Supplementary Material

Multiomics-Identified Intervention to Restore Ethanol-Induced Dysregulated Proteostasis and Secondary Sarcopenia in Alcoholic Liver Disease

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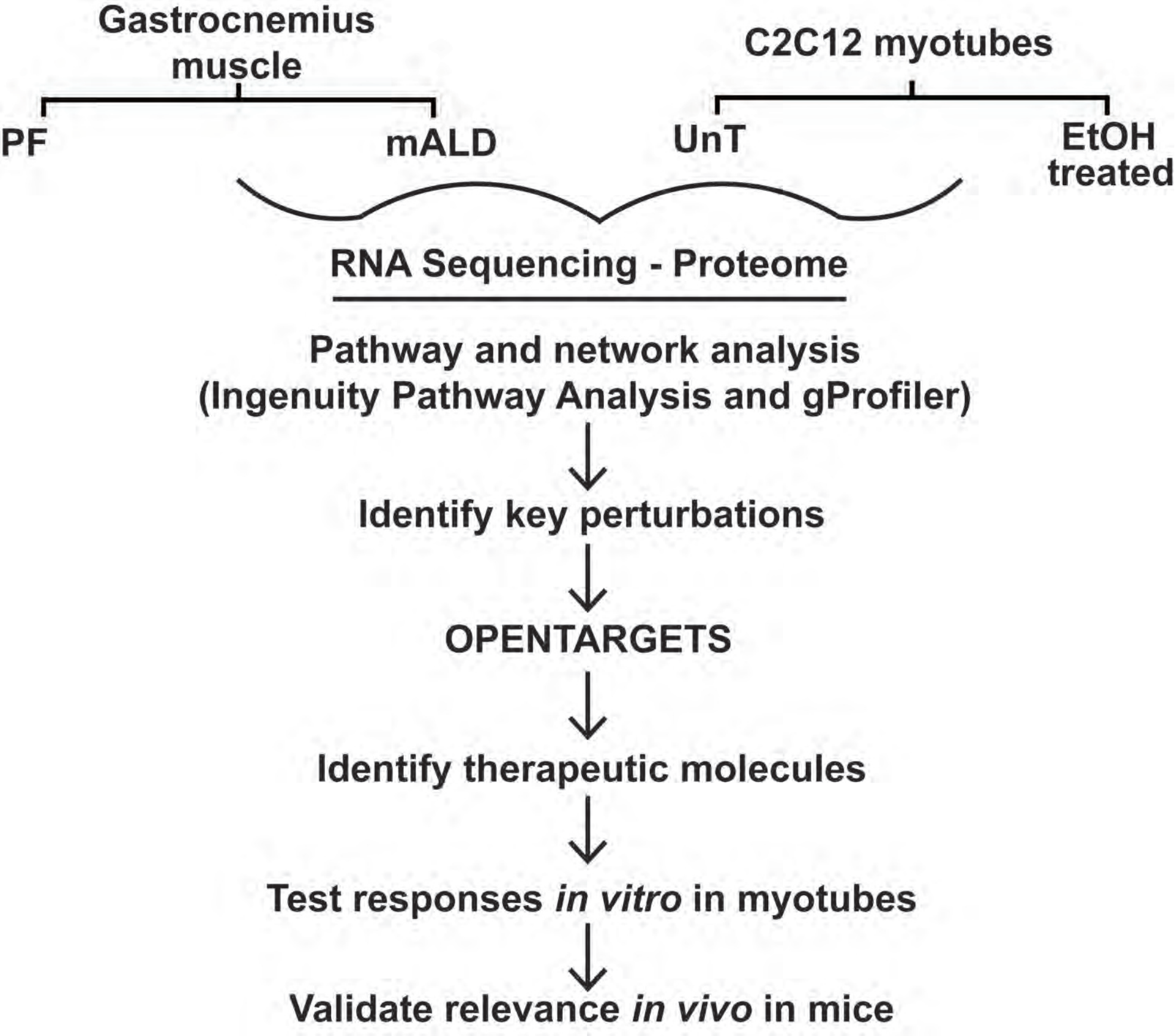
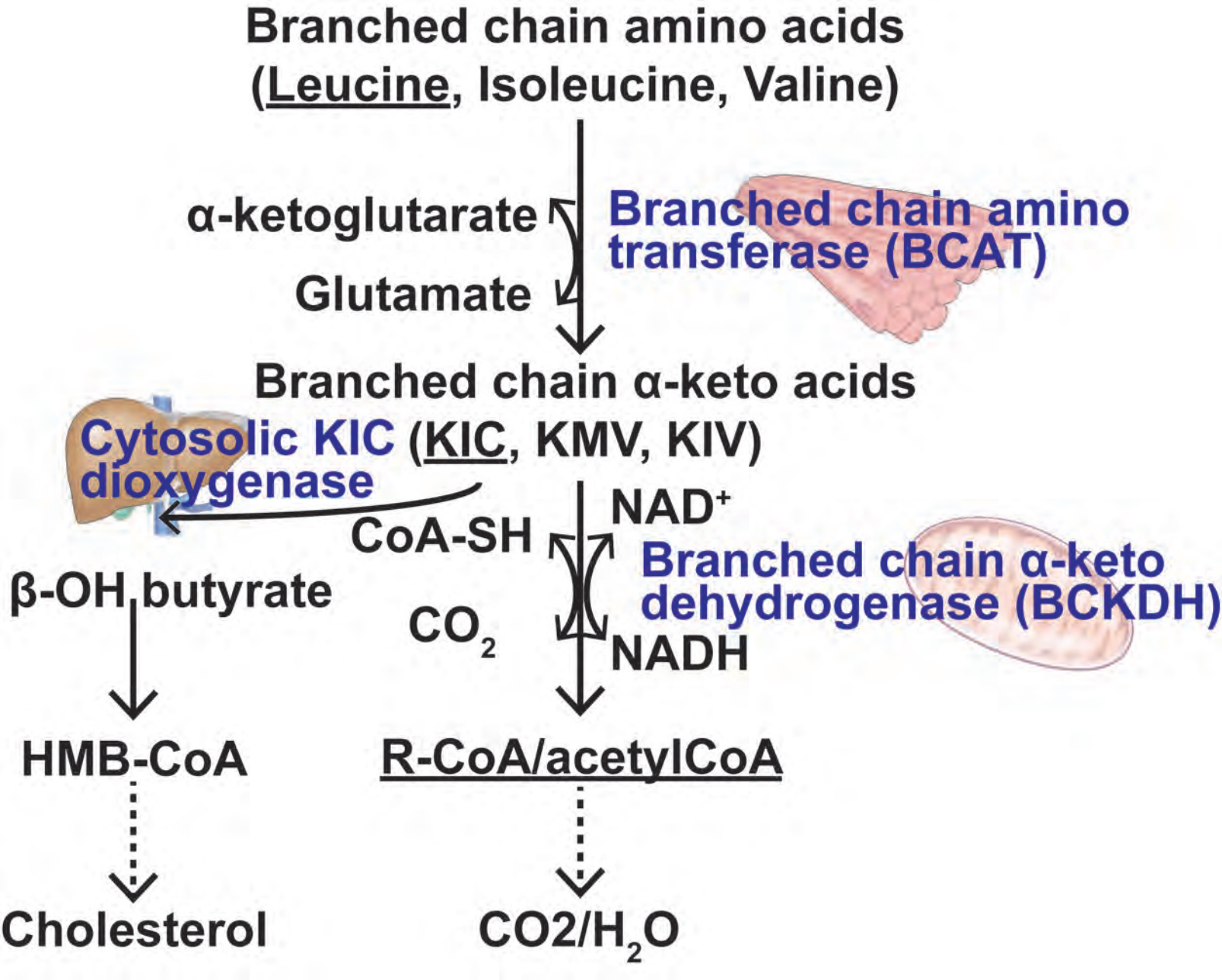
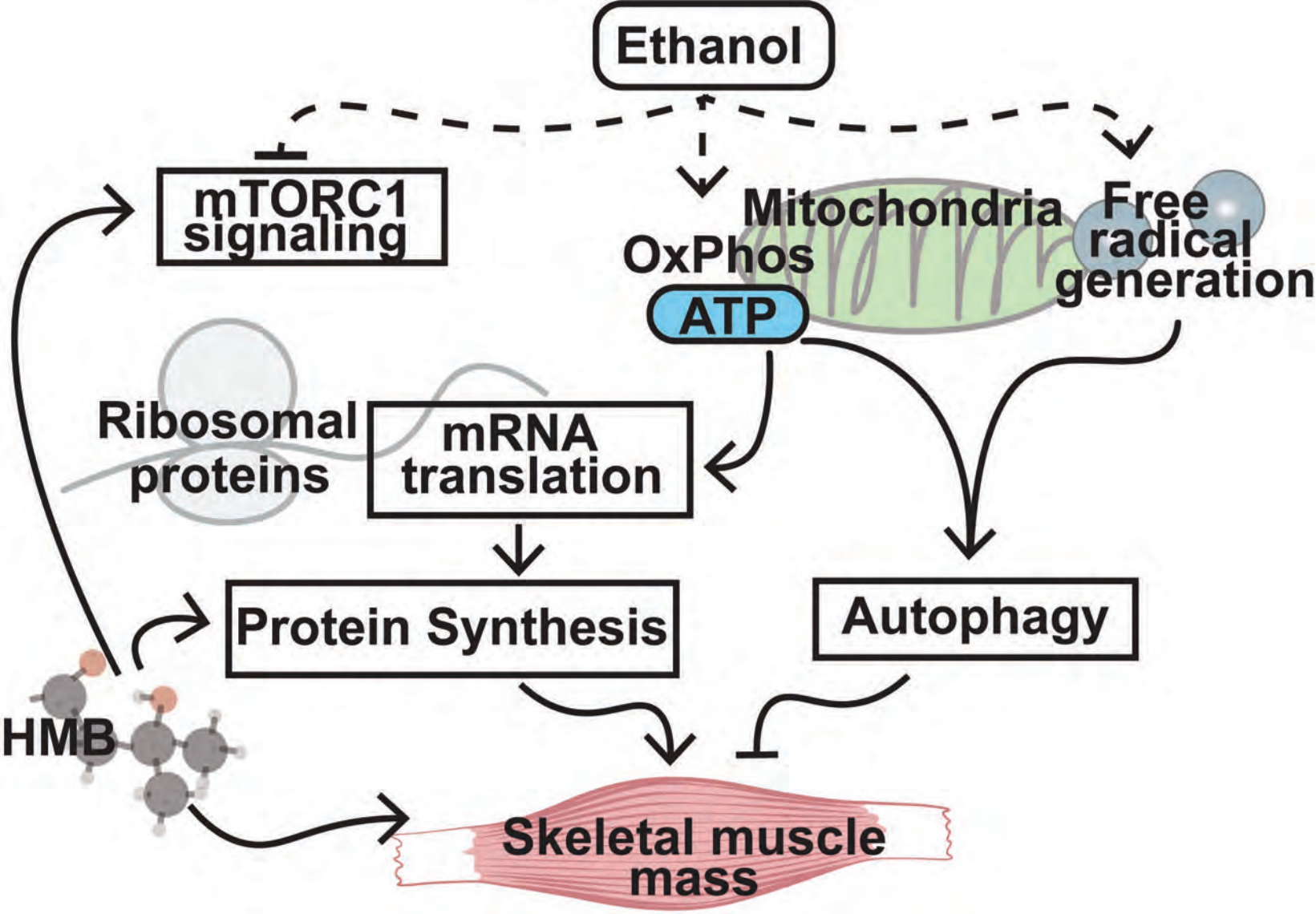

Gastrocnemius muscle
PF
mALD
C2C12 myotubes
UnT
EtOH treated
RNA Sequencing - Proteome
Pathway and network analysis
(Ingenuity Pathway Analysis and gProfiler)
Identify key perturbations
OPENTARGETS
Identify therapeutic molecules
Test responses *in vitro* in myotubes
Validate relevance *in vivo* in mice

Supplementary Figure 1. Schematic of approach. Using a complementary bioinformatics and experimental approach, HMB was identified as a mechanism based therapeutic for sarcopenia in alcohol-related liver disease. EtOH 100 mM ethanol; mALD mouse model of alcohol related liver disease; PF pair-fed mice; UnT untreated.


Branched chain amino acids
(Leucine, Isoleucine, Valine)
α-ketoglutarate
Glutamate
Branched chain amino transferase (BCAT)
Branched chain α-keto acids
Cytosolic KIC (KIC, KMV, KIV)
dioxygenase
NAD+
CoA-SH
Branched chain α-keto dehydrogenase (BCKDH)
β-OH butyrate
CO2
NADH
HMB-CoA
R-CoA/acetylCoA
Cholesterol
CO2/H2O

Supplementary Figure 2. Metabolism of branched chain amino acids. Pathways of branched chain amino acid metabolism in the skeletal muscle and generation of β-hydroxybutyrate in the cytosol.


Ethanol
mTORC1 signaling
Mitochondria
OxPhos
ATP
Free radical generation
Ribosomal proteins
mRNA translation
Protein Synthesis
Autophagy
HMB
Skeletal muscle mass

Supplementary Fig. 3. Identification of HMB as a regulatory molecule. Manual curation of different pathways and molecular responses to published anabolic metabolites show HMB targets ethanol-induced perturbations.

Supplementary Tables

Due to their size, please use the following links to download and access the Supplementary Tables:

Supplementary Table 1: List of Antibodies used in HMB study.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_1.xlsx

Supplementary Table 2: C2C12 transcriptomic heatmap NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_2.xlsx

Supplementary Table 3: RNAseq cell mtorc pathway NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_3.xlsx

Supplementary Table 4: Proteomics C2C12 mtorc pathway NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_4.xlsx

Supplementary Table 5: IGF-1 6h EtOH v UnT RNAseq pathway NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_5.xlsx

Supplementary Table 6: Ubiquitination heatmap NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_6.xlsx

Supplementary Table 7: gProfiler_mmusculus NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_7.xlsx

Supplementary Table 8: Open Targets Venn Diagram NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_8.xlsx

Supplementary Table 9: Mouse RNAseq Bar Graph NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_9.xlsx

Supplementary Table 10: BCAT data 8-10-20.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_10.xlsx

Supplementary Table 11: Biosynthesis muscle AA Table new 08-03-20 NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_11.docx

Supplementary Table 12: Degradation muscle AA Table new 08-03-20 NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_12.docx

Supplementary Table 13: Biosynthesis liver AA Table new 08-03-20 NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_13.docx

Supplementary Table 14: Degradation liver AA Table new 08-03-20 NW.
https://www.cellphysiolbiochem.com/Articles/000327/SM/Supplementary_Table_14.docx