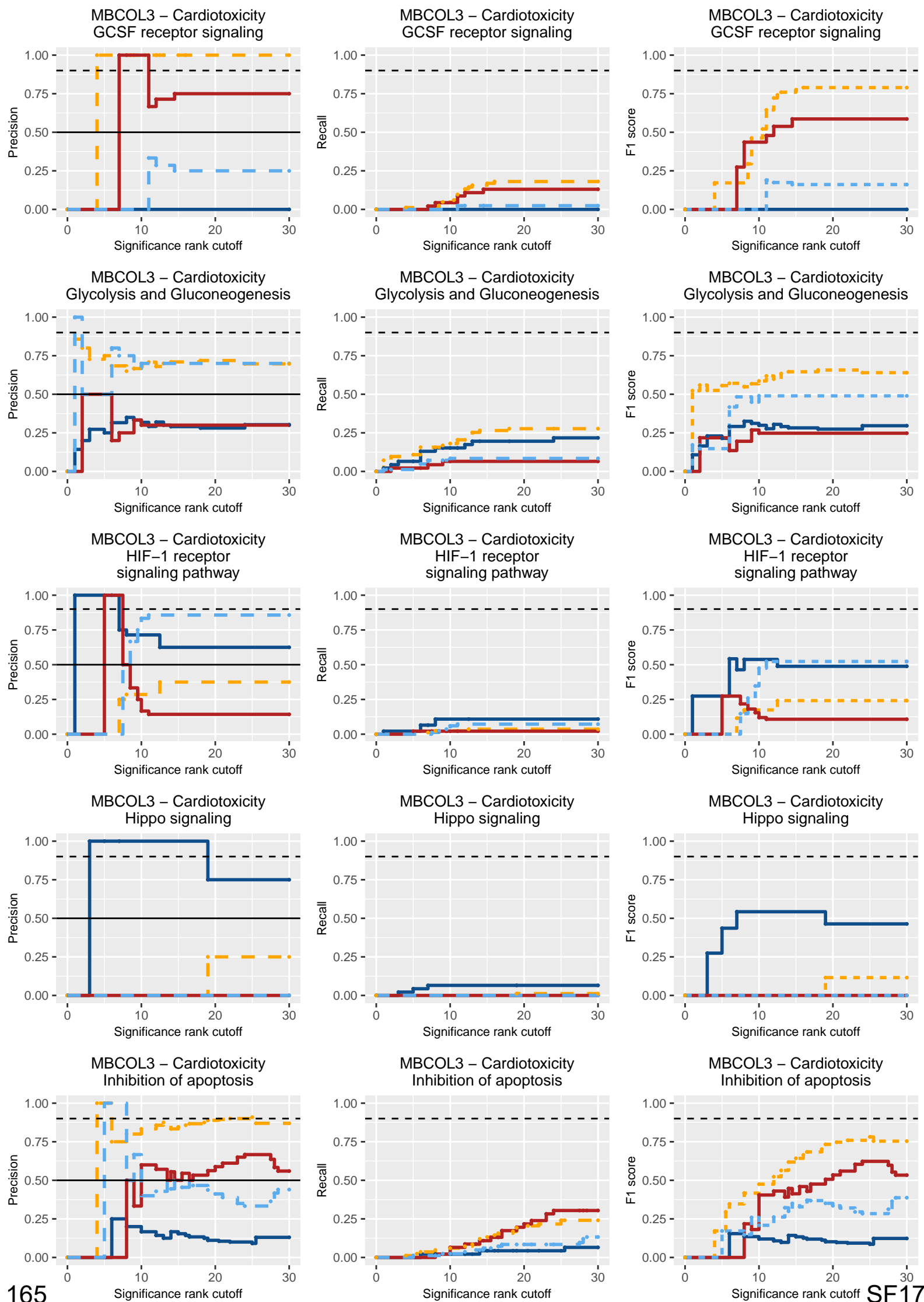


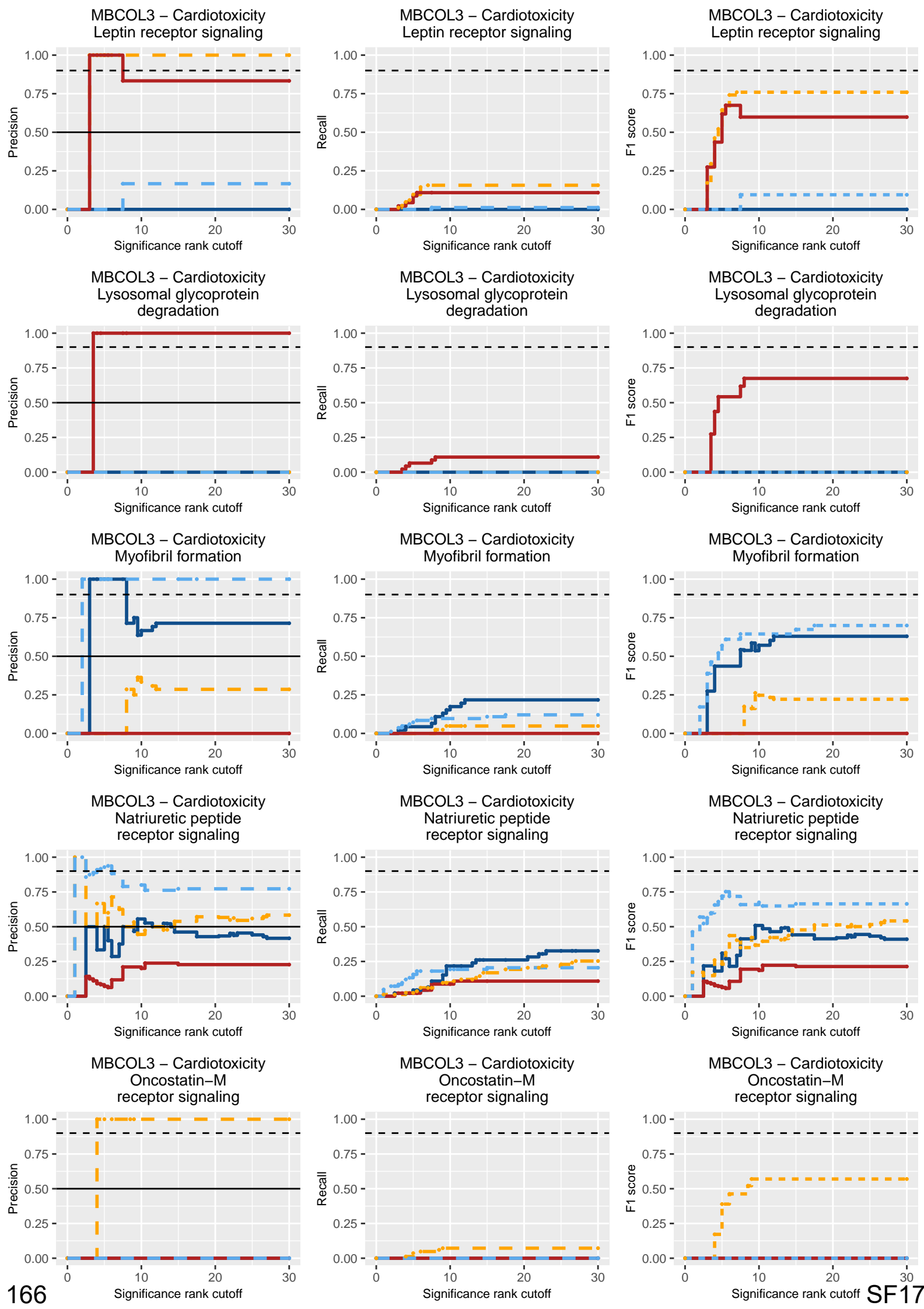
MBCOL3 – Cardiotoxicity
Gap junction organization

MBCOL3 – Cardiotoxicity
Gap junction organization

MBCOL3 – Cardiotoxicity
Gap junction organization



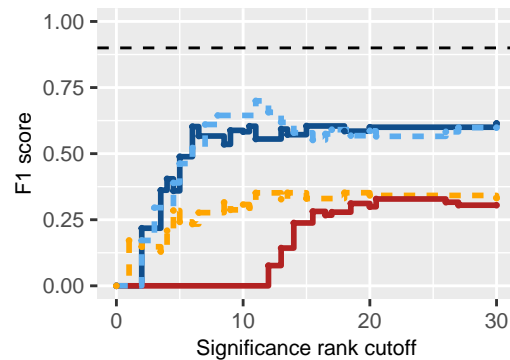
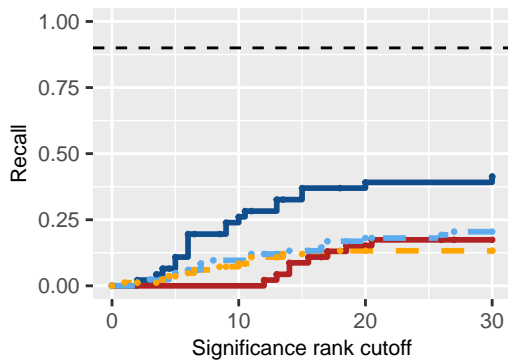
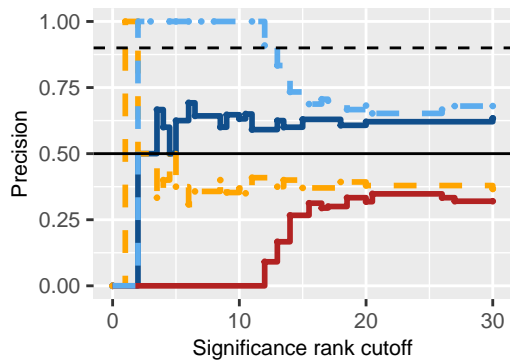




MBCOL3 – Cardiotoxicity
PDGF receptor signaling

MBCOL3 – Cardiotoxicity
PDGF receptor signaling

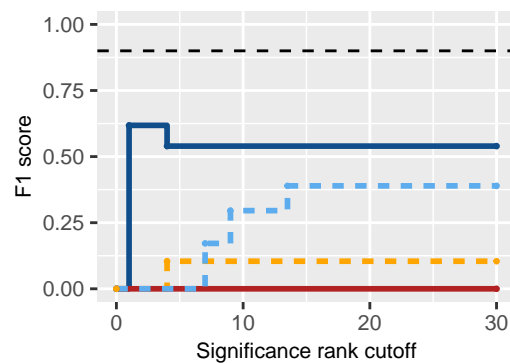
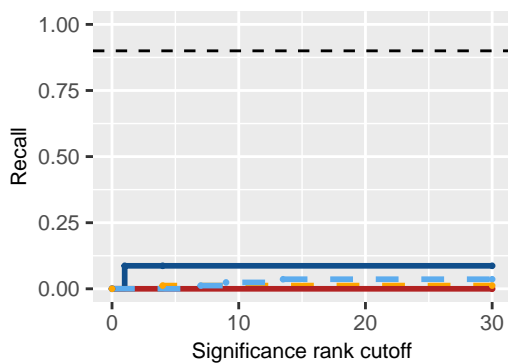
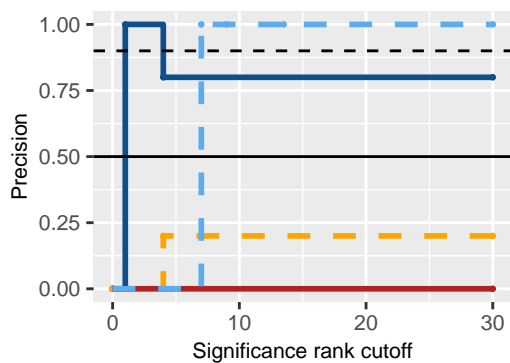
MBCOL3 – Cardiotoxicity
PDGF receptor signaling



MBCOL3 – Cardiotoxicity
Polyol pathway

MBCOL3 – Cardiotoxicity
Polyol pathway

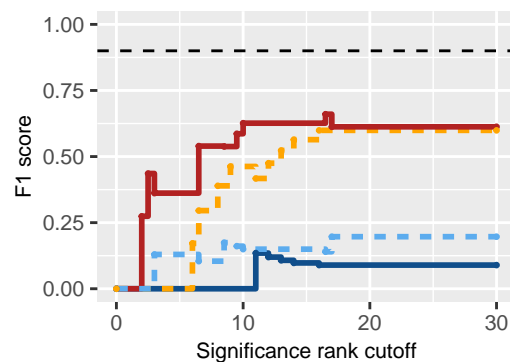
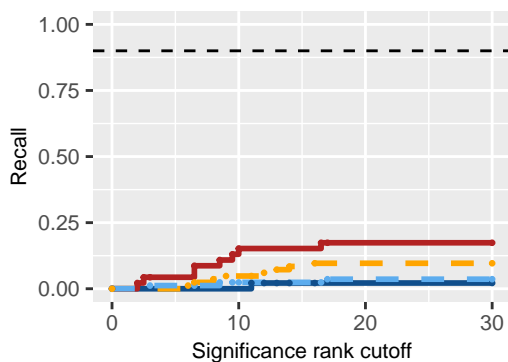
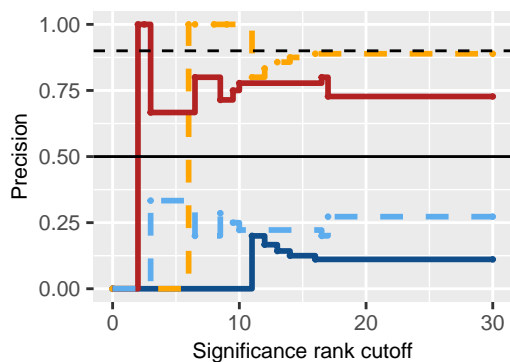
MBCOL3 – Cardiotoxicity
Polyol pathway



MBCOL3 – Cardiotoxicity
Potassium TM transport

MBCOL3 – Cardiotoxicity
Potassium TM transport

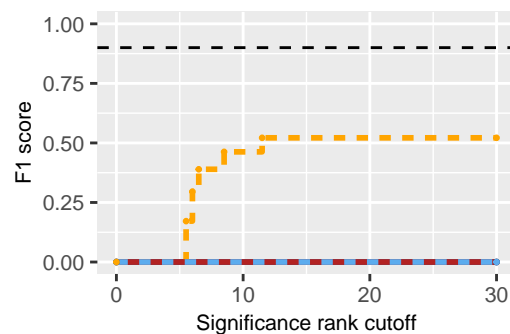
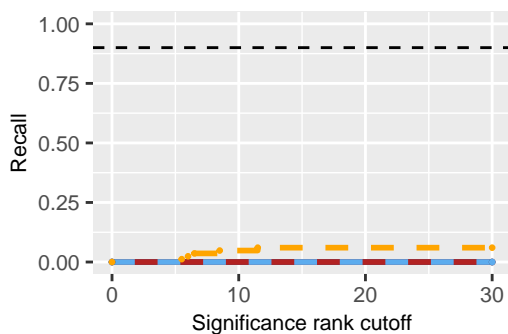
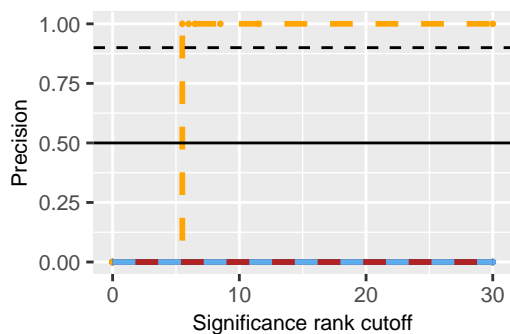
MBCOL3 – Cardiotoxicity
Potassium TM transport



MBCOL3 – Cardiotoxicity
Prostaglandin E2
receptor signaling

MBCOL3 – Cardiotoxicity
Prostaglandin E2
receptor signaling

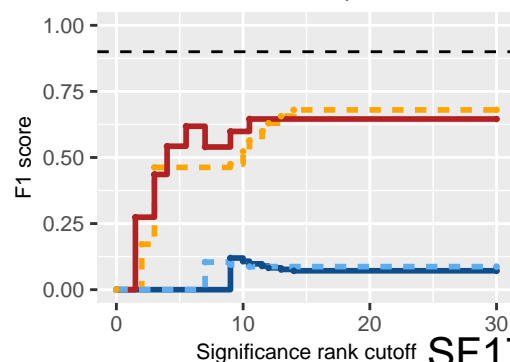
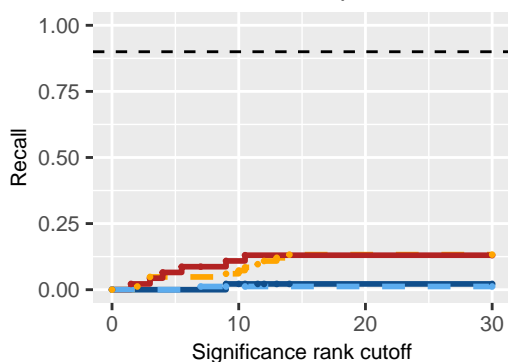
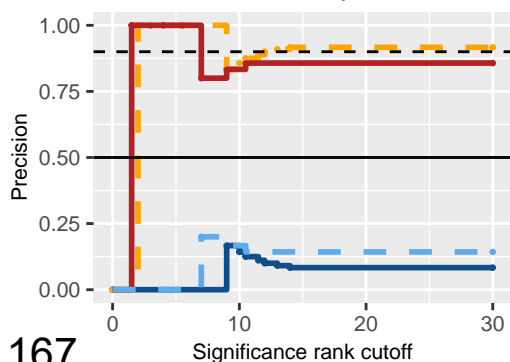
MBCOL3 – Cardiotoxicity
Prostaglandin E2
receptor signaling



MBCOL3 – Cardiotoxicity
Restriction point

MBCOL3 – Cardiotoxicity
Restriction point

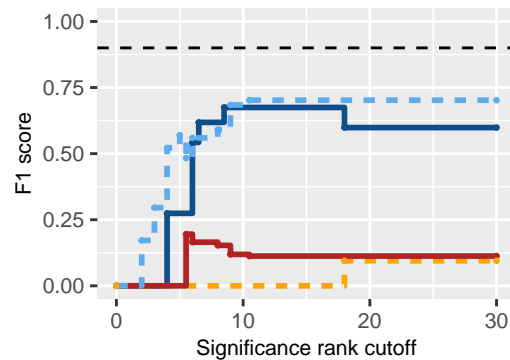
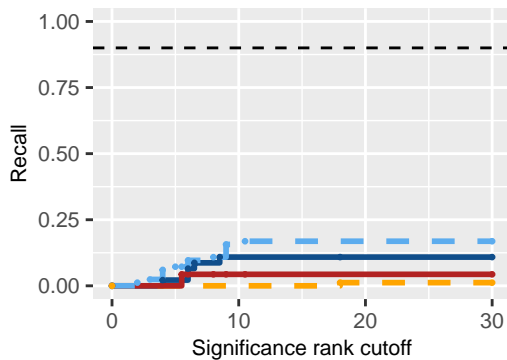
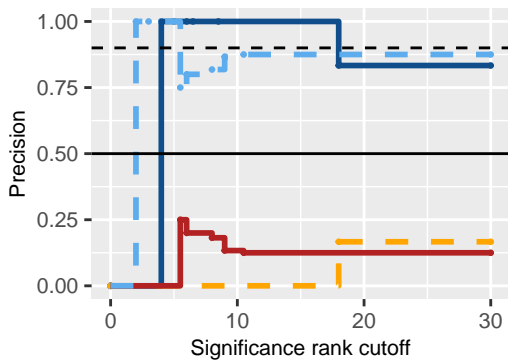
MBCOL3 – Cardiotoxicity
Restriction point



MBCOL3 – Cardiotoxicity
Water TM transport

MBCOL3 – Cardiotoxicity
Water TM transport

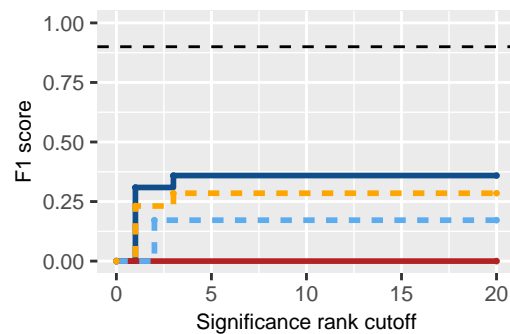
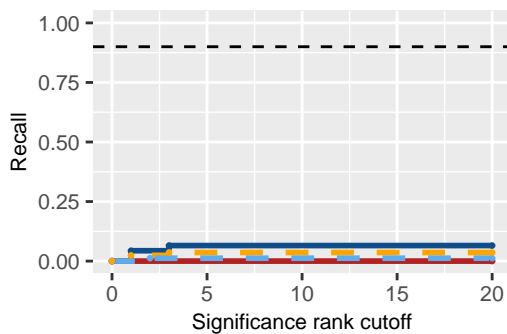
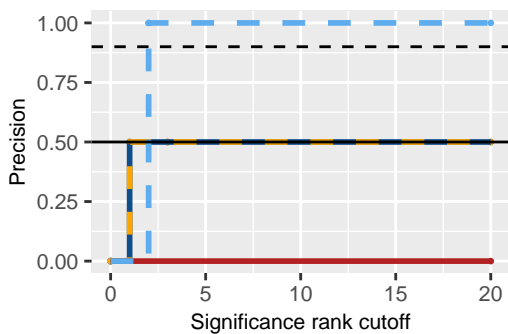
MBCOL3 – Cardiotoxicity
Water TM transport



MBCOL4 – Cardiotoxicity
Actin filament
depolymerization

MBCOL4 – Cardiotoxicity
Actin filament
depolymerization

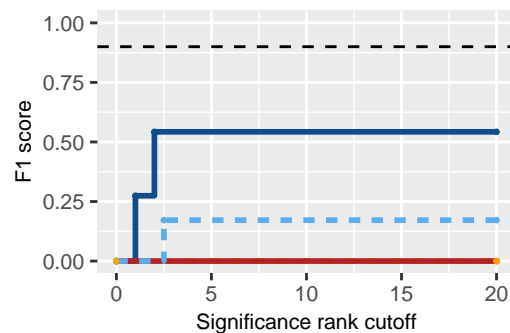
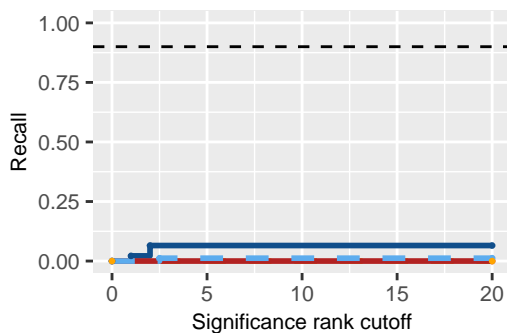
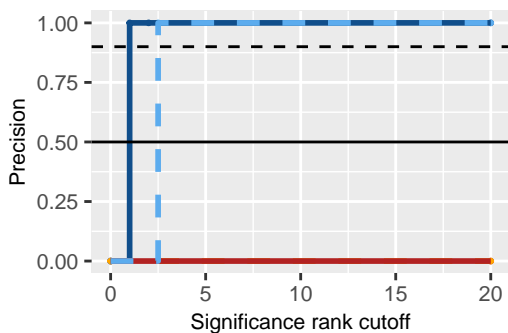
MBCOL4 – Cardiotoxicity
Actin filament
depolymerization



MBCOL4 – Cardiotoxicity
Apoptosis initiator
caspase cascade

MBCOL4 – Cardiotoxicity
Apoptosis initiator
caspase cascade

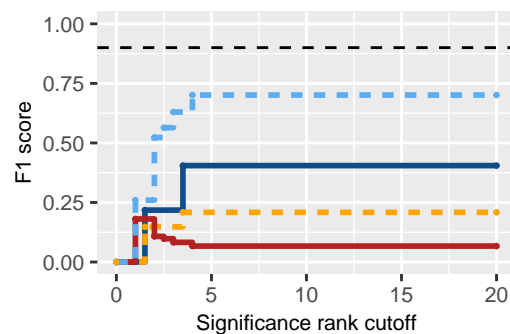
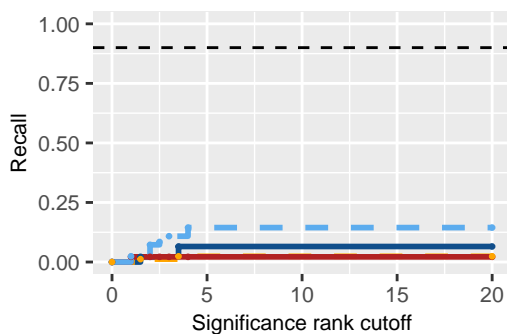
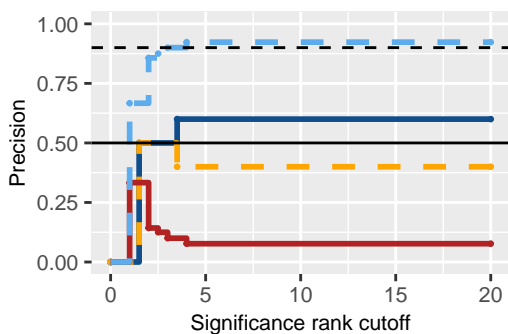
MBCOL4 – Cardiotoxicity
Apoptosis initiator
caspase cascade



MBCOL4 – Cardiotoxicity
Atrial natriuretic peptide
receptor signaling

MBCOL4 – Cardiotoxicity
Atrial natriuretic peptide
receptor signaling

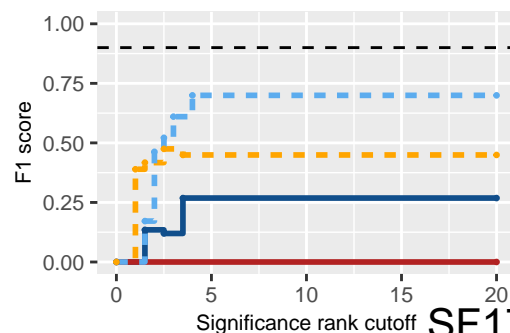
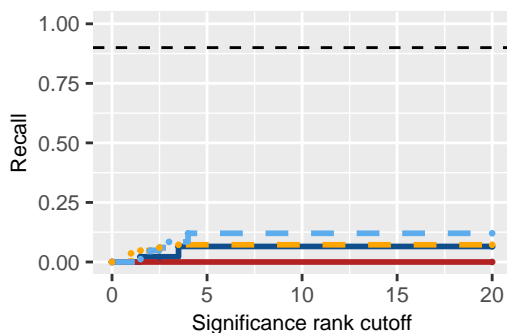
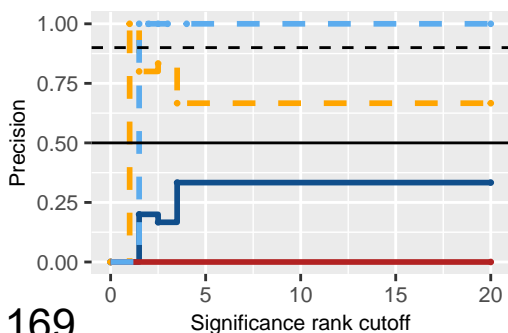
MBCOL4 – Cardiotoxicity
Atrial natriuretic peptide
receptor signaling

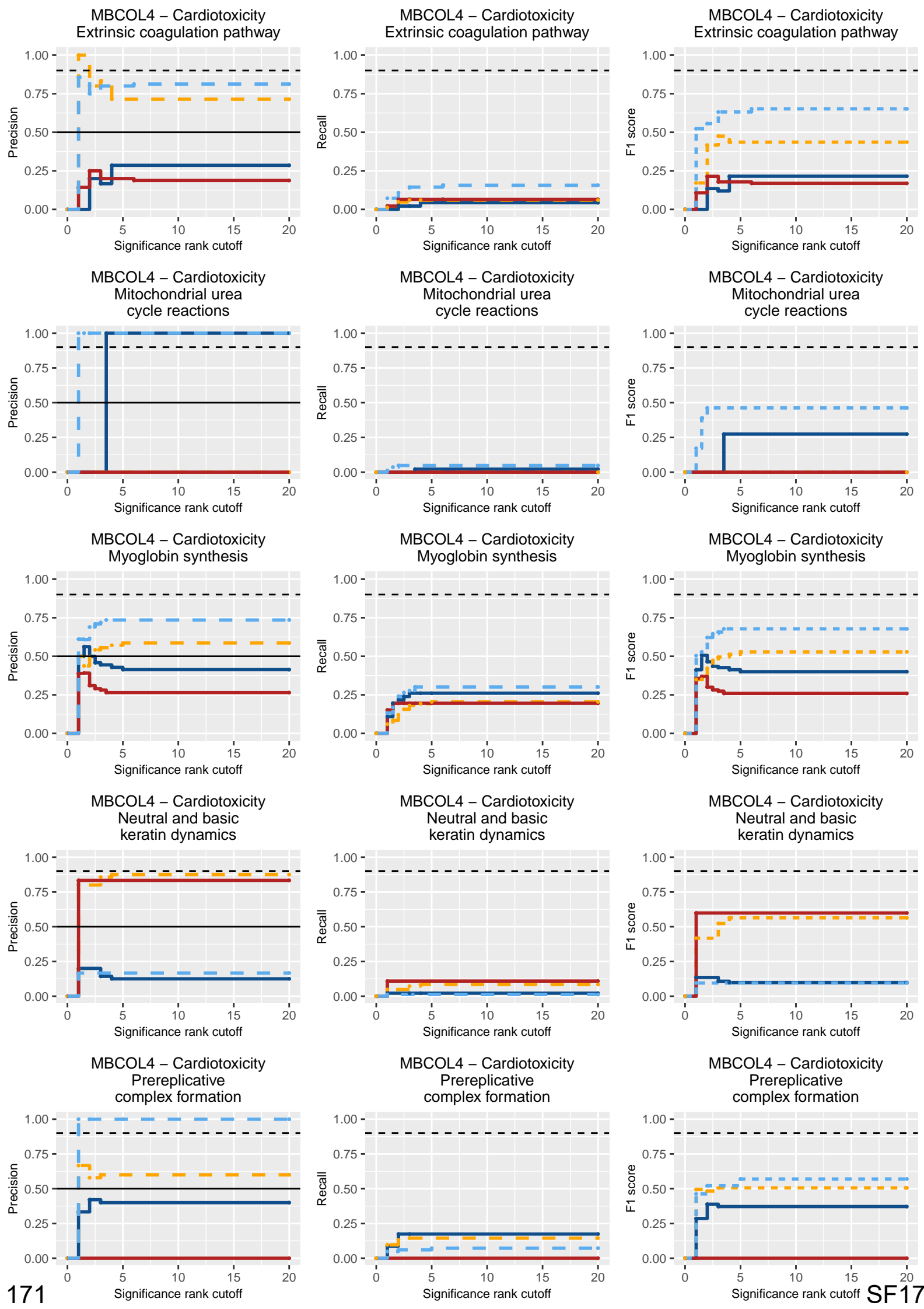


MBCOL4 – Cardiotoxicity
Brain natriuretic peptide
receptor signaling

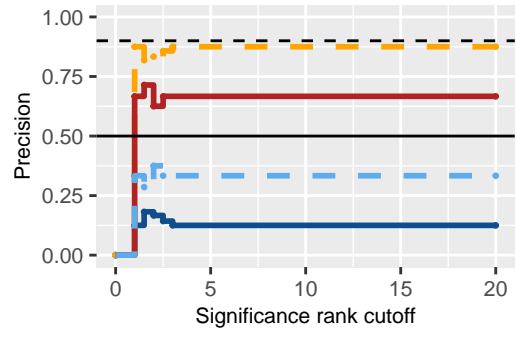
MBCOL4 – Cardiotoxicity
Brain natriuretic peptide
receptor signaling

MBCOL4 – Cardiotoxicity
Brain natriuretic peptide
receptor signaling

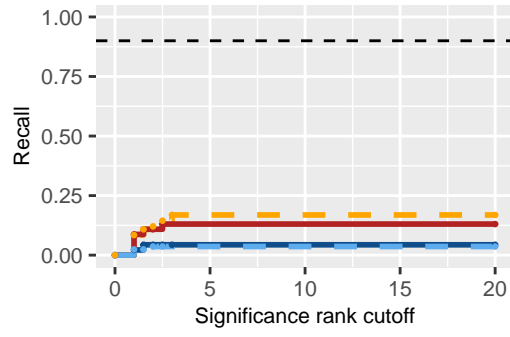




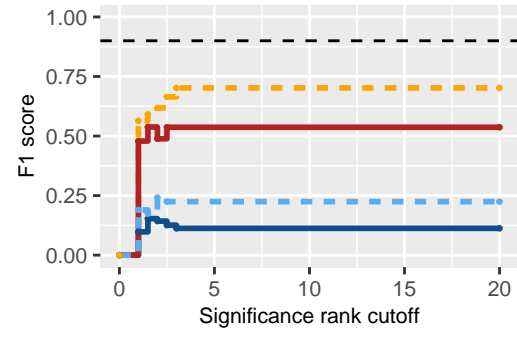
MBCOL4 – Cardiotoxicity
Triacylglycerol transport
by chylomicrons



MBCOL4 – Cardiotoxicity
Triacylglycerol transport
by chylomicrons



MBCOL4 – Cardiotoxicity
Triacylglycerol transport
by chylomicrons



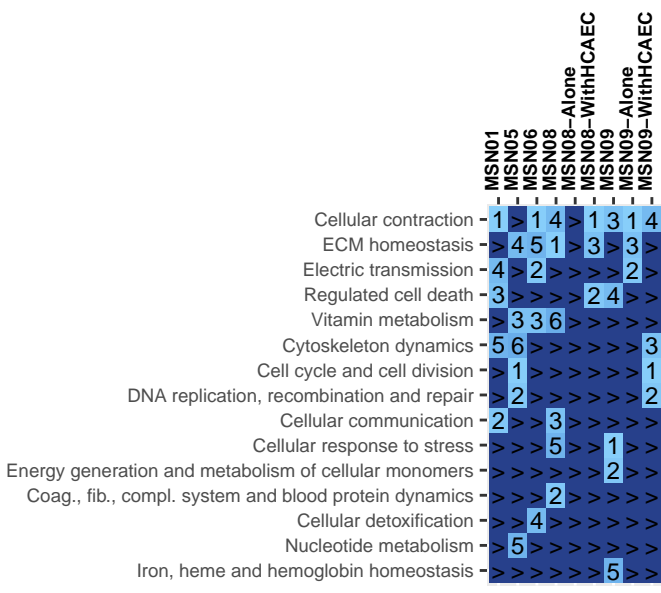
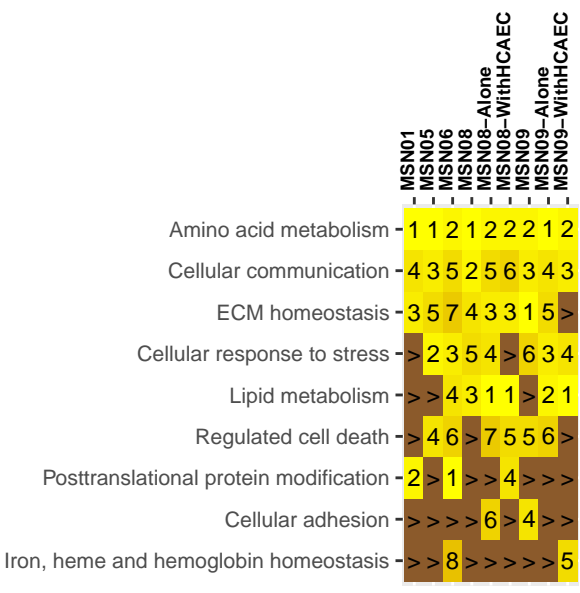
Supplementary Figure 17. F1 score and Area under the Curve statistics. At each significance rank cutoff we counted how many cardiotoxic or non-cardiotoxic TKIs up- or down-regulate a particular SCP with a significance rank below or equal to the current cutoff. Results were used to calculate precision, recall and F1 score (beta = 0.2) of each SCP at each rank to be either up- or downregulated by either the cardiotoxic or noncardiotoxic drugs. Shown are the results for the SCPs that our algorithm selected to be associated with a cardiotoxic or non-cardiotoxic response. See methods for description of the algorithm. Solid lines indicate results for the SCP, if up- (red) or downregulated (dark blue) by cardiotoxic TKIs, dashed lines indicate results for the SCP, if up- (light blue) or downregulated (orange) by non-cardiotoxic TKIs. Color combinations were selected to indicate if the higher (red, orange) or lower (dark blue, light blue) activity of an SCP favors a cardiotoxic response.

MBCOL1 dabrafenib (is c.toxic: yes)

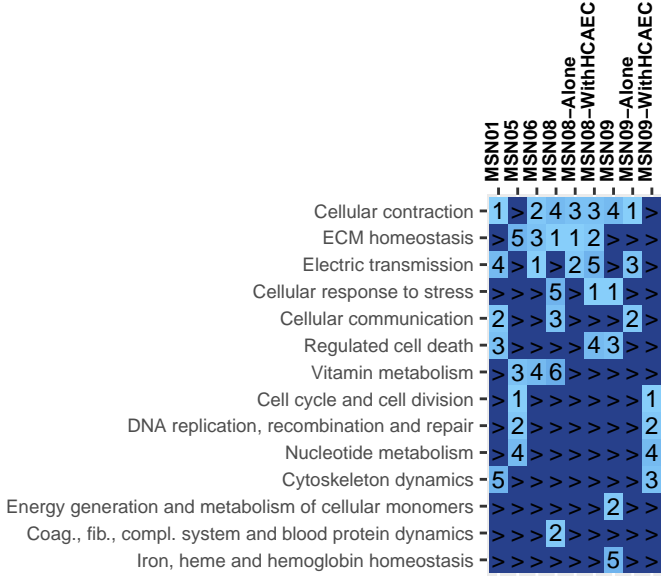
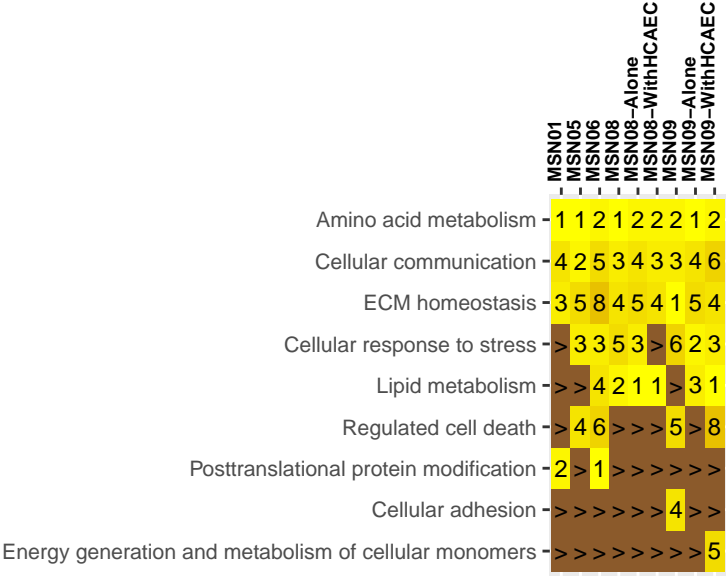
Upregulated

Downregulated

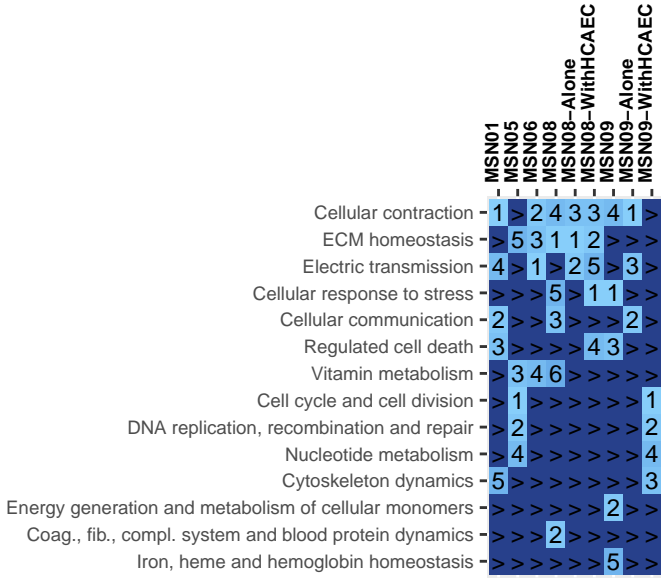
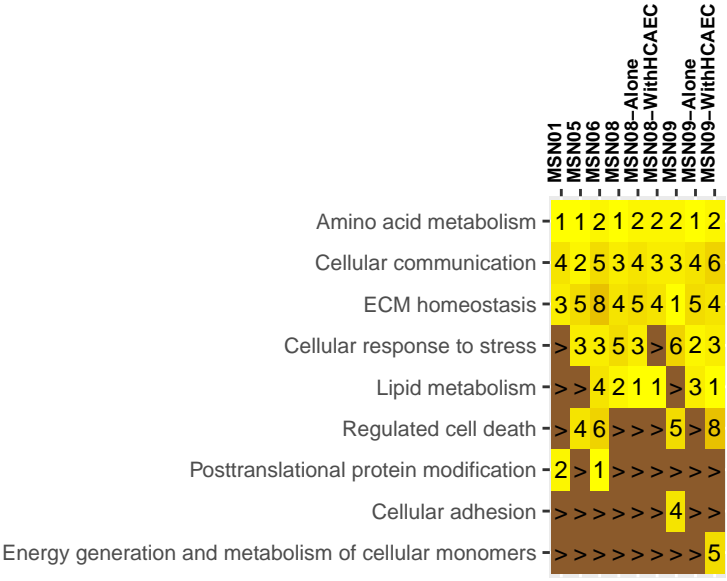
complete



no1stSVD



decomposed



MBCOL1
pazopanib
(is c.toxic: yes)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Lipid metabolism	4	4	1	1	1	1	3	1	1
Energy generation and metabolism of cellular monomers	1	1	4	2	2	2	3	3	3
Amino acid metabolism	2	2	2	3	3	3	2	2	2
Cellular response to stress	3	7	4	7	4	7	4	4	4
Cell cycle and cell division	>	>	>	>	>	>	1	2	1
Nucleotide metabolism	>	>	>	>	>	4	5	3	5
DNA replication, recombination and repair	>	>	>	>	>	>	4	2	2
ECM homeostasis	5	3	>	>	>	>	>	>	>
Cellular redox homeostasis	>	3	>	>	>	>	>	>	>
Electric transmission	>	>	>	4	>	>	>	>	>
Intracellular degradation pathways	>	5	>	>	>	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Cellular communication	1	2	1	1	3	4	2	2	4
Cellular adhesion	2	3	4	4	2	6	4	4	7
ECM homeostasis	>	1	2	2	1	1	5	1	1
Cellular response to stress	3	6	6	>	>	2	1	3	2
Cellular contraction	>	>	>	5	4	5	3	5	5
Cytoskeleton dynamics	>	7	3	>	>	7	>	>	>
Energy generation and metabolism of cellular monomers	>	>	>	>	>	3	>	3	3
Electric transmission	>	5	3	>	>	>	>	>	>
Regulated cell death	4	>	>	>	>	6	>	>	>
Amino acid metabolism	>	5	>	>	>	>	>	8	>
Vitamin metabolism	>	4	>	>	>	>	>	>	>

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Lipid metabolism	4	3	1	1	2	2	1	2	>
Energy generation and metabolism of cellular monomers	1	1	4	2	1	3	3	4	>
Amino acid metabolism	2	2	2	3	4	>	2	6	5
Cellular response to stress	3	7	4	3	7	4	5	5	>
Cell cycle and cell division	>	>	>	>	1	>	1	1	>
DNA replication, recombination and repair	>	>	>	>	4	>	3	2	>
ECM homeostasis	>	3	>	>	>	4	>	>	>
Cellular redox homeostasis	5	4	>	>	>	>	>	>	>
Cellular contraction	7	>	>	5	>	>	>	>	>
Nucleotide metabolism	>	>	>	>	>	>	3	>	>
Cytoskeleton dynamics	>	>	>	>	>	>	4	>	>
Vitamin metabolism	>	5	>	>	>	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Cellular communication	1	2	1	1	2	4	2	2	5
ECM homeostasis	>	1	2	2	1	1	5	1	1
Cellular response to stress	2	6	6	>	>	2	1	3	2
Regulated cell death	3	>	5	5	4	5	8	8	8
Cellular contraction	>	>	6	4	3	3	4	4	4
Cellular adhesion	4	3	5	4	3	>	7	>	>
Cytoskeleton dynamics	>	7	4	7	6	7	>	7	>
Amino acid metabolism	>	5	>	>	>	>	6	6	6
Electric transmission	>	3	3	>	>	>	>	>	>
Energy generation and metabolism of cellular monomers	>	>	>	>	6	>	3	3	3
Vitamin metabolism	>	4	>	>	>	>	8	8	8

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Lipid metabolism	4	3	1	1	2	2	1	2	>
Energy generation and metabolism of cellular monomers	1	1	4	2	1	3	3	4	>
Amino acid metabolism	2	2	2	3	4	>	2	6	5
Cellular response to stress	3	7	4	3	7	4	5	5	>
Cell cycle and cell division	>	>	>	>	1	>	1	1	>
DNA replication, recombination and repair	>	>	>	>	4	>	3	2	>
ECM homeostasis	>	3	>	>	>	4	>	>	>
Cellular redox homeostasis	5	4	>	>	>	>	>	>	>
Cellular contraction	7	>	>	5	>	>	>	>	>
Nucleotide metabolism	>	>	>	>	>	>	3	>	>
Cytoskeleton dynamics	>	>	>	>	>	>	4	>	>
Vitamin metabolism	>	5	>	>	>	>	>	>	>

	MSN01	MSN05	MSN06	MSN08	MSN08- Alone	MSN08- WithHCAEC	MSN09	MSN09- Alone	MSN09- WithHCAEC
Cellular communication	1	2	1	1	2	4	2	2	5
ECM homeostasis	>	1	2	2	1	1	5	1	1
Cellular response to stress	2	6	6	>	>	2	1	3	2
Regulated cell death	3	>	5	5	4	5	8	8	8
Cellular contraction	>	>	6	4	3	3	4	4	4
Cellular adhesion	4	3	5	4	3	>	7	>	>
Cytoskeleton dynamics	>	7	4	7	6	7	>	7	>
Amino acid metabolism	>	5	>	>	>	>	6	6	6
Electric transmission	>	3	3	>	>	>	>	>	>
Energy generation and metabolism of cellular monomers	>	>	>	>	6	>	3	3	3
Vitamin metabolism	>	4	>	>	>	>	8	8	8

MBCOL2 dabrafenib (is c.toxic: yes)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Metabolism of non-essential amino acids	1	1	2	1	2	1	1	1	2
Cellular response to oxidative stress	6	2	4	10	1	1	9	4	3
Apoptosis	3	6	12	8	6	6	5	4	3
Metabolism and transport of cholesterol, steroids and bile acids	v	v	v	v	1	2	v	v	v
Matricellular protein signaling	v	7	5	3	4	1	v	5	1
Cellular response to hypoxia	v	6	11	6	3	2	v	8	5
Signaling pathways involved in hematopoiesis	8	5	8	7	9	7	v	9	v
Sig. pathways that control cell prol. and diff.	v	8	3	6	4	2	v	7	v
Signaling pathways regulating water homeostasis	v	9	13	5	5	7	v	7	v
Glycosaminoglycan metabolism	v	v	v	6	11	4	v	v	v
PT protein modification and QC during secretory pathway	2	1	v	v	3	v	v	v	v
ECM breakdown	v	4	v	v	6	3	v	v	v
Fatty acid metabolism	v	v	v	v	10	5	v	v	4
Signaling by extracellular matrix components	v	v	v	4	v	v	v	6	10
Collagen biosynthesis	3	7	v	v	v	v	v	v	v
Intracellular common signaling cascades of multiple pathways	5	10	v	v	v	v	v	v	v
Basement membrane dynamics	4	v	v	v	v	v	v	v	v
Neuronal signaling pathways	v	v	5	v	v	v	v	v	v

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Myofibril formation and organization	2	4	1	6	v	1	3	1	11
Cardiomyocyte action potential generation and propagation	v	v	v	v	v	v	v	v	v
Metabolism of fat-soluble vitamins	5	6	4	5	v	v	v	v	v
Apoptosis	10	4	2	v	v	v	v	v	v
Centrosome cycle	v	v	v	v	v	v	v	v	v
ECM breakdown	v	1	9	v	v	v	v	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	v	v	v	v
Cellular response to hypoxia	v	v	v	v	v	v	v	v	v
Eukaryotic DNA replication	v	2	v	v	v	v	v	1	v
Epidermal growth factor family signaling	1	v	v	v	v	v	v	v	v
Basement membrane dynamics	v	v	v	v	v	v	v	v	v
Mitotic cell cycle checkpoints	v	3	v	v	v	v	v	v	v
Thyroid hormone related signaling	7	v	v	v	v	2	v	v	v
Matricellular protein signaling	v	5	7	3	v	v	v	v	v
Cytokinesis	v	v	v	v	v	v	v	v	v
Collagen biosynthesis	3	v	9	7	v	v	v	v	v
Elastogenesis	v	v	v	v	v	5	v	v	v
Complement pathway and regulation	v	v	1	v	v	v	v	v	v
Carbohydrate metabolism and transport	v	v	v	v	v	v	2	v	v
Neuronal action potential generation and propagation	v	v	v	v	v	v	v	4	v
Fatty acid metabolism	v	v	v	v	v	v	v	v	v
Metabolism of tryptophan products	v	v	5	v	v	v	v	v	v

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Metabolism of non-essential amino acids	1	1	2	1	2	1	1	1	2
Cellular response to oxidative stress	8	2	4	11	1	2	4	3	2
Matricellular protein signaling	v	7	4	6	6	7	v	6	3
Signaling pathways involved in hematopoiesis	10	5	3	8	11	9	v	v	v
Metabolism and transport of cholesterol, steroids and bile acids	v	v	v	v	1	1	v	v	1
Cellular response to hypoxia	v	8	10	10	3	1	v	5	3
ECM breakdown	4	4	v	v	7	8	6	v	13
Collagen biosynthesis	3	v	7	v	v	12	6	v	5
Sig. pathways that control cell prol. and diff.	v	9	11	v	5	10	2	v	7
Fatty acid metabolism	v	v	v	v	4	3	v	v	v
Apoptosis	v	3	5	v	v	v	9	v	9
Signaling by extracellular matrix components	v	v	v	v	8	v	v	4	11
Glycosaminoglycan metabolism	v	v	v	v	11	3	v	v	v
Neuronal signaling pathways	v	v	v	v	v	v	10	9	v
PT protein modification and QC during secretory pathway	5	1	v	v	v	v	v	v	v
Actin filament dynamics	5	v	v	v	v	v	5	v	v
Carbohydrate metabolism and transport	v	v	v	v	9	v	v	v	4
Signaling pathways regulating cardiovascular homeostasis	v	v	v	v	v	4	v	v	v
Steroid hormone metabolism	v	v	v	v	v	5	v	v	v

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Myofibril formation and organization	v	v	v	v	v	v	v	v	v
Cardiomyocyte action potential generation and propagation	v	v	v	v	v	v	v	v	v
Metabolism of fat-soluble vitamins	v	v	4	5	v	v	v	v	v
ECM breakdown	10	v	v	v	v	v	v	v	v
Cellular response to hypoxia	v	6	v	v	v	v	v	v	v
Thyroid hormone related signaling	v	v	v	v	v	v	v	v	v
Epidermal growth factor family signaling	v	v	v	v	v	v	v	v	v
Apoptosis	5	v	v	v	v	v	v	v	v
Collagen biosynthesis	v	v	v	v	v	v	v	v	v
Elastogenesis	v	v	8	v	4	v	v	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	v	v	v	v
Eukaryotic DNA replication	v	2	v	v	v	v	v	v	v
Basement membrane dynamics	v	v	v	v	v	v	v	v	v
Mitotic cell cycle checkpoints	v	v	v	v	v	v	v	v	v
Centrosome cycle	v	v	v	v	v	v	v	v	v
Cytokinesis	v	v	v	v	v	v	v	v	v
Matricellular protein signaling	v	7	v	3	v	v	v	v	v
Actin filament dynamics	v	v	v	v	v	v	v	v	v
Carbohydrate metabolism and transport	v	v	v	v	v	v	v	v	v
Complement pathway and regulation	v	v	1	v	v	v	v	v	v
Neuronal action potential generation and propagation	v	v	v	v	v	v	v	v	v
Metabolism of tryptophan products	v	v	5	v	v	v	v	v	v

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Metabolism of non-essential amino acids	1	1	2	1	2	1	1	1	2
Cellular response to oxidative stress	8	2	4	11	1	2	4	3	2
Matricellular protein signaling	v	7	4	6	6	7	v	6	3
Signaling pathways involved in hematopoiesis	10	5	3	8	11	9	v	v	v
Metabolism and transport of cholesterol, steroids and bile acids	v	v	v	v	1	1	v	v	1
Cellular response to hypoxia	v	8	10	10	3	1	v	5	3
ECM breakdown	4	4	v	v	7	8	6	v	13
Collagen biosynthesis	3	v	7	v	v	12	6	v	5
Sig. pathways that control cell prol. and diff.	v	9	11	v	5	10	2	v	7
Fatty acid metabolism	v	v	v	v	4	3	v	v	v
Apoptosis	v	3	5	v	v	v	9	v	9
Signaling by extracellular matrix components	v	v	v	v	8	v	v	4	11
Glycosaminoglycan metabolism	v	v	v	v	11	3	v	v	v
Neuronal signaling pathways	v	v	v	v	v	v	10	9	v
PT protein modification and QC during secretory pathway	5	1	v	v	v	v	v	v	v
Actin filament dynamics	5	v	v	v	v	v	5	v	v
Carbohydrate metabolism and transport	v	v	v	v	9	v	v	v	4
Signaling pathways regulating cardiovascular homeostasis	v	v	v	v	v	4	v	v	v
Steroid hormone metabolism	v	v	v	v	v	5	v	v	v

	MSN01	MSN05	MSN06	MSN08	MSN08- -Alone	MSN08- -WithHCAEC	MSN09	MSN09- -Alone	MSN09- -WithHCAEC
Myofibril formation and organization	v	v	v	v	v	v	v	v	v
Cardiomyocyte action potential generation and propagation	v	v	v	v	v	v	v	v	v
Metabolism of fat-soluble vitamins	v	v	4	5	v	v	v	v	v
ECM breakdown	10	v	v	v	v	v	v	v	v
Cellular response to hypoxia	v	6	v	v	v	v	v	v	v
Thyroid hormone related signaling	v	v	v	v	v	v	v	v	v
Epidermal growth factor family signaling	v	v	v	v	v	v	v	v	v
Apoptosis	5	v	v	v	v	v	v	v	v
Collagen biosynthesis	v	v	v	v	v	v	v	v	v
Elastogenesis	v	v	8	v	4	v	v	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	v	v	v	v
Eukaryotic DNA replication	v	2	v	v	v	v	v	v	v
Basement membrane dynamics	v	v	v	v	v	v	v	v	v
Mitotic cell cycle checkpoints	v	v	v	v	v	v	v	v	v
Centrosome cycle	v	v	v	v	v	v	v	v	v
Cytokinesis	v	v	v	v	v	v	v	v	v
Matricellular protein signaling	v	7	v	3	v	v	v	v	v
Actin filament dynamics	v	v	v	v	v	v	v	v	v
Carbohydrate metabolism and transport	v	v	v	v	v	v	v	v	v
Complement pathway and regulation	v	v	1	v	v	v	v	v	v
Neuronal action potential generation and propagation	v	v	v	v	v	v	v	v	v
Metabolism of tryptophan products	v	v	5	v	v	v	v	v	v

MBCOL2 pazopanib (is c.toxic: yes)

Upregulated

Downregulated

complete

	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Fatty acid metabolism	11	6	6	1	1	2	3	3	v
Mitochondrial energy production	1	1	8	4	2	3	v	v	v
Carbohydrate metabolism and transport	3	4	10	3	4	v	4	8	v
Metabolism and transport of cholesterol, steroids and bile acids	8	v	2	5	4	v	1	1	v
Metabolism of non-essential amino acids	2	2	1	2	v	v	2	v	v
PT protein modification in mitochondria	4	5	11	6	v	v	5	v	v
Triacylglycerol metabolism and transport	v	7	v	v	3	4	10	10	v
Degradation by lysosomal enzymes	5	v	4	v	7	v	8	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	1	v	2	1
DNA interstrand cross-links repair	v	v	v	v	v	7	v	5	3
Centrosome cycle	v	v	v	v	v	6	v	6	4
Ammonium metabolism	9	v	5	8	v	v	v	v	v
Metabolism of purines and pyrimidines	v	v	v	v	v	5	v	9	9
Mitotic cell cycle checkpoints	v	v	v	v	v	8	v	11	5
Eukaryotic DNA replication	v	v	v	v	v	v	v	v	2
Collagen biosynthesis	v	v	3	v	v	v	v	v	v
Cellular antioxidant systems	v	3	v	v	v	v	v	v	v

	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Sig. pathways that control cell prol. and diff.	1	4	1	7	4	10	3	4	5
ECM breakdown	6	3	4	5	5	7	10	6	6
Cellular response to hypoxia	v	11	6	14	v	1	1	3	1
Matricellular protein signaling	v	1	v	13	9	6	4	2	7
Cell-cell adhesion	2	6	3	12	6	v	6	11	v
Collagen biosynthesis	v	2	v	1	1	2	v	1	3
Myofibril formation and organization	v	v	v	8	13	8	2	13	4
Elastogenesis	v	5	v	v	7	4	v	5	11
Basement membrane dynamics	v	v	v	v	2	5	v	10	9
Cardiomyocyte action potential generation and propagation	v	v	5	4	10	v	12	v	v
Cellular response to radiation	3	9	v	v	v	v	v	8	16
Apoptosis	5	v	v	v	14	v	5	20	v
Neuronal signaling pathways	v	v	2	v	3	v	v	15	v
Carbohydrate metabolism and transport	v	v	v	v	v	3	v	17	2
TGF-beta superfamily signaling	v	v	v	2	v	v	v	7	v
Epidermal growth factor family signaling	4	v	v	9	v	v	v	v	v
Signaling by extracellular matrix components	v	v	v	4	v	v	12	v	v

no1stSVD

	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Fatty acid metabolism	12	4	5	1	2	4	3	6	v
Mitochondrial energy production	1	1	8	2	1	10	8	9	v
Metabolism and transport of cholesterol, steroids and bile acids	9	v	1	5	3	6	1	2	v
Metabolism of non-essential amino acids	3	2	2	3	8	v	2	v	11
Carbohydrate metabolism and transport	2	3	11	4	6	v	4	10	v
Triacylglycerol metabolism and transport	v	7	v	v	4	8	10	11	16
PT protein modification in mitochondria	4	6	10	6	v	v	5	v	v
Cellular response to hypoxia	6	v	v	10	5	v	11	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	1	v	1	1
Mitotic cell cycle checkpoints	v	v	v	v	v	2	v	5	5
Cytokinesis	v	v	v	v	v	3	v	3	3
Centrosome cycle	v	v	v	v	v	7	v	7	4
DNA interstrand cross-links repair	v	v	v	v	v	5	v	4	6
Degradation by lysosomal enzymes	5	v	4	v	v	v	8	v	v
Cellular antioxidant systems	v	7	5	v	v	v	v	v	v
Eukaryotic DNA replication	v	v	v	v	v	12	v	v	2
Collagen biosynthesis	v	v	3	v	v	v	v	v	v

	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Sig. pathways that control cell prol. and diff.	1	4	1	4	2	5	3	5	12
ECM breakdown	v	3	3	2	1	6	6	6	6
Matricellular protein signaling	v	1	v	11	4	10	2	3	4
Cellular response to hypoxia	v	12	6	15	v	1	1	2	1
Apoptosis	5	v	v	10	11	7	5	10	18
Collagen biosynthesis	v	2	v	7	3	3	v	1	2
Myofibril formation and organization	v	v	v	13	9	2	4	8	5
Signaling pathways involved in hematopoiesis	3	7	10	3	7	v	v	18	v
Cellular response to radiation	2	9	v	v	16	11	v	7	13
Elastogenesis	v	6	v	v	5	12	v	4	8
Cell-cell adhesion	6	5	7	8	v	v	v	v	v
Cardiomyocyte action potential generation and propagation	v	v	5	1	17	v	9	v	v
Epidermal growth factor family signaling	4	v	v	6	13	14	v	v	v
Neuronal signaling pathways	v	v	2	v	8	9	v	v	v
Carbohydrate metabolism and transport	v	v	v	v	v	4	v	16	3
Microtubule dynamics	v	v	4	12	v	v	v	v	v
TGF-beta superfamily signaling	v	v	v	5	v	v	v	v	v

decomposed

	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Fatty acid metabolism	12	4	5	1	2	4	3	6	v
Mitochondrial energy production	1	1	8	2	1	10	8	9	v
Metabolism and transport of cholesterol, steroids and bile acids	9	v	1	5	3	6	1	2	v
Metabolism of non-essential amino acids	3	2	2	3	8	v	2	v	11
Carbohydrate metabolism and transport	2	3	11	4	6	v	4	10	v
Triacylglycerol metabolism and transport	v	7	v	v	4	8	10	11	16
PT protein modification in mitochondria	4	6	10	6	v	v	5	v	v
Cellular response to hypoxia	6	v	v	10	5	v	11	v	v
Chromosome segregation by mitotic spindle	v	v	v	v	v	1	v	1	1
Mitotic cell cycle checkpoints	v	v	v	v	v	2	v	5	5
Cytokinesis	v	v	v	v	v	3	v	3	3
Centrosome cycle	v	v	v	v	v	7	v	7	4
DNA interstrand cross-links repair	v	v	v	v	v	5	v	4	6
Degradation by lysosomal enzymes	5	v	4	v	v	v	8	v	v
Cellular antioxidant systems	v	7	5	v	v	v	v	v	v
Eukaryotic DNA replication	v	v	v	v	v	12	v	v	2
Collagen biosynthesis	v	v	3	v	v	v	v	v	v

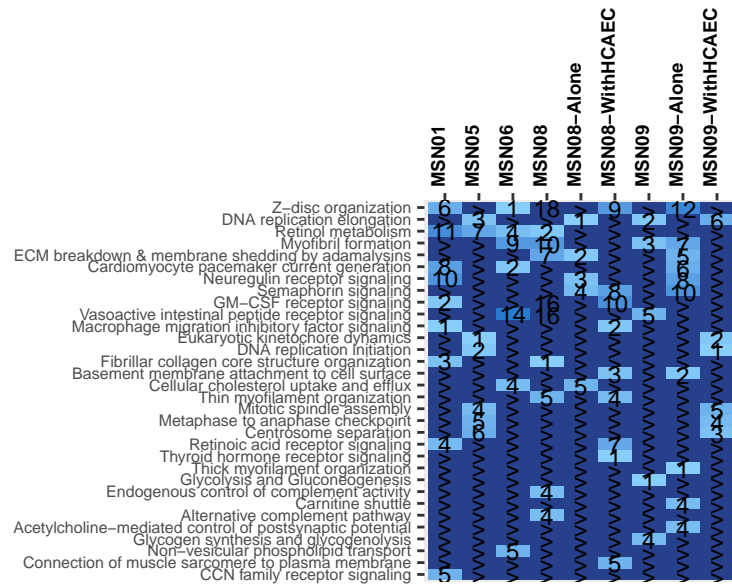
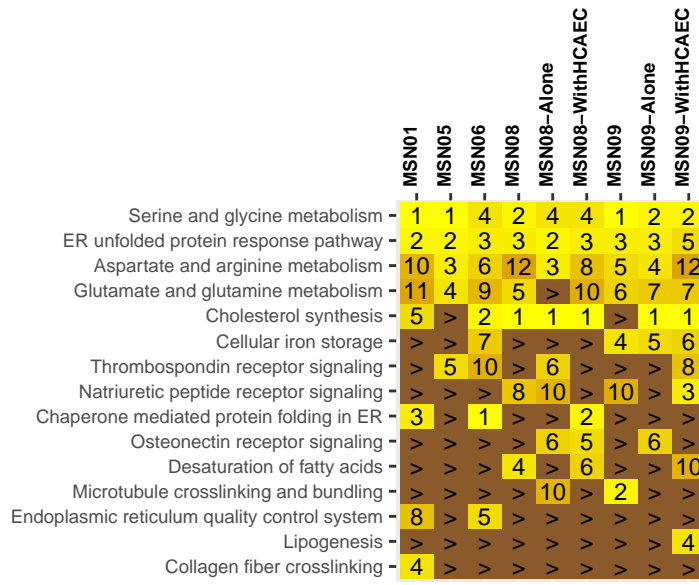
	MSN01	MSN05	MSN06	MSN08	MSN08-Along	MSN08-WithHCAEC	MSN09	MSN09-Along	MSN09-WithHCAEC
Sig. pathways that control cell prol. and diff.	1	4	1	4	2	5	3	5	12
ECM breakdown	v	3	3	2	1	6	6	6	6
Matricellular protein signaling	v	1	v	11	4	10	2	3	4
Cellular response to hypoxia	v	12	6	15	v	1	1	2	1
Apoptosis	5	v	v	10	11	7	5	10	18
Collagen biosynthesis	v	2	v	7	3	3	v	1	2
Myofibril formation and organization	v	v	v	13	9	2	4	8	5
Signaling pathways involved in hematopoiesis	3	7	10	3	7	v	v	18	v
Cellular response to radiation	2	9	v	v	16	11	v	7	13
Elastogenesis	v	6	v	v	5	12	v	4	8
Cell-cell adhesion	6	5	7	8	v	v	v	v	v
Cardiomyocyte action potential generation and propagation	v	v	5	1	17	v	9	v	v
Epidermal growth factor family signaling	4	v	v	6	13	14	v	v	v
Neuronal signaling pathways	v	v	2	v	8	9	v	v	v
Carbohydrate metabolism and transport	v	v	v	v	v	4	v	16	3
Microtubule dynamics	v	v	4	12	v	v	v	v	v
TGF-beta superfamily signaling	v	v	v	5	v	v	v	v	v

MBCOL3 dabrafenib (is c.toxic: yes)

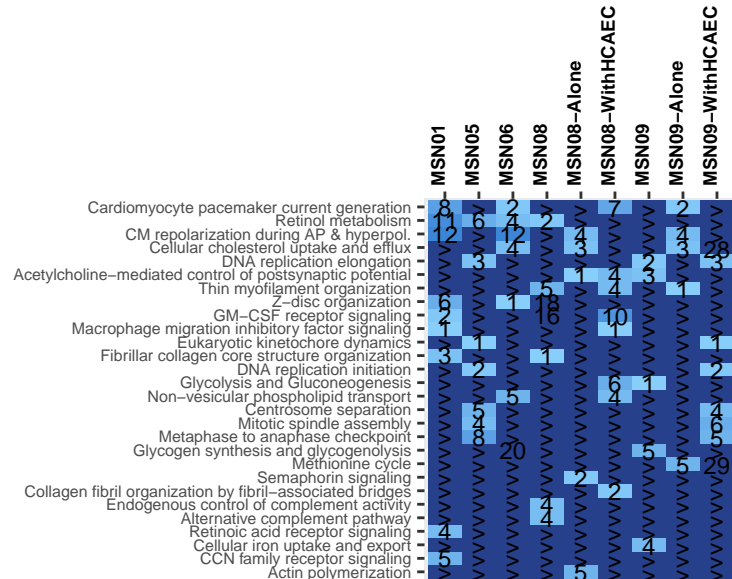
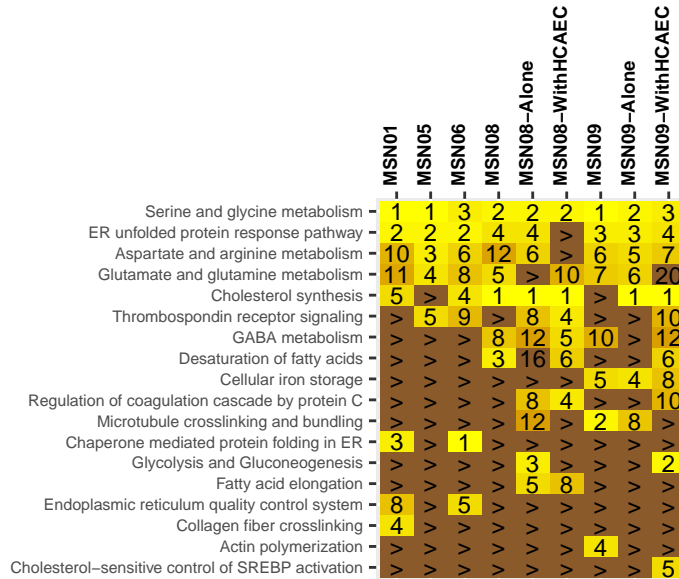
Upregulated

Downregulated

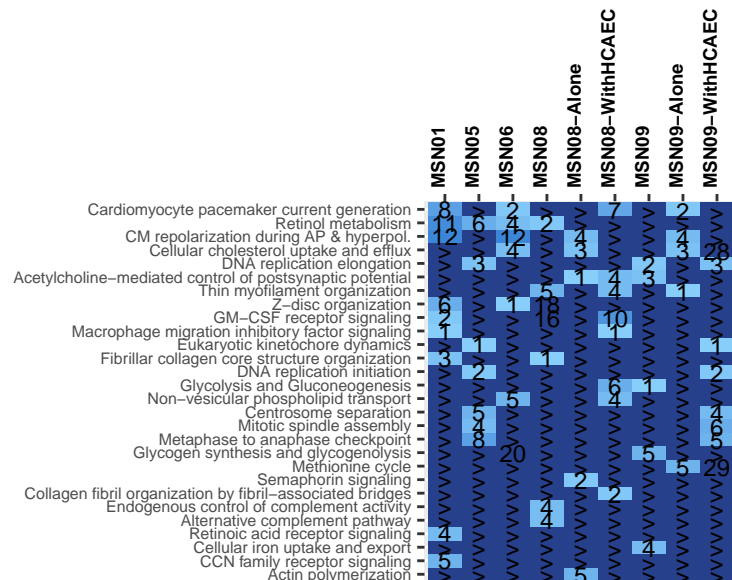
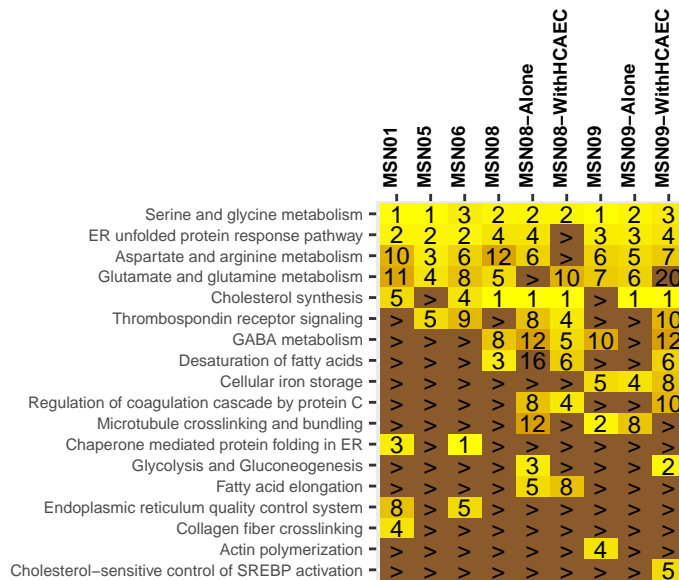
complete



no1stSVD



decomposed

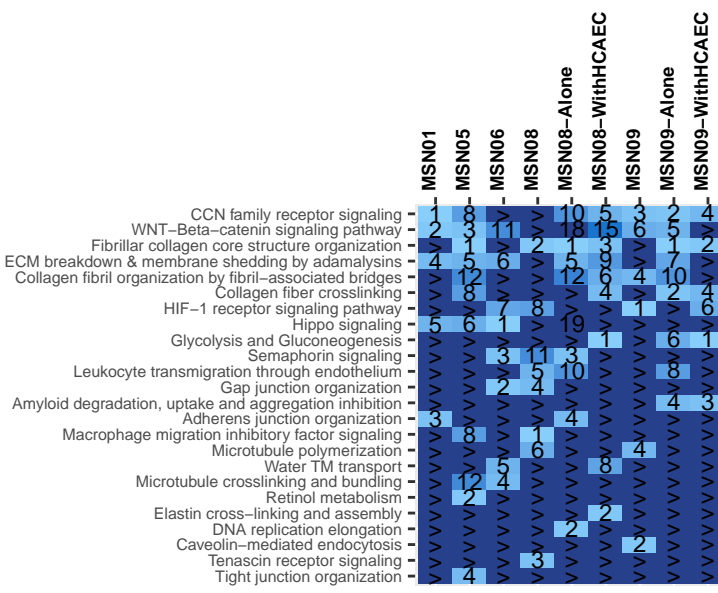
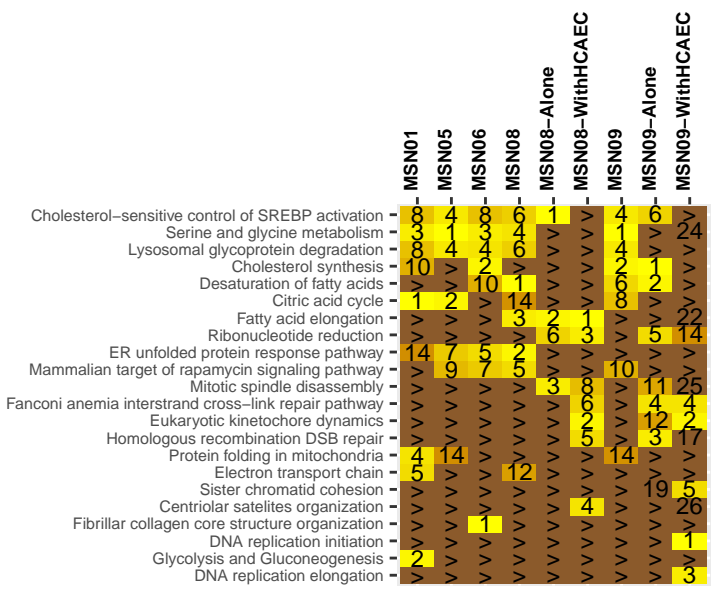


**MBCOL3
pazopanib
(is c.toxic: yes)**

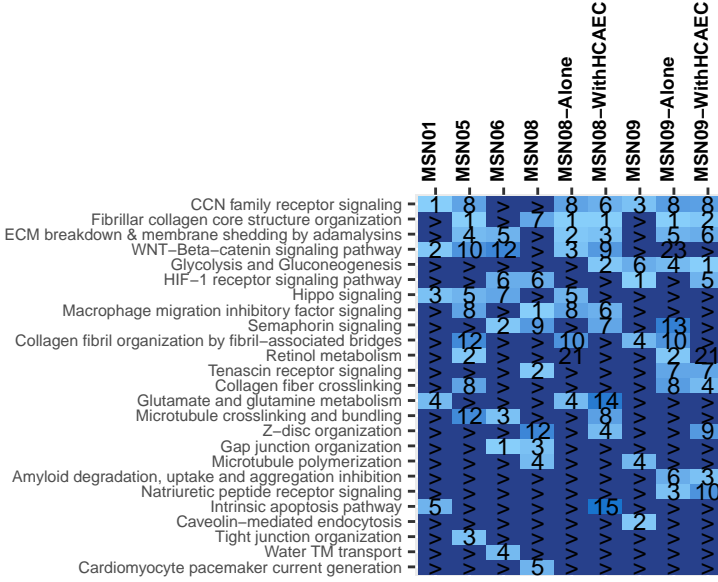
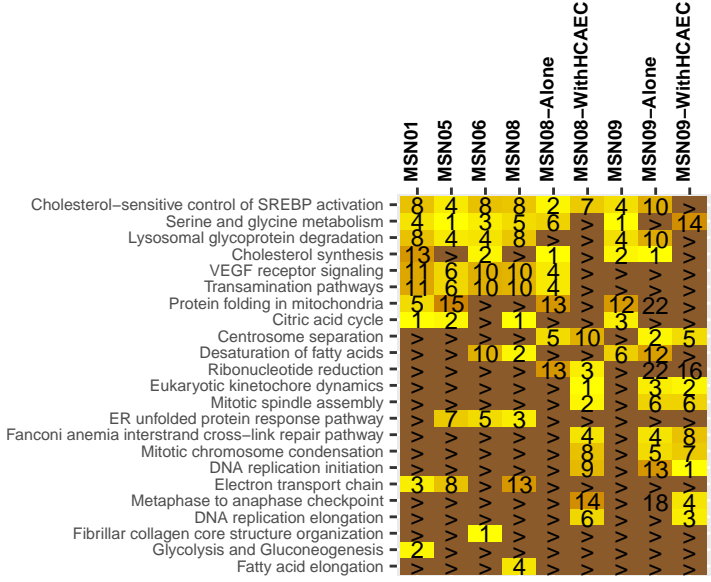
Upregulated

Downregulated

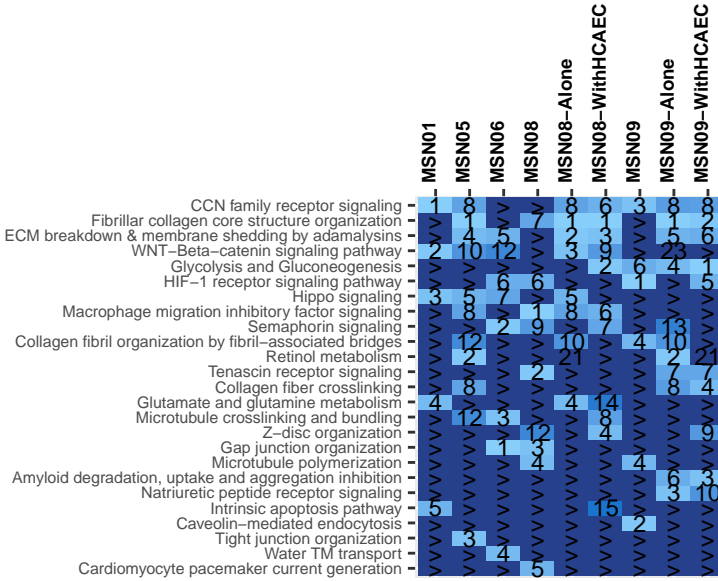
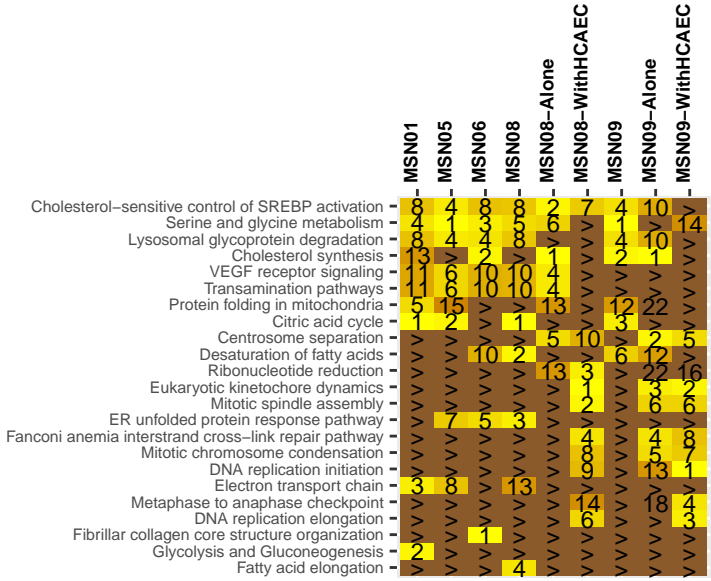
complete



no1stSVD



decomposed

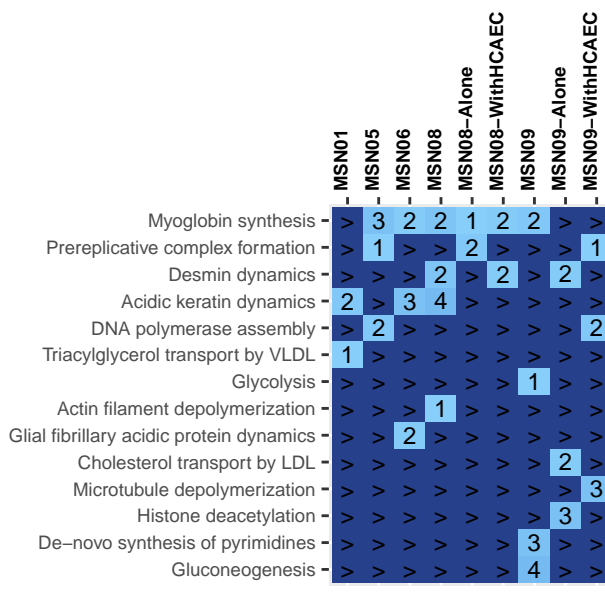
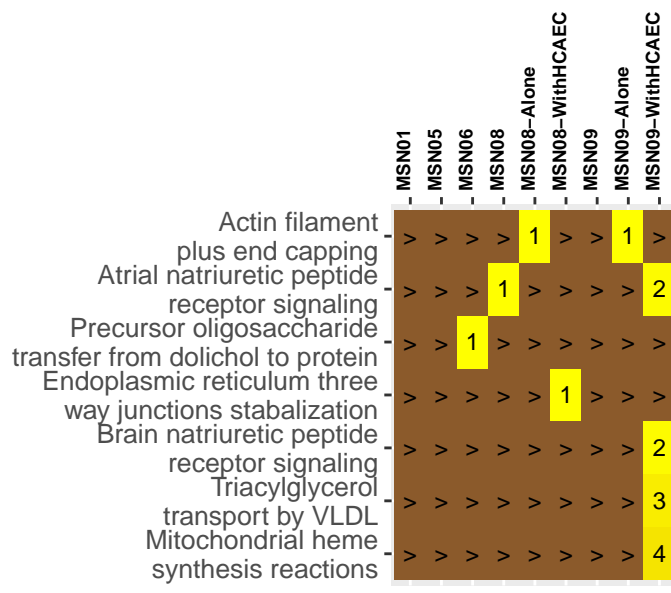


MBCOL4 dabrafenib (is c.toxic: yes)

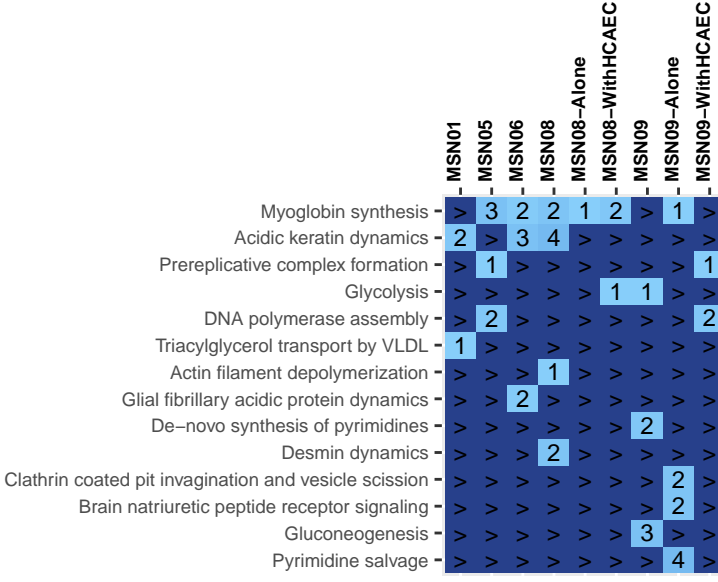
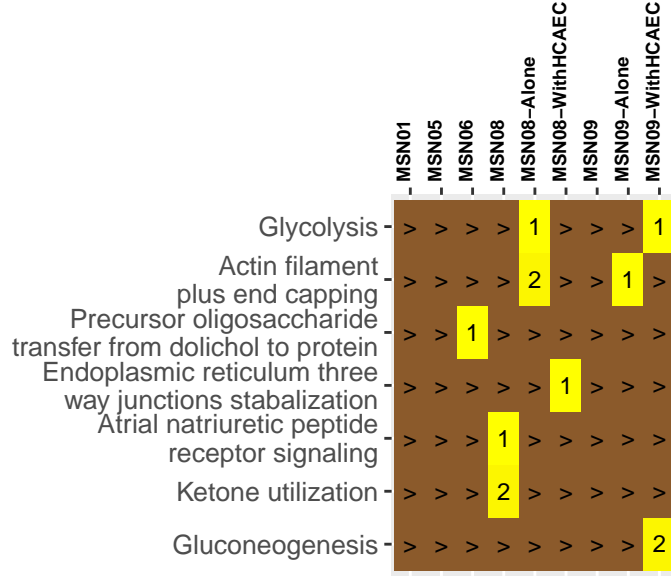
Upregulated

Downregulated

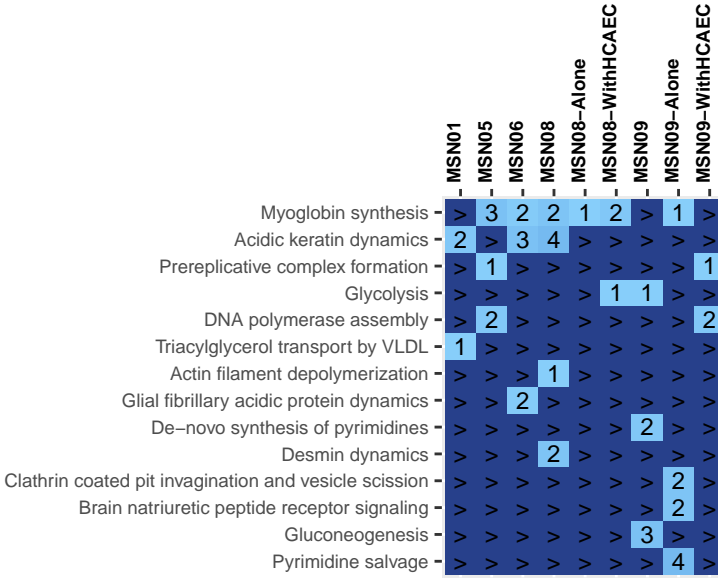
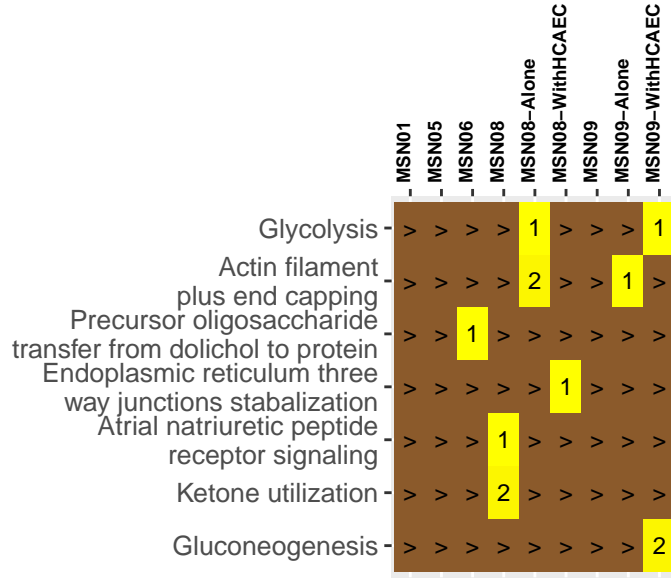
complete



no1stSVD



decomposed

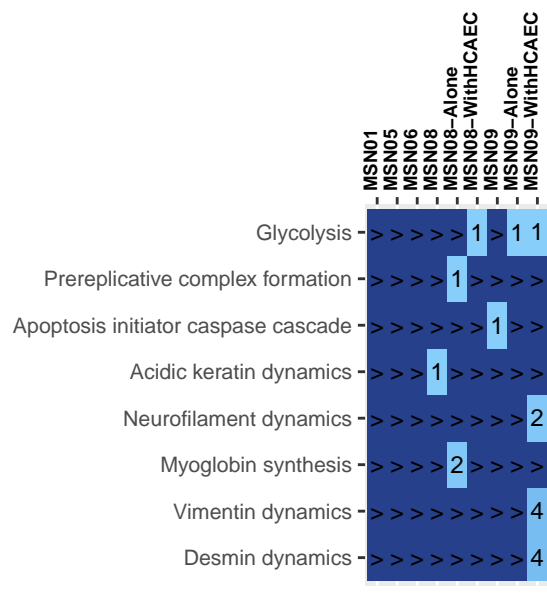
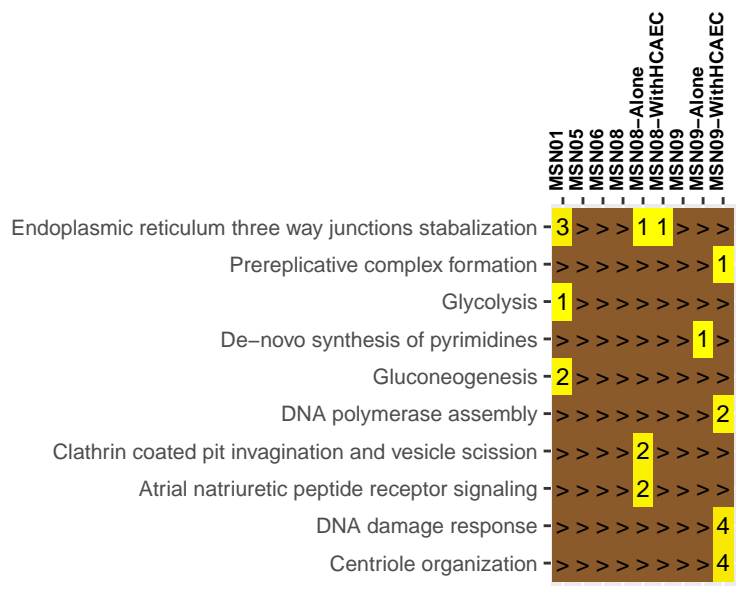


MBCOL4
pazopanib
(is c.toxic: yes)

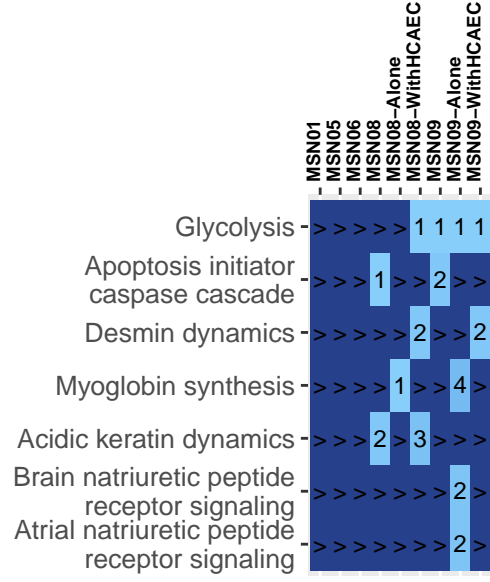
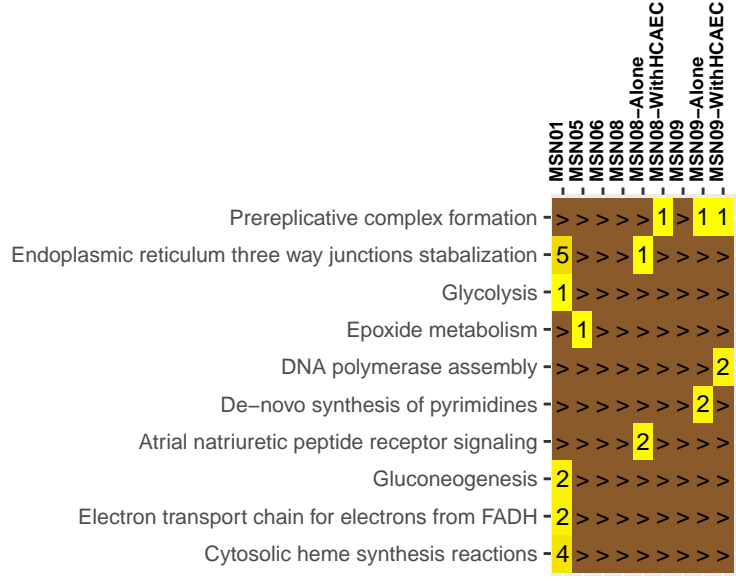
Upregulated

Downregulated

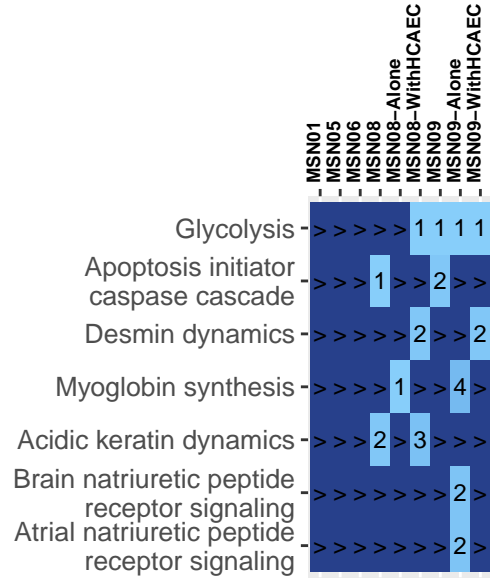
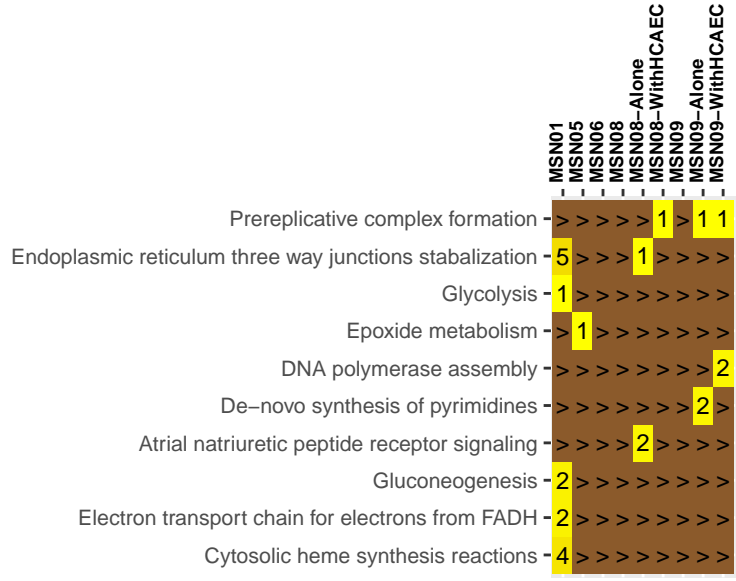
complete



no1stSVD



decomposed



Supplementary Figure 29. Top Subcellular Processes predicted from complete gene expression profiles, after removal of first eigenarray and from drug-selective gene expression profiles of all dabrafenib or pazopanib-treated samples. **(A)** Complete, decomposed gene expression profiles and gene expression profiles after removal of the first eigenarray of the original and new dabrafenib or pazopanib treated samples were subjected to pathway enrichment analysis using the Molecular Biology of the Cell Ontology and Fisher's Exact Test to identify up- and downregulated subcellular processes (SCPs). Significant up- or downregulated **(B)** level-1, **(C)** -2, **(D)** -3 and **(E)** -4 SCPs (pvalue ≤ 0.05) were separately ranked by significance for each cell line/drug combination. SCPs predicted for each drug are shown if they are among the top five ranked SCPs for at least one cell line. Numbers indicate ranks, '>' indicates that an SCP was not predicted or predicted with a rank above 99. 'Alone' and 'With HCAEC' label additional datasets obtained without or with endothelial cell cocultures, respectively. Results for the original samples are also shown in Supplemental figure 14.

- 100 Herrmann, J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev*
Cardiol **17**, 474-502 (2020). <https://doi.org/10.1038/s41569-020-0348-1>
- 101 Gammella, E., Maccarinelli, F., Buratti, P., Recalcatti, S. & Cairo, G. The role of iron in
anthracycline cardiotoxicity. *Front Pharmacol* **5**, 25 (2014).
<https://doi.org/10.3389/fphar.2014.00025>
- 102 Cole, D. C. & Frishman, W. H. Cardiovascular Complications of Proteasome Inhibitors Used in
Multiple Myeloma. *Cardiol Rev* **26**, 122-129 (2018).
<https://doi.org/10.1097/CRD.000000000000183>
- 103 Fabarius, A. *et al.* Centrosome aberrations after nilotinib and imatinib treatment in vitro are
associated with mitotic spindle defects and genetic instability. *Br J Haematol* **138**, 369-373
(2007). <https://doi.org/10.1111/j.1365-2141.2007.06678.x>
- 104 Giehl, M. *et al.* Detection of centrosome aberrations in disease-unrelated cells from patients
with tumor treated with tyrosine kinase inhibitors. *Eur J Haematol* **85**, 139-148 (2010).
<https://doi.org/10.1111/j.1600-0609.2010.01459.x>
- 105 Sethunath, V. *et al.* Targeting the Mevalonate Pathway to Overcome Acquired Anti-HER2
Treatment Resistance in Breast Cancer. *Mol Cancer Res* **17**, 2318-2330 (2019).
<https://doi.org/10.1158/1541-7786.MCR-19-0756>
- 106 Bienengraeber, M. *et al.* ABCC9 mutations identified in human dilated cardiomyopathy disrupt
catalytic KATP channel gating. *Nat Genet* **36**, 382-387 (2004). <https://doi.org/10.1038/ng1329>
- 107 Dupont, E. *et al.* Altered connexin expression in human congestive heart failure. *J Mol Cell*
Cardiol **33**, 359-371 (2001). <https://doi.org/10.1006/jmcc.2000.1308>
- 108 Perea-Gil, I. *et al.* Serine biosynthesis as a novel therapeutic target for dilated cardiomyopathy.
Eur Heart J **43**, 3477-3489 (2022). <https://doi.org/10.1093/eurheartj/ehac305>
- 109 Gorabi, A. M. *et al.* Statins Attenuate Fibrotic Manifestations of Cardiac Tissue Damage. *Curr Mol*
Pharmacol **14**, 782-797 (2021). <https://doi.org/10.2174/1874467214666210210123206>
- 110 Okuyama, H. *et al.* Statins stimulate atherosclerosis and heart failure: pharmacological
mechanisms. *Expert Rev Clin Pharmacol* **8**, 189-199 (2015).
<https://doi.org/10.1586/17512433.2015.1011125>
- 111 Rotariu, D. *et al.* Oxidative stress - Complex pathological issues concerning the hallmark of
cardiovascular and metabolic disorders. *Biomed Pharmacother* **152**, 113238 (2022).
<https://doi.org/10.1016/j.biopha.2022.113238>
- 112 Groenendyk, J., Sreenivasaiah, P. K., Kim, D. H., Agellon, L. B. & Michalak, M. Biology of
endoplasmic reticulum stress in the heart. *Circ Res* **107**, 1185-1197 (2010).
<https://doi.org/10.1161/CIRCRESAHA.110.227033>
- 113 Medamana, J., Clark, R. A. & Butler, J. Platelet-Derived Growth Factor in Heart Failure. *Handb*
Exp Pharmacol **243**, 355-369 (2017). https://doi.org/10.1007/164_2016_80
- 114 Cheng, M., Park, H., Engelmayer, G. C., Moretti, M. & Freed, L. E. Effects of regulatory factors on
engineered cardiac tissue in vitro. *Tissue Eng* **13**, 2709-2719 (2007).
<https://doi.org/10.1089/ten.2006.0414>
- 115 Vantler, M. *et al.* PDGF-BB protects cardiomyocytes from apoptosis and improves contractile
function of engineered heart tissue. *J Mol Cell Cardiol* **48**, 1316-1323 (2010).
<https://doi.org/10.1016/j.yjmcc.2010.03.008>
- 116 McGrath, M. F., de Bold, M. L. & de Bold, A. J. The endocrine function of the heart. *Trends*
Endocrinol Metab **16**, 469-477 (2005). <https://doi.org/10.1016/j.tem.2005.10.007>
- 117 Ding, K., Gui, Y., Hou, X., Ye, L. & Wang, L. Transient Receptor Potential Channels, Natriuretic
Peptides, and Angiotensin Receptor-Nephrilysin Inhibitors in Patients With Heart Failure. *Front*
Cardiovasc Med **9**, 904881 (2022). <https://doi.org/10.3389/fcvm.2022.904881>

- 118 Ong, S. G. & Hausenloy, D. J. Hypoxia-inducible factor as a therapeutic target for cardioprotection. *Pharmacol Ther* **136**, 69-81 (2012). <https://doi.org:10.1016/j.pharmthera.2012.07.005>
- 119 Kubin, T. *et al.* The Role of Oncostatin M and Its Receptor Complexes in Cardiomyocyte Protection, Regeneration, and Failure. *Int J Mol Sci* **23** (2022). <https://doi.org:10.3390/ijms23031811>
- 120 Wang, P. *et al.* The alteration of Hippo/YAP signaling in the development of hypertrophic cardiomyopathy. *Basic Res Cardiol* **109**, 435 (2014). <https://doi.org:10.1007/s00395-014-0435-8>
- 121 Horn, M. A. & Trafford, A. W. Aging and the cardiac collagen matrix: Novel mediators of fibrotic remodelling. *J Mol Cell Cardiol* **93**, 175-185 (2016). <https://doi.org:10.1016/j.yjmcc.2015.11.005>
- 122 Baiocchi, A. *et al.* Extracellular Matrix Molecular Remodeling in Human Liver Fibrosis Evolution. *PLoS One* **11**, e0151736 (2016). <https://doi.org:10.1371/journal.pone.0151736>
- 123 Shangzu, Z. *et al.* Aquaporins: Important players in the cardiovascular pathophysiology. *Pharmacol Res* **183**, 106363 (2022). <https://doi.org:10.1016/j.phrs.2022.106363>