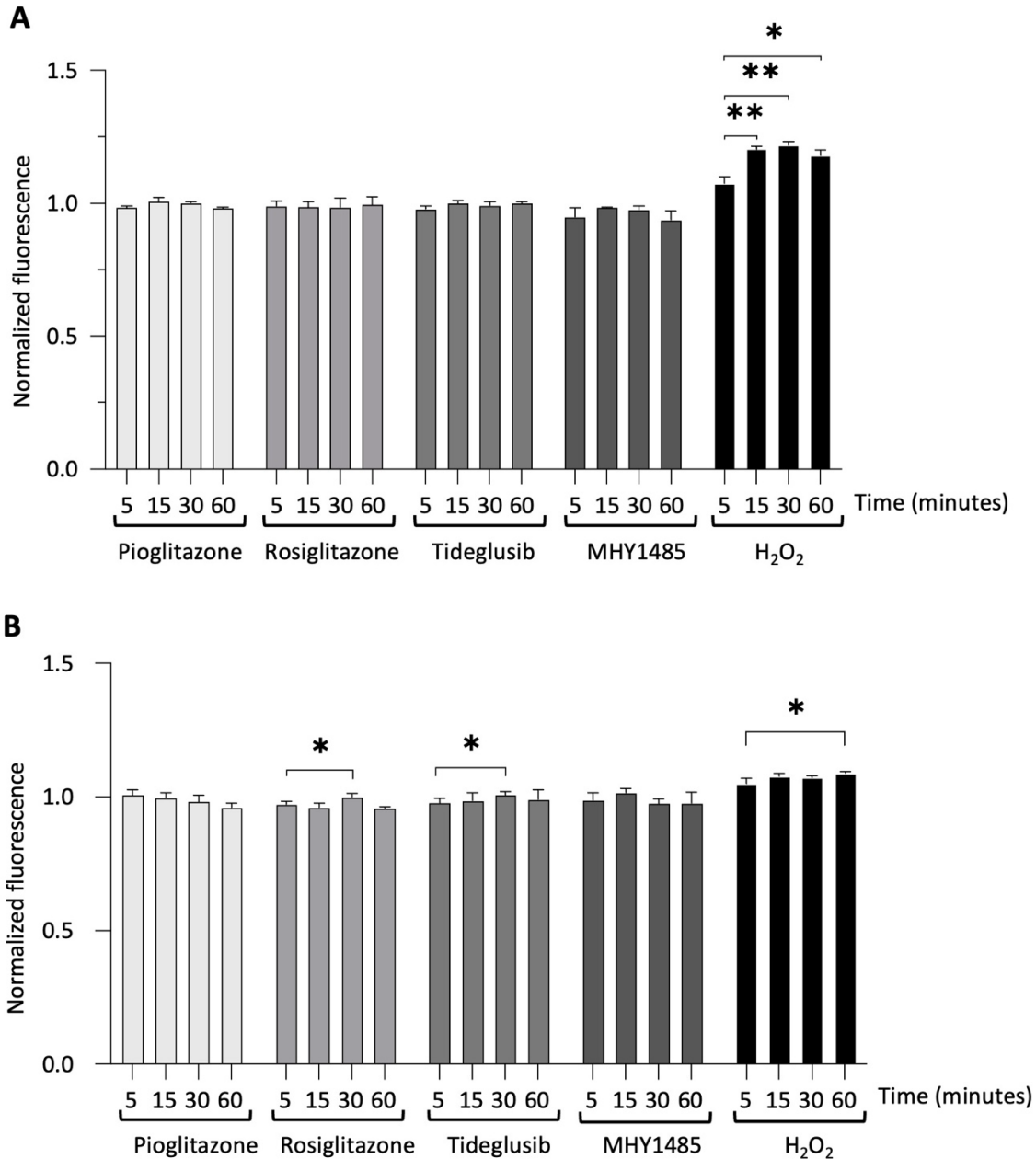
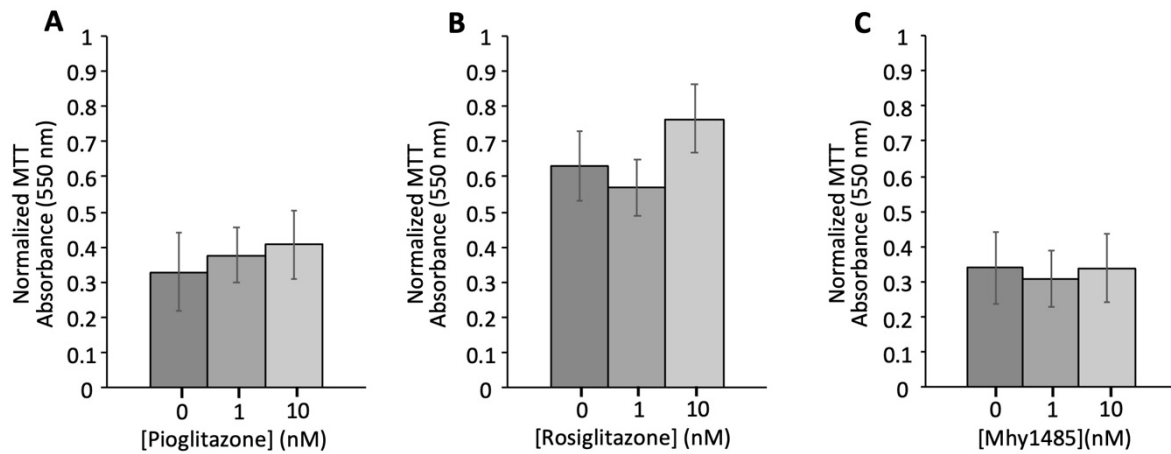


Supplementary Figure 1. CMap analysis of ME/CFS gene networks. The 21 upregulated genes together with the 25 downregulated genes common to GSE14577 and GSE227375 depicted in Table 1, and Table 2 were subjected to CMap analysis to identify genetic perturbagens involved in functional signalling networks. The CMap output provided a ranked list of 286,962 genetic perturbagens with connectivity scores between -0.74 and +0.74 and $-\log_{10}(\text{FDR})$ ranging between 15.65 and 0 (A). The boxed inset region of (A) is expanded to show 83 top-ranked genetic perturbagens with connectivity scores < -0.65 and $-\log_{10}(\text{FDR}) > 15.35$ (B). The 83 genetic perturbagens depicted in (B) are listed in Supplementary Table 1.



Supplementary Figure 2. The effect of Pioglitazone, Rosiglitazone, Tideglusib, and MHY1485 on reactive oxygen species (ROS) production. The C2C12 myoblasts (A) and myotubes (B) were treated with a 1 nM concentration of selected drugs, and ROS were estimated using MitoSox Red assay over 60 minutes. Values shown as mean \pm standard deviation. *p-values* were calculated using an unpaired t-test. Significant differences are denoted with asterisks * *p-value* <0.05.



Supplementary Figure 3. The effect of A) Pioglitazone, B) Rosiglitazone, and C) MHY1485 on cell growth. The C2C12 myotubes were treated with either vehicle (0 nM), 1 nM, or 10 nM of the indicated compounds, and cell growth was measured using the MTT assay at 24 hours. Values shown as mean \pm standard deviation. *P-values* were calculated using an unpaired t-test.

Supplementary Table 1. Genes (genetic perturbagens) identified by CMap. ♦Connectivity Score; * False Discovery Rate

Gene Symbol	Gene name	FDR*	CS ♦
DHRS3	dehydrogenase/reductase 3	15.6536	-0.735
NT5C2	5'-Nucleotidase, Cytosolic II	15.6536	-0.7234
ME3	Malic Enzyme 3	15.6536	-0.7135
PRDX2	Peroxiredoxin 2	15.6536	-0.7121
IGFBP4	Insulin Like Growth Factor Binding Protein 4	15.6536	-0.7053
INS	Insulin	15.6536	-0.7028
ECSCR	Endothelial Cell Surface Expressed Chemotaxis And Apoptosis Regulator	15.6536	-0.6967
TLE1	TLE Family Member 1, Transcriptional Corepressor	15.6536	-0.6949
CD2BP2	CD2 Cytoplasmic Tail Binding Protein 2	15.6536	-0.6919
ABCA1	ATP Binding Cassette Subfamily A Member 1	15.6536	-0.6881
UBC	Ubiquitin C	15.6536	-0.685
CPLX1	Complexin 1	15.6536	-0.6818
RPS6KB2	Ribosomal Protein S6 Kinase B2	15.6536	-0.6803
UBA52	Ubiquitin A-52 Residue Ribosomal Protein Fusion Product 1	15.6536	-0.6799
STK11	Serine/Threonine Kinase 11	15.6536	-0.6798
SPTLC2	Serine Palmitoyltransferase Long Chain Base Subunit 2	15.6536	-0.6789
APEX1	Apurinic/Apyrimidinic Endodeoxyribonuclease 1	15.6536	-0.6785
MTHFR	Methylenetetrahydrofolate Reductase	15.6536	-0.6781
TFDP2	Transcription Factor Dp-2	15.6536	-0.678
SERPINA7	Serpin Family A Member 7	15.6536	-0.6758
GTF2I	General Transcription Factor Iii	15.6536	-0.6749
ADCY3	Adenylate Cyclase 3	15.6536	-0.674
CYBB	Cytochrome B-245 Beta Chain	15.6536	-0.6738
IARS	Isoleucyl-TRNA Synthetase 1	15.3525	-0.6717
CISH	Cytokine Inducible SH2 Containing Protein	15.3525	-0.6708
AKT1	AKT Serine/Threonine Kinase 1	15.3525	-0.6707
SWAP70	Switching B Cell Complex Subunit SWAP70	15.3525	-0.6704
NPEPL1	Aminopeptidase Like 1	15.3525	-0.6694
MRPS16	Mitochondrial Ribosomal Protein S16	15.3525	-0.6694
CLNK	Cytokine Dependent Hematopoietic Cell Linker	15.3525	-0.6692
HBEGF	Heparin Binding EGF Like Growth Factor	15.3525	-0.6691
PPP4C	Protein Phosphatase 4 Catalytic Subunit	15.3525	-0.6687
ALAS2	5'-Aminolevulinatase Synthase 2	15.3525	-0.6682
DHCR24	24-Dehydrocholesterol Reductase	15.3525	-0.668
CTTN	Cortactin	15.3525	-0.6678
MIXL1	Mix Paired-Like Homeobox	15.3525	-0.6677
LPAR2	Lysophosphatidic Acid Receptor 2	15.3525	-0.6673
RGL1	Ral Guanine Nucleotide Dissociation Stimulator Like 1	15.3525	-0.6666
WIPF1	WAS/WASL Interacting Protein Family Member 1	15.3525	-0.6662
LTB	Lymphotoxin Beta	15.3525	-0.6641
RAVER1	Ribonucleoprotein, PTB Binding 1	15.3525	-0.664
EIF2AK2	Eukaryotic Translation Initiation Factor 2 Alpha Kinase 2	15.3525	-0.6637
SLC12A7	Solute Carrier Family 12 Member 7	15.3525	-0.6634

CCDC50	Coiled-Coil Domain Containing 50	15.3525	-0.6628
ARNTL	Aryl Hydrocarbon Receptor Nuclear Translocator Like	15.3525	-0.6623
MYB	MYB Proto-Oncogene, Transcription Factor	15.3525	-0.6616
RDH14	Retinol Dehydrogenase 14	15.3525	-0.6611
HTD2	Hydroxyacyl-Thioester Dehydratase Type 2	15.3525	-0.6609
CRIM1	Cysteine Rich Transmembrane BMP Regulator 1	15.3525	-0.6606
LPL	Lipoprotein Lipase	15.3525	-0.6606
HLA-DQA1	Major Histocompatibility Complex, Class II, DQ Alpha 1	15.3525	-0.6604
NUP85	Nucleoporin 85	15.3525	-0.66
CFD	Complement Factor D	15.3525	-0.659
APOC2	Apolipoprotein C2	15.3525	-0.659
SLF1	SMC5-SMC6 Complex Localization Factor 1	15.3525	-0.6589
CSNK1A1L	Casein Kinase 1 Alpha 1 Like	15.3525	-0.6579
HDAC2	Histone Deacetylase 2	15.3525	-0.6572
INTS12	Integrator Complex Subunit 12	15.3525	-0.6566
FUT3	Fucosyltransferase 3	15.3525	-0.6563
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1	15.3525	-0.6561
IMPDH2	Inosine Monophosphate Dehydrogenase 2	15.3525	-0.6559
CASP10	Caspase 10	15.3525	-0.6558
STK32C	Serine/Threonine Kinase 32C	15.3525	-0.6556
PIM2	Pim-2 Proto-Oncogene, Serine/Threonine Kinase	15.3525	-0.6551
STXBP2	Syntaxin Binding Protein 2	15.3525	-0.6548
CLK4	CDC Like Kinase 4	15.3525	-0.6545
GAS6	Growth Arrest Specific 6	15.3525	-0.6541
MAP2K7	Mitogen-Activated Protein Kinase Kinase 7	15.3525	-0.6535
IDE	Insulin Degrading Enzyme	15.3525	-0.6534
HRH2	Histamine Receptor H2	15.3525	-0.6532
GCKR	Glucokinase Regulator	15.3525	-0.653
NDUFS5	NADH:Ubiquinone Oxidoreductase Subunit S5	15.3525	-0.653
NQO1	NAD(P)H Quinone Dehydrogenase 1	15.3525	-0.6518
TNFAIP3	TNF Alpha Induced Protein 3	15.3525	-0.6514
POR	Cytochrome P450 Oxidoreductase	15.3525	-0.6509
FER	FER Tyrosine Kinase	15.3525	-0.6504
PTGFR	Prostaglandin F Receptor	15.3525	-0.6497
MYLK2	Myosin Light Chain Kinase 2	15.3525	-0.6496
EXT1	Exostosin Glycosyltransferase 1	15.3525	-0.6488
MGAT4A	Alpha-1,3-Mannosyl-Glycoprotein 4-Beta-N-Acetylglucosaminyltransferase A	15.3525	-0.6484
MAPK8	Mitogen-Activated Protein Kinase 8	15.3525	-0.6483
IL10	Interleukin 10	15.3525	-0.6481
KIR3DL1	Killer Cell Immunoglobulin Like Receptor, Three Ig Domains And Long Cytoplasmic Tail 1	15.3525	-0.6473

Supplementary Table 2. Drugs with a negative connectivity score and $-\log_{10}(\text{FDR}) > 15.35$ identified by CMap. ♦ Connectivity Score; * False Discovery Rate

Compounds	Primary target	Classification	Clinically tested	Indication(s)	CS ♦	FDR*
SB-705498	TRPV antagonist	Nociceptor antagonist, anti-inflammatory	Yes	Pain, rhinitis, chronic cough	-0.73	15.65
GDC-0152	XIAP inhibitor	Antagonist of inhibitor of apoptosis (IAP) proteins (SMAC mimetic)	Yes	Cancer	-0.69	15.65
Mefenamic acid	Cyclooxygenase 1 and 2 inhibitor	Non-steroidal anti-inflammatory drug (NSAID)	Yes	Acute and chronic pain, inflammation	-0.69	15.65
Skimmianine	Not determined	Potential antioxidant, antiviral, antimicrobial, and anti-inflammatory	No	Not known	-0.69	15.65
Indoximod	Indoleamine 2,3-dioxygenase inhibitor, mTORC1 activator	Immuno-metabolic adjuvant	Yes	Cancer	-0.67	15.35
Arcyriaflavin-a	Multi-targeted kinase inhibitor, PIM, CDK inhibitor,	Not known	No	Not known	-0.67	15.35
Ginkgolide-a	Platelet activating factor (PAF) receptor antagonist	Anti-inflammatory, anti-allergy	Yes	Stroke, cognition	-0.67	15.35
Idalopirdine	Antagonist of the 5-HT ₆ serotonin receptor	Serotonin, glutamate and cholinergic neurotransmission	Yes	Dementia, schizophrenia	-0.67	15.35
PF-750	Fatty acid amide hydrolase (FAAH) inhibitor	Cannabinoid receptor activation	No	Not known	-0.67	15.35
PRE-084	Sigma receptor agonist	Neuroprotective, anti-inflammatory	No	Not known	-0.66	15.35
Pracinostat (SB-939)	Histone deacetylase inhibitor	Epigenetic regulation	Yes	Cancer	-0.66	15.35
Buspirone	Partial 5-HT _{1A} serotonin receptor agonist and low affinity antagonist of the dopamine D2 receptor	Serotonin and dopamine neurotransmission	Yes	Anxiety, depression	-0.66	15.35
Timofibrate	Peroxisome proliferator-activated receptor agonist	Mitochondrial and peroxisomal fatty acid oxidation	No	Not known	-0.66	15.35
VX-702	p38 mitogen-activated kinase inhibitor	Anti-inflammatory	Yes	Rheumatoid arthritis	-0.65	15.35