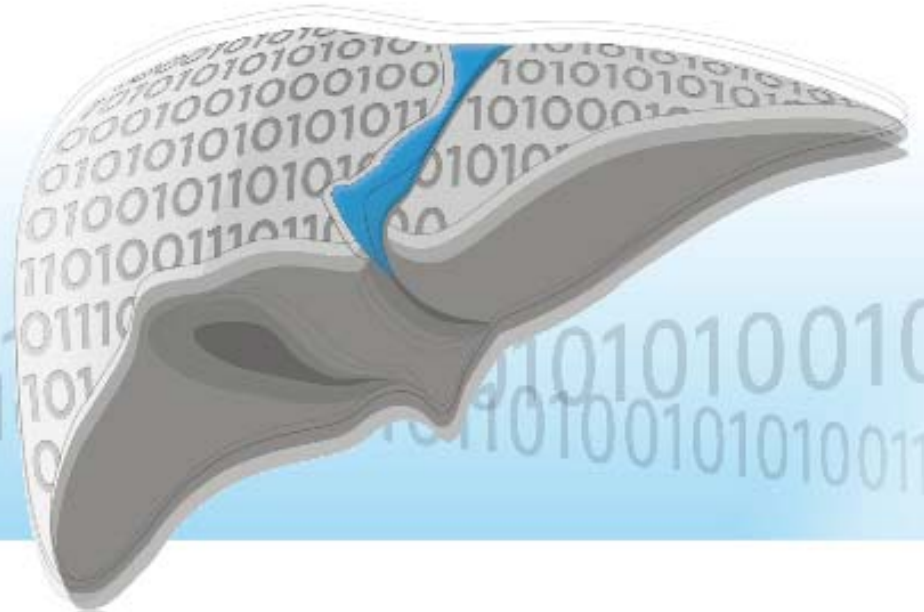
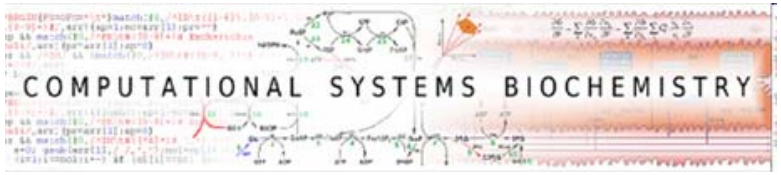
virtual liver network



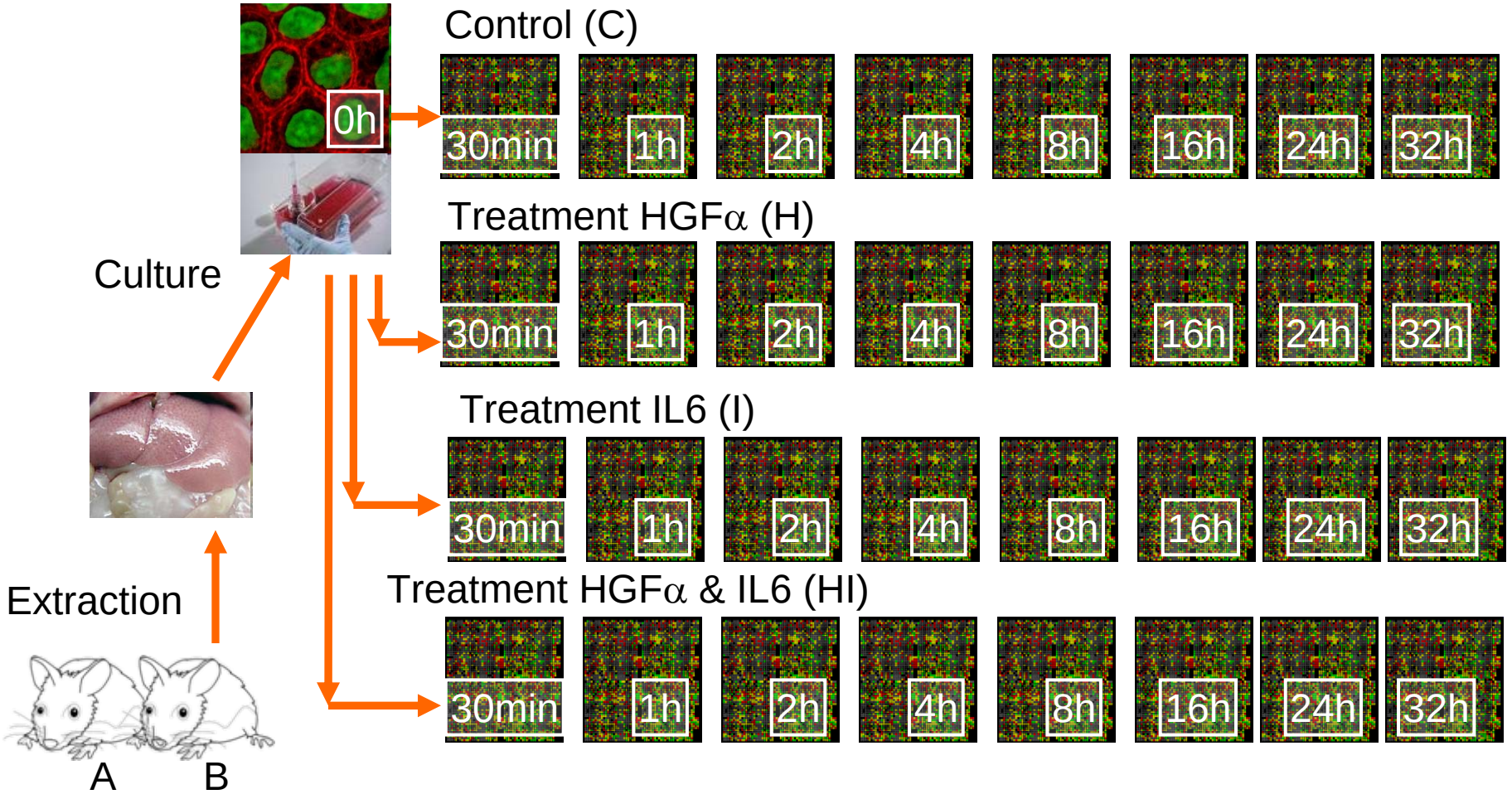
Remarkable gene regulations in the HGF and IL-6 treatment of hepatocyte cultures

Andreas Hoppe, Charité Universtitätsmedizin Berlin
Computational systems biochemistry group



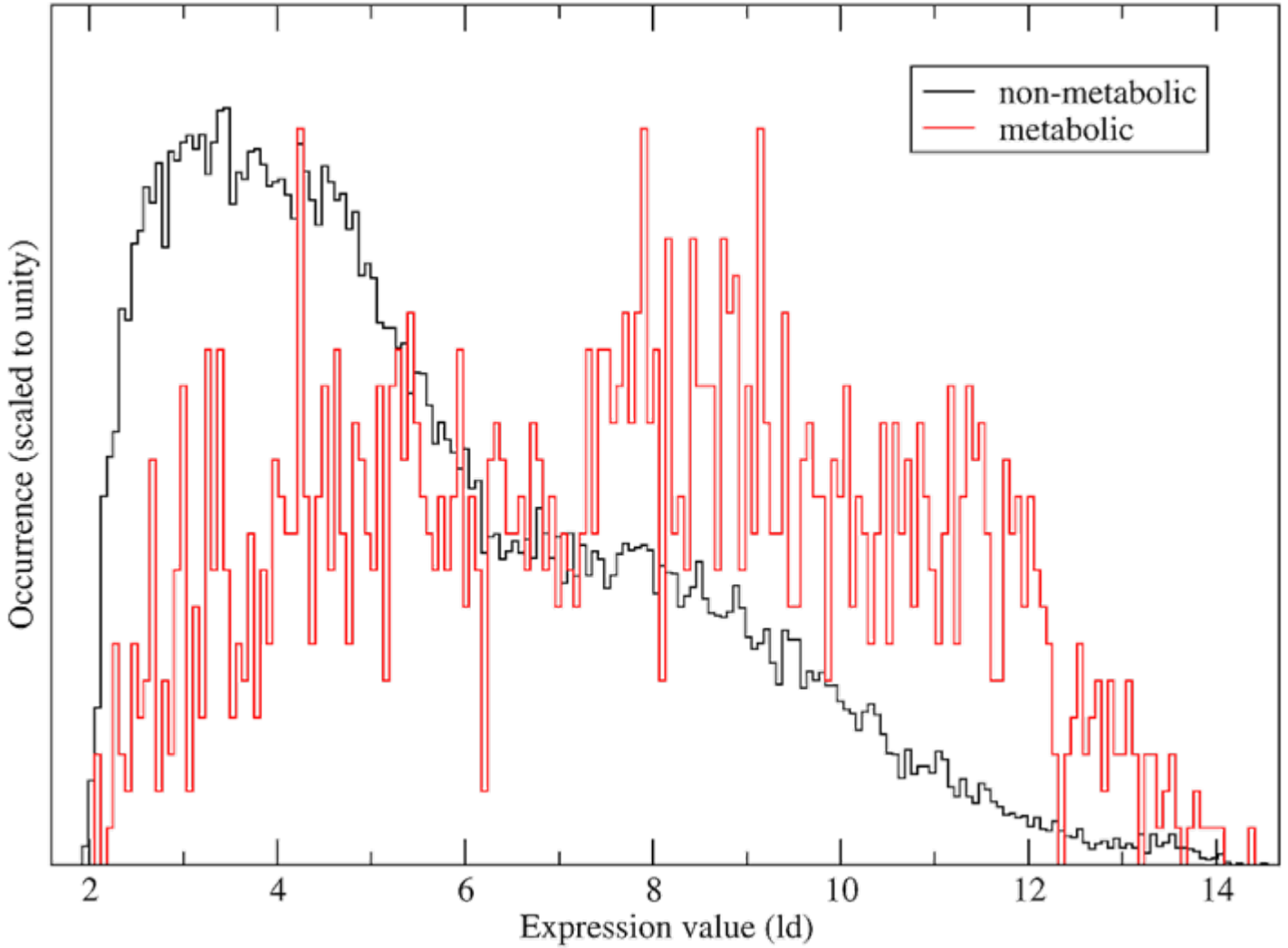
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Hepatocyte culture/HGFα/IL6 treatment

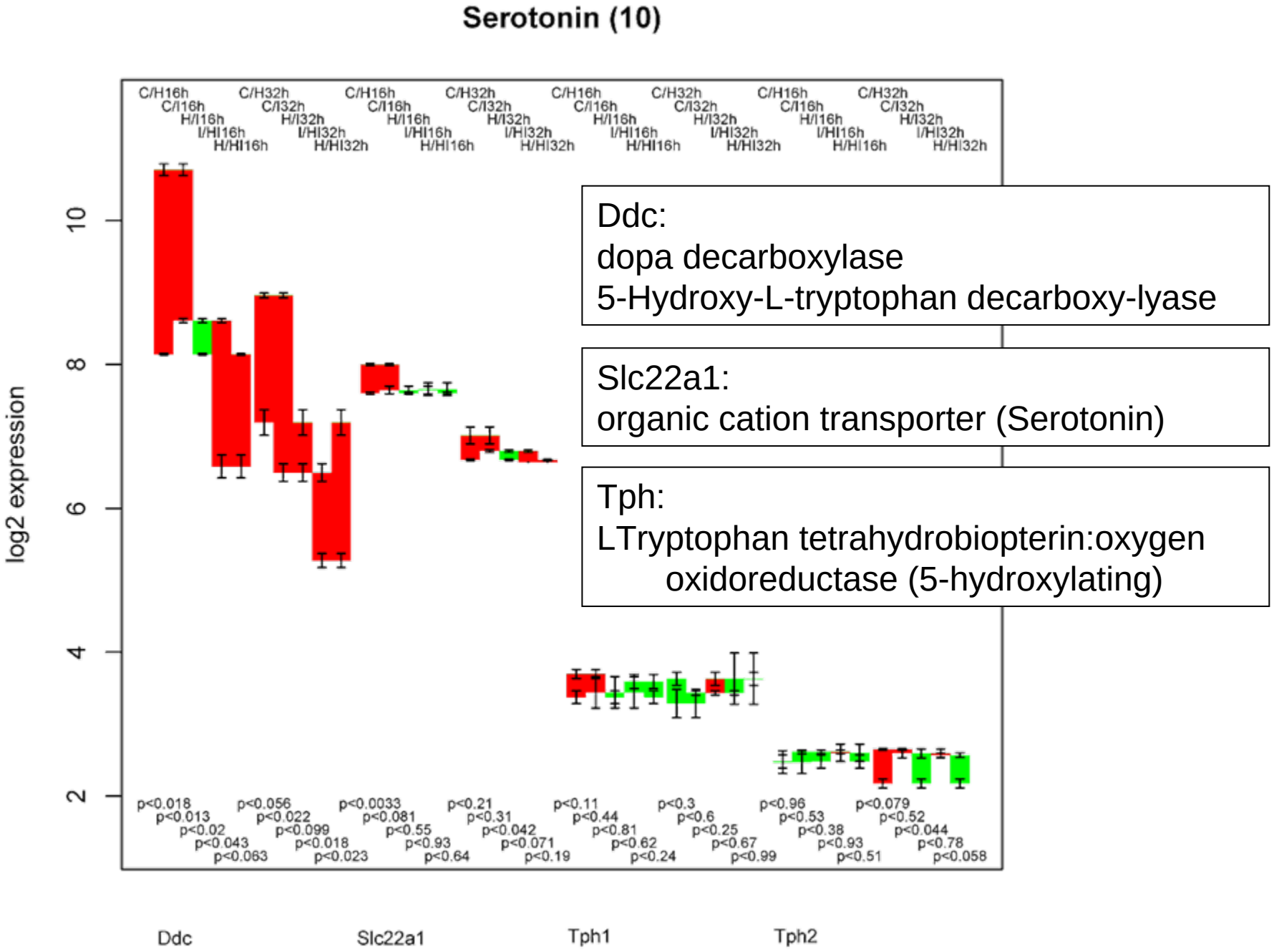


Busch, Freiburg

Expression values



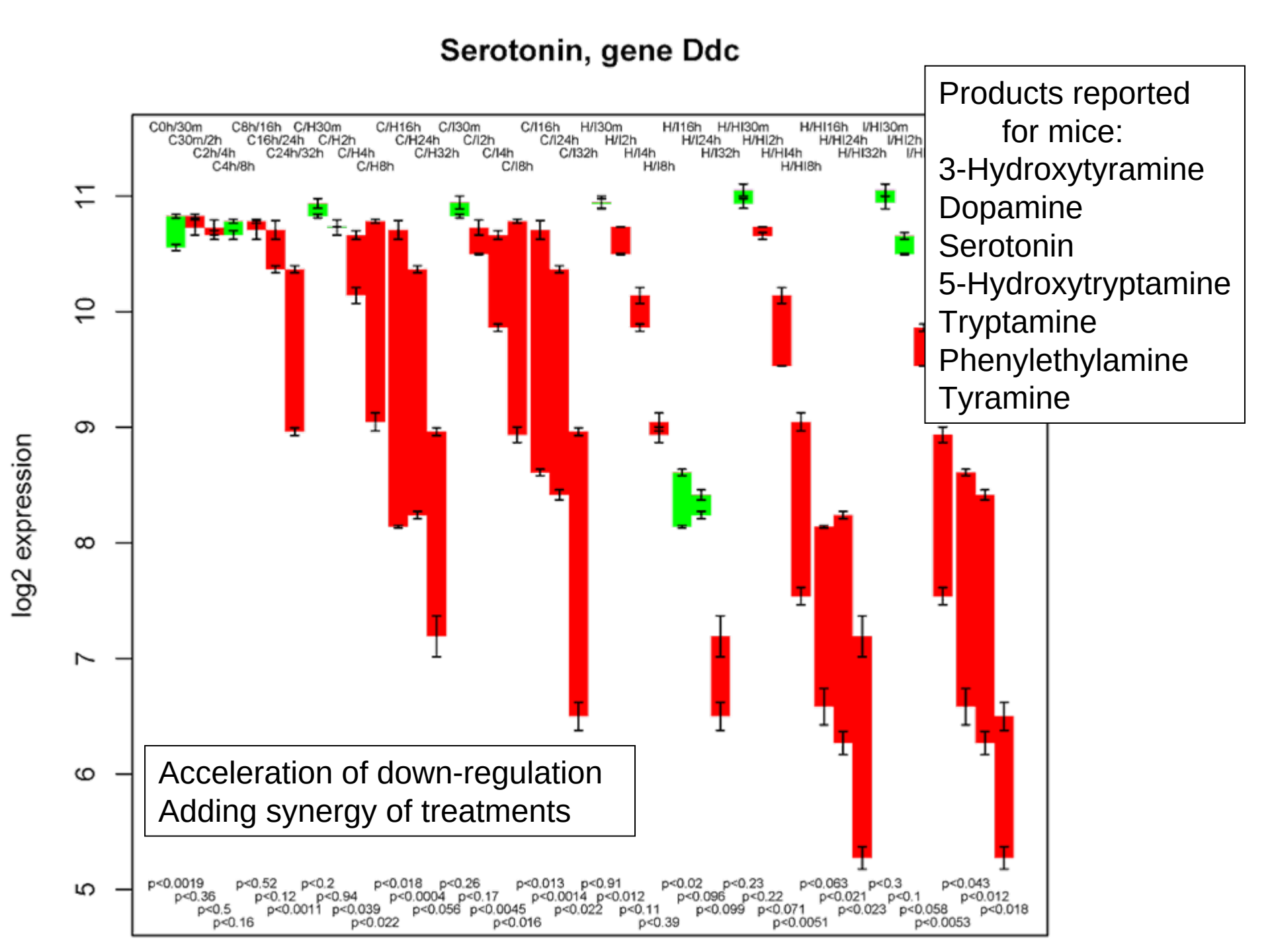
Hebenstreit et al.: RNA sequencing reveals two major classes of gene expression levels in metazoan cells. Mol. Syst. Biol. 2011, 7,



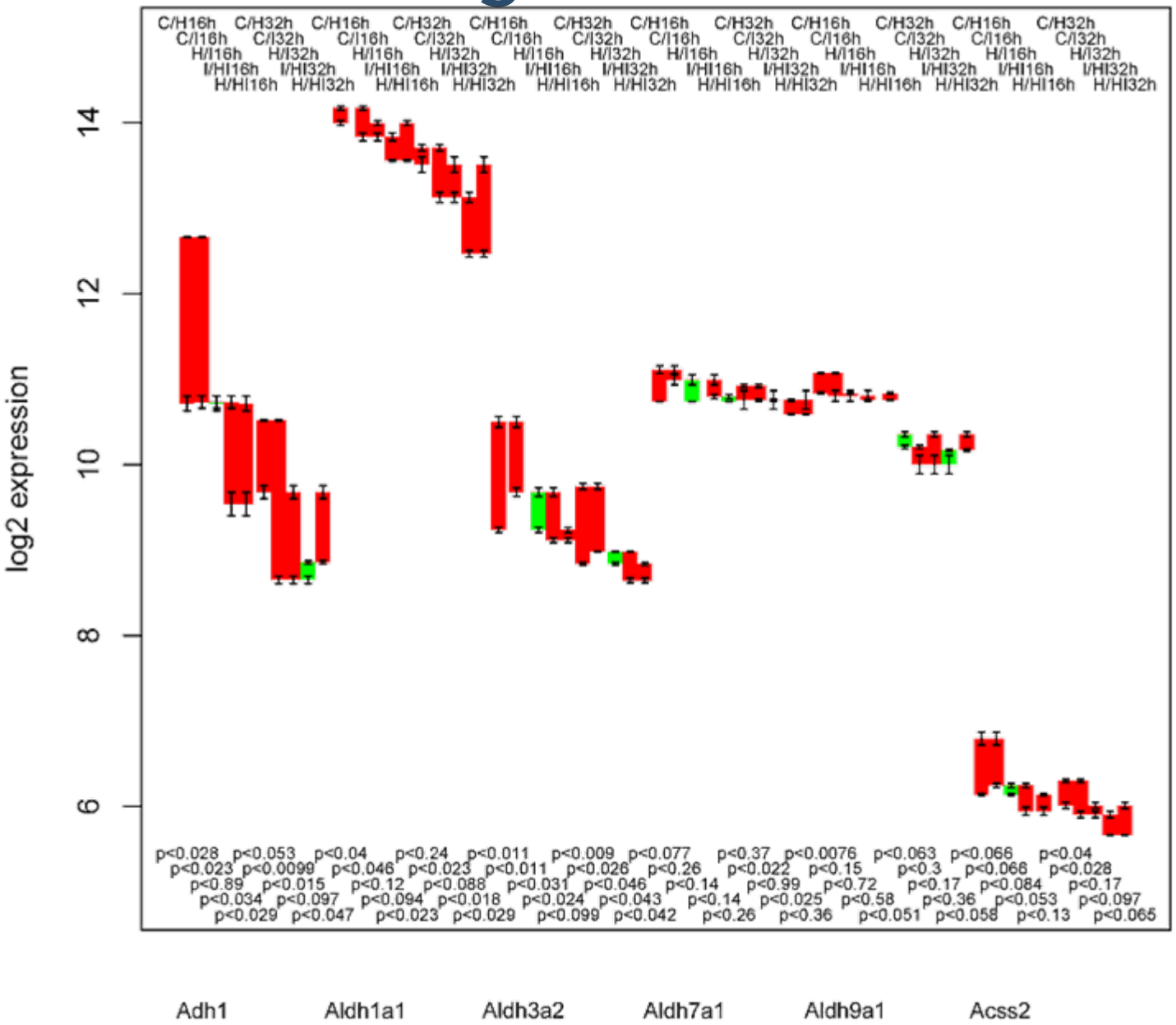
Ddc:
dopa decarboxylase
5-Hydroxy-L-tryptophan decarboxy-lyase

Slc22a1:
organic cation transporter (Serotonin)

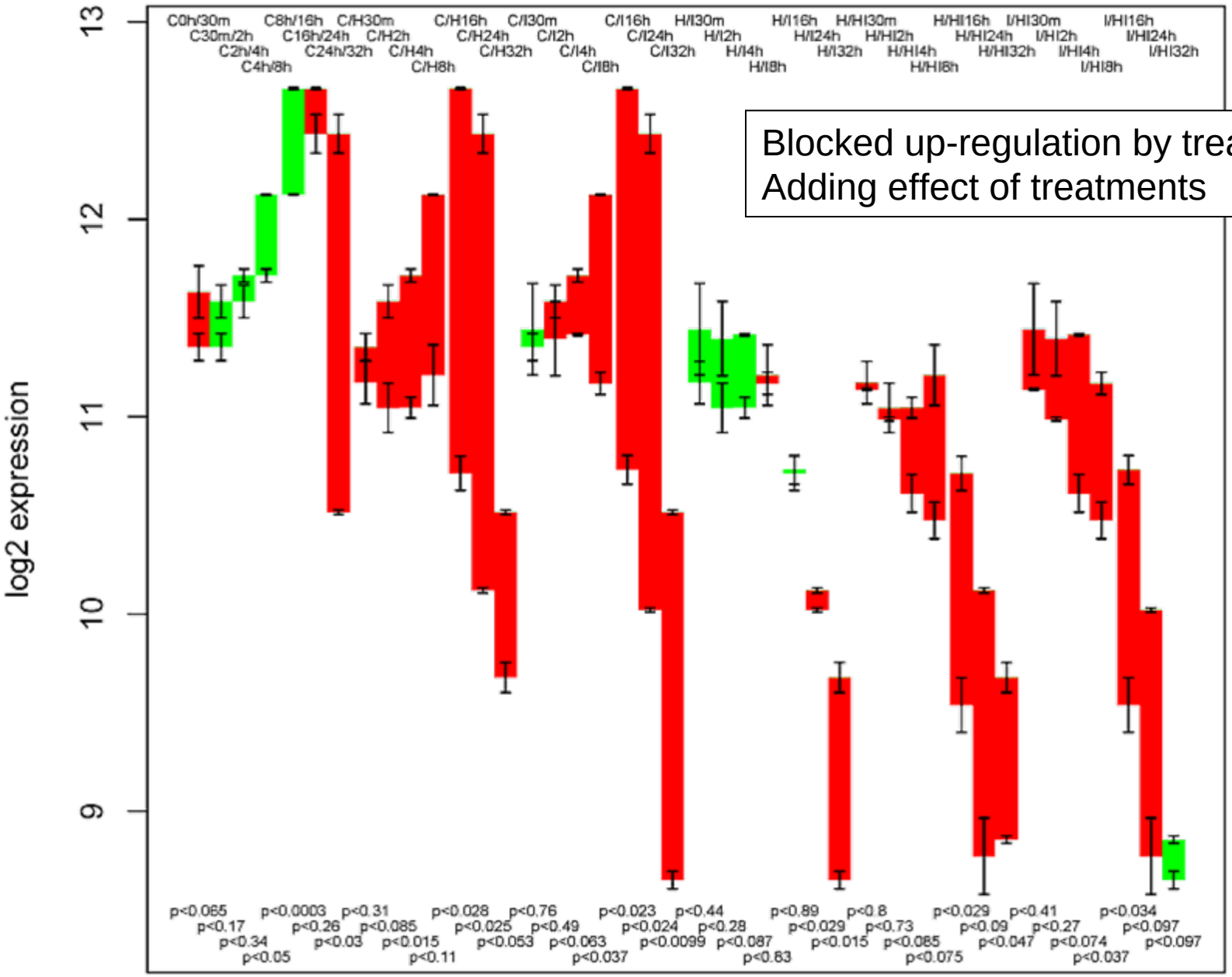
Tph:
LTryptophan tetrahydrobiopterin:oxygen oxidoreductase (5-hydroxylating)


Serotonin, gene Ddc
log2 expression
5
6
7
8
9
10
11
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I8h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI8h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
p<0.0019
p<0.36
p<0.5
p<0.16
p<0.52
p<0.12
p<0.0011
p<0.2
p<0.94
p<0.039
p<0.022
p<0.018
p<0.0004
p<0.056
p<0.26
p<0.17
p<0.0045
p<0.016
p<0.013
p<0.0014
p<0.022
p<0.91
p<0.012
p<0.11
p<0.39
p<0.02
p<0.096
p<0.099
p<0.23
p<0.22
p<0.071
p<0.0051
p<0.063
p<0.021
p<0.023
p<0.3
p<0.1
p<0.058
p<0.0053
p<0.043
p<0.012
p<0.018
Products reported
for mice:
3-Hydroxytyramine
Dopamine
Serotonin
5-Hydroxytryptamine
Tryptamine
Phenylethylamine
Tyramine
Acceleration of down-regulation
Adding synergy of treatments

Ethanol degradation

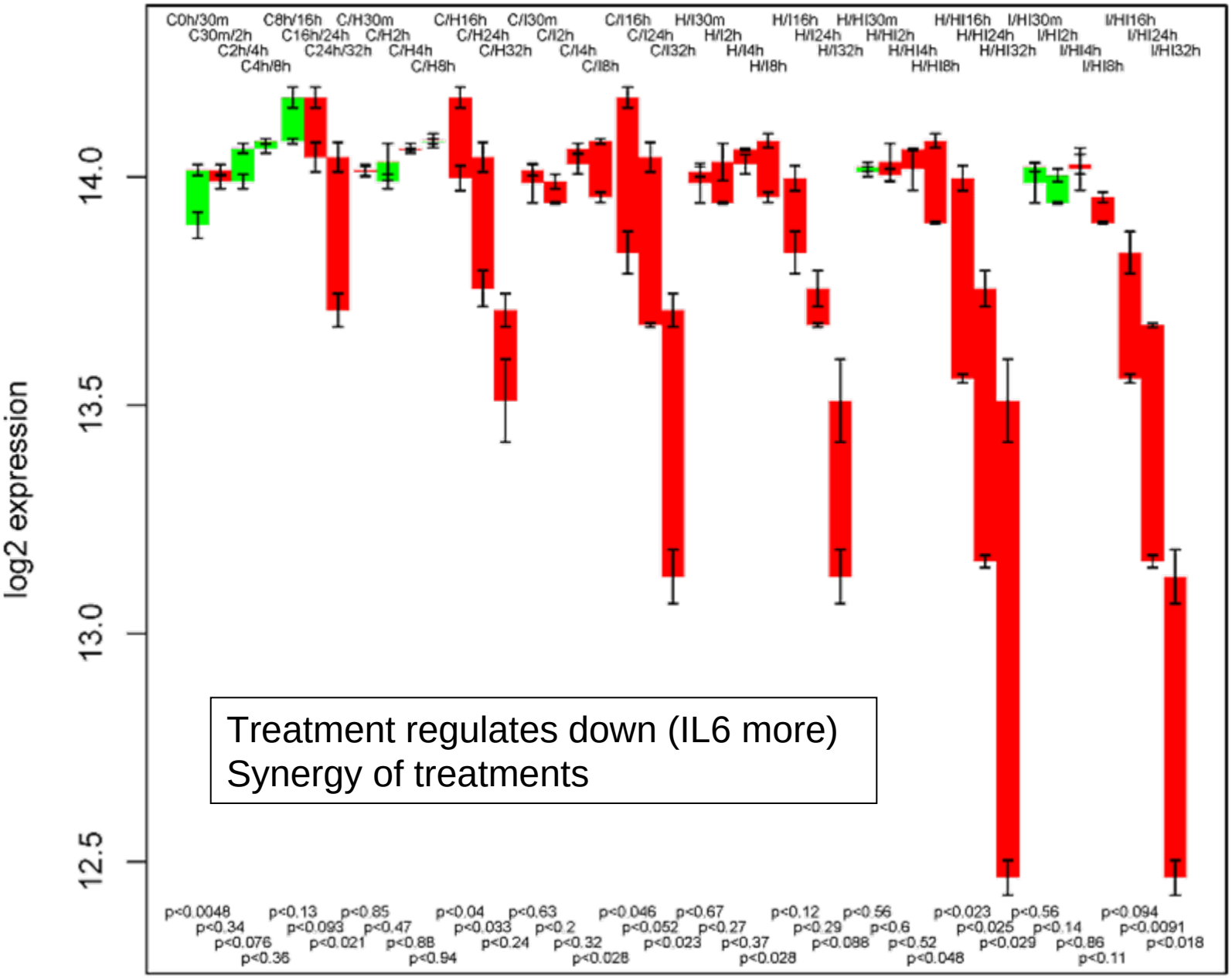


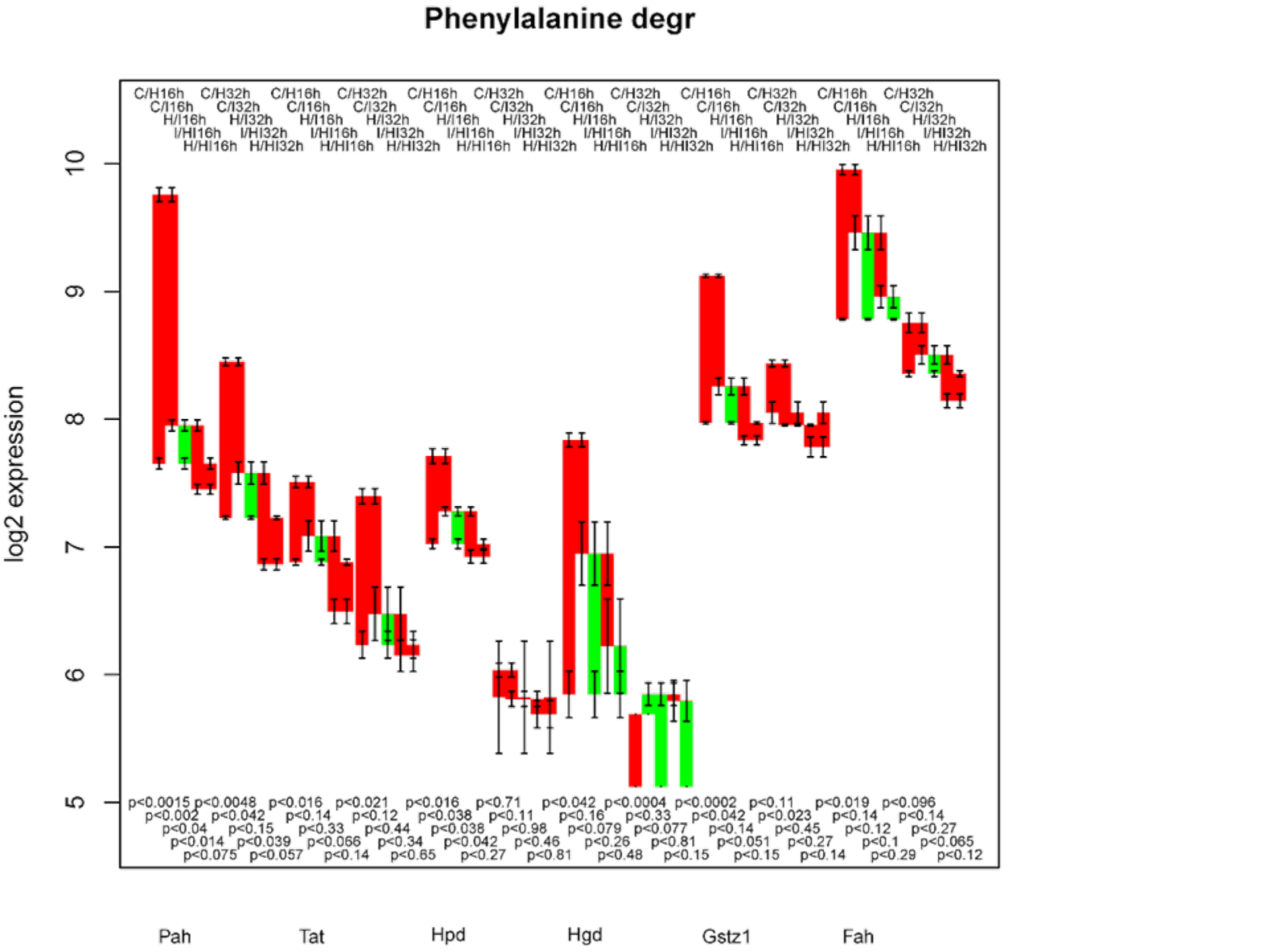
Ethanol degradation, gene Adh1



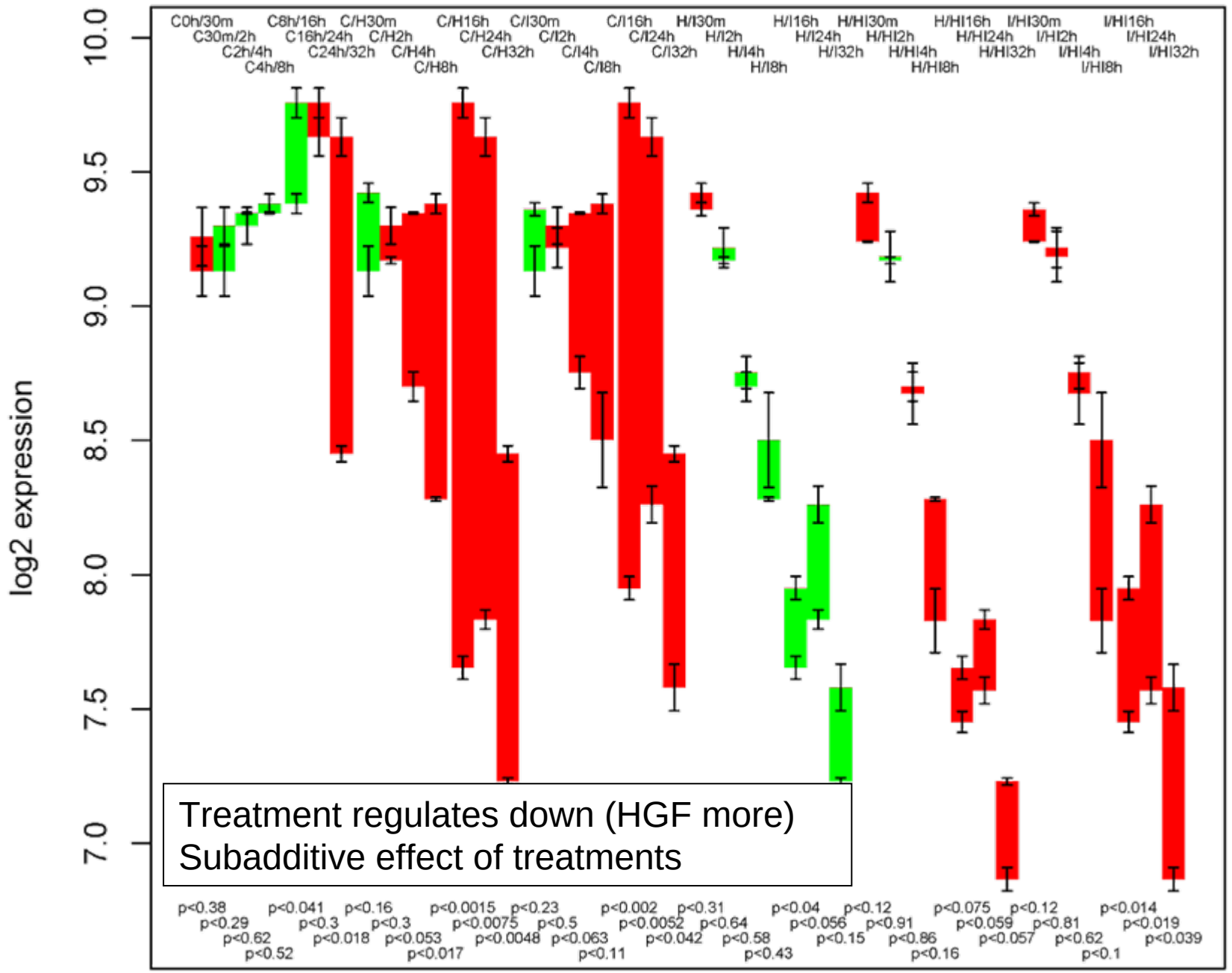
Blocked up-regulation by treatment
Adding effect of treatments

Ethanol degradation, gene Aldh1

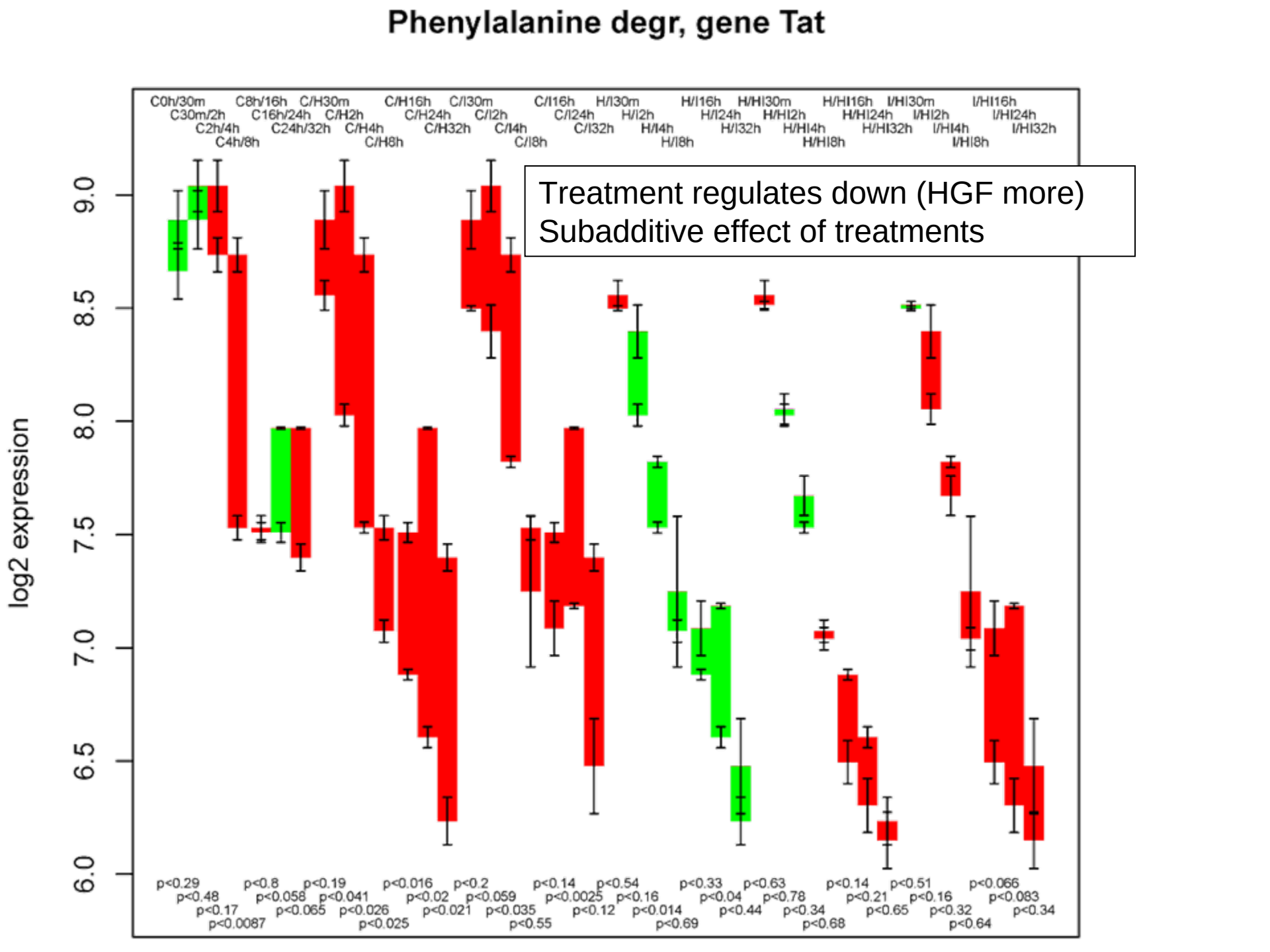


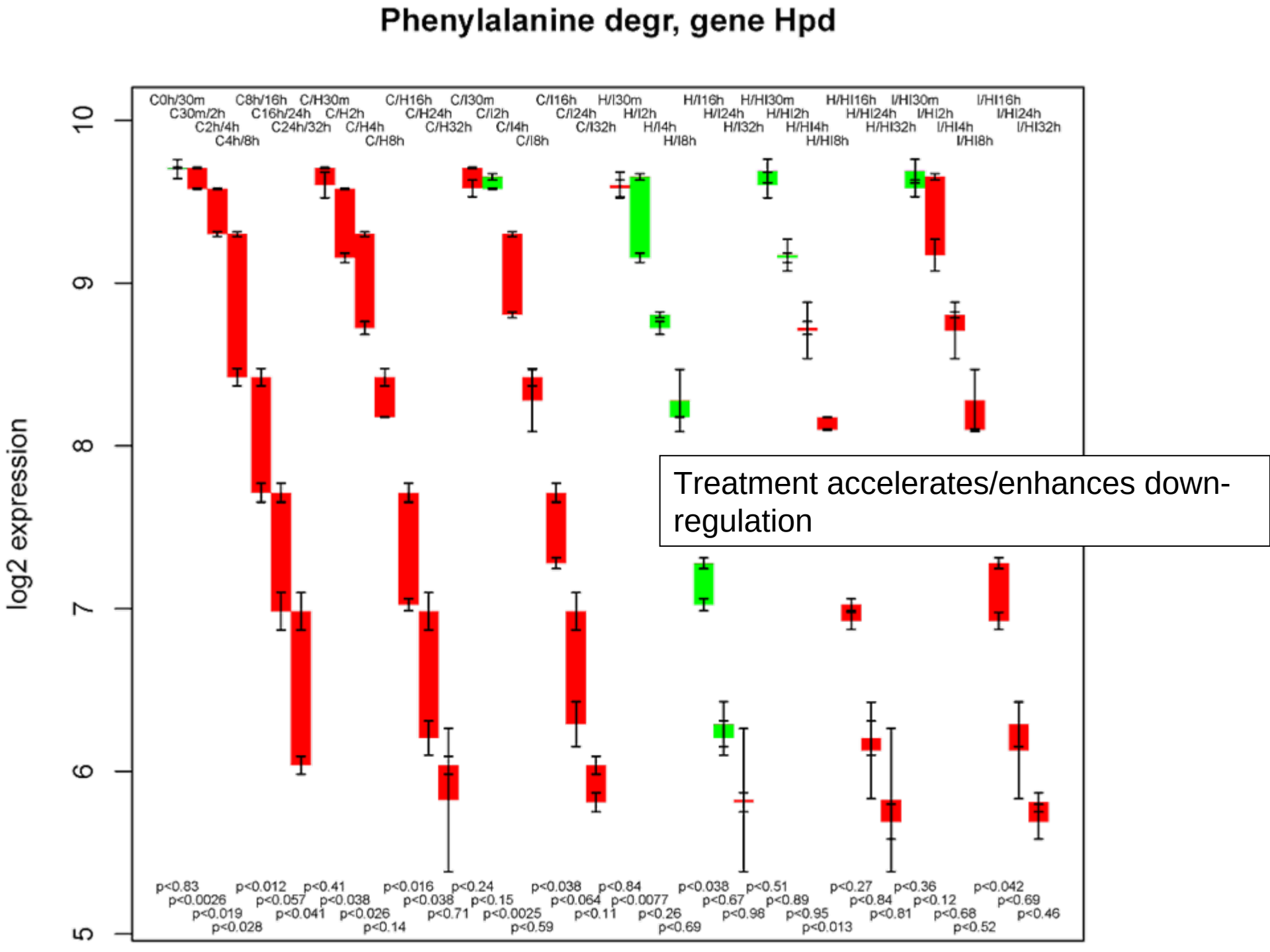

Phenylalanine degr
log2 expression
5
6
7
8
9
10
C/H16h C/H32h C/H16h C/H32h C/H16h C/H32h C/H16h C/H32h C/H16h C/H32h C/H16h C/H32h
C/I16h C/I32h C/I16h C/I32h C/I16h C/I32h C/I16h C/I32h C/I16h C/I32h C/I16h C/I32h
H/I16h H/I32h H/I16h H/I32h H/I16h H/I32h H/I16h H/I32h H/I16h H/I32h H/I16h H/I32h
I/HI16h I/HI32h I/HI16h I/HI32h I/HI16h I/HI32h I/HI16h I/HI32h I/HI16h I/HI32h I/HI16h I/HI32h
H/HI16h H/HI32h H/HI16h H/HI32h H/HI16h H/HI32h H/HI16h H/HI32h H/HI16h H/HI32h H/HI16h H/HI32h
p<0.0015 p<0.0048 p<0.016 p<0.021 p<0.016 p<0.71 p<0.042 p<0.0004 p<0.0002 p<0.11 p<0.019 p<0.096
p<0.002 p<0.042 p<0.14 p<0.12 p<0.038 p<0.11 p<0.16 p<0.33 p<0.042 p<0.023 p<0.14 p<0.14
p<0.04 p<0.15 p<0.33 p<0.44 p<0.038 p<0.98 p<0.079 p<0.077 p<0.14 p<0.45 p<0.12 p<0.27
p<0.014 p<0.039 p<0.066 p<0.34 p<0.042 p<0.46 p<0.26 p<0.81 p<0.051 p<0.27 p<0.1 p<0.065
p<0.075 p<0.057 p<0.14 p<0.65 p<0.27 p<0.81 p<0.48 p<0.15 p<0.15 p<0.14 p<0.29 p<0.12
Pah
Tat
Hpd
Hgd
Gstz1
Fah

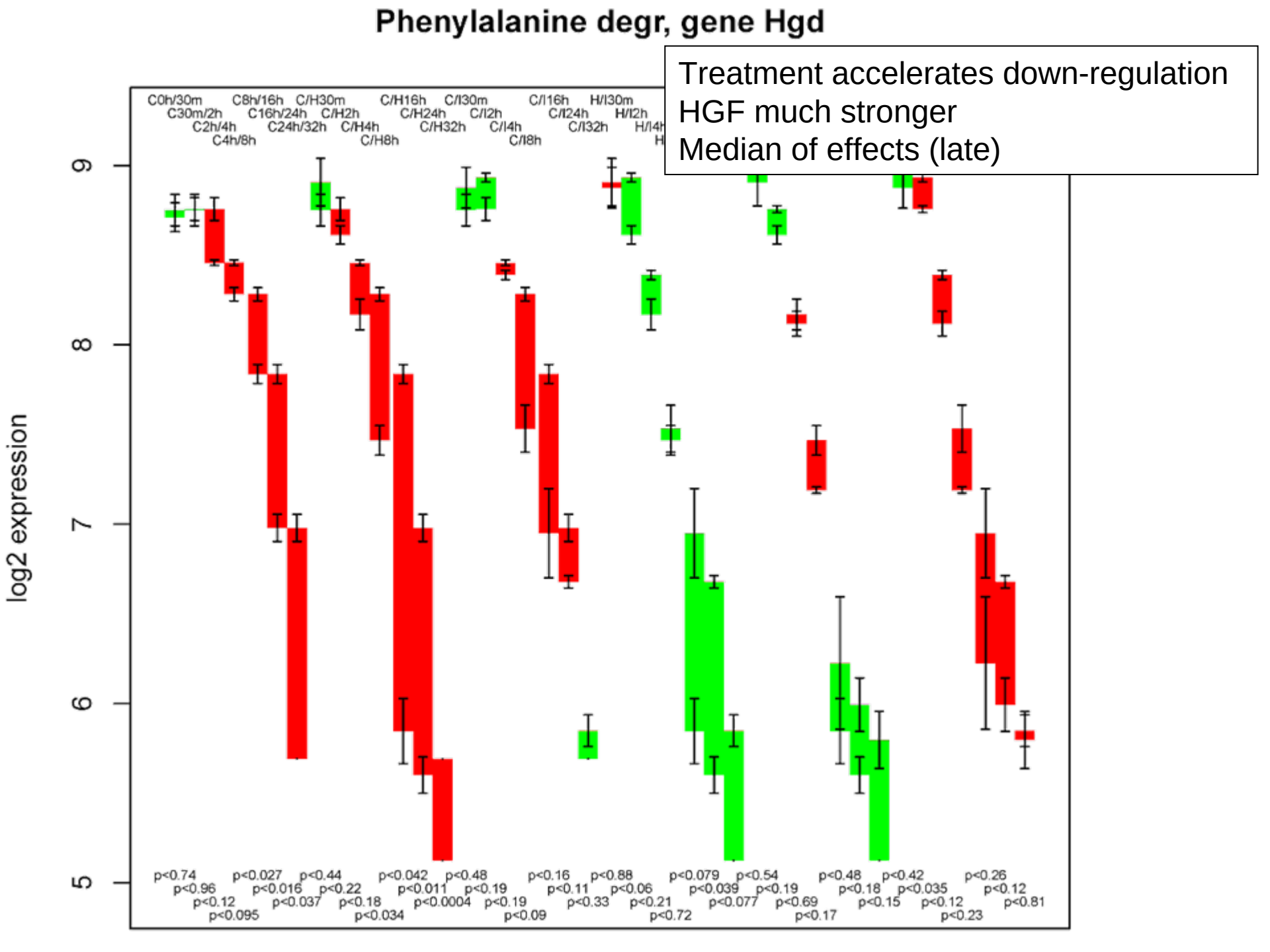
Phenylalanine degr, gene Pah

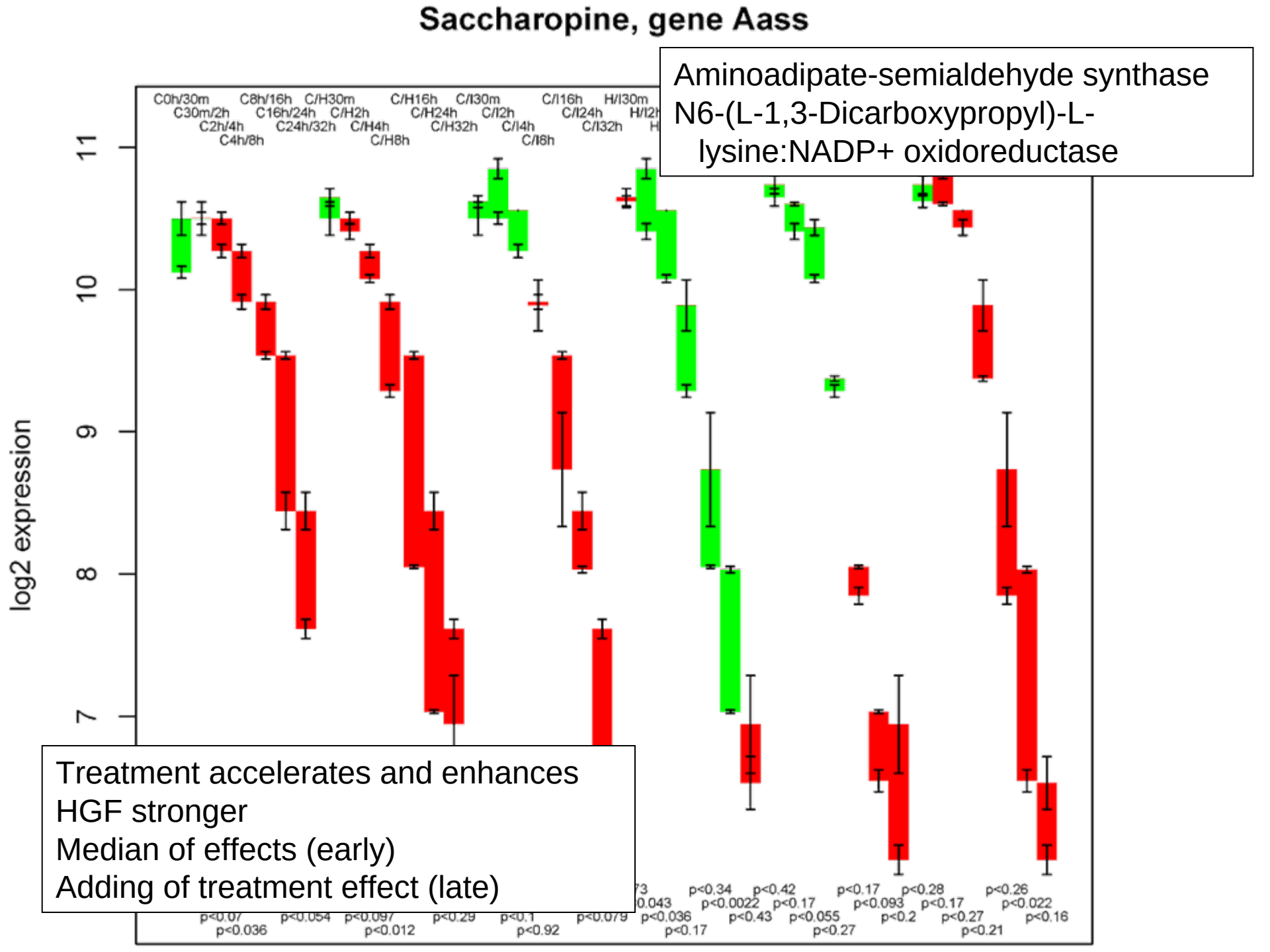


Treatment regulates down (HGF more)
Subadditive effect of treatments


Phenylalanine degr, gene Tat
log2 expression
9.0
8.5
8.0
7.5
7.0
6.5
6.0
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I8h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI8h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
I/HI4h
I/HI8h
I/HI16h
I/HI24h
I/HI32h
Treatment regulates down (HGF more)
Subadditive effect of treatments
p<0.29
p<0.48
p<0.17
p<0.0087
p<0.8
p<0.058
p<0.065
p<0.19
p<0.041
p<0.026
p<0.025
p<0.016
p<0.02
p<0.021
p<0.2
p<0.059
p<0.035
p<0.55
p<0.14
p<0.0025
p<0.12
p<0.54
p<0.16
p<0.014
p<0.69
p<0.33
p<0.04
p<0.44
p<0.63
p<0.78
p<0.34
p<0.68
p<0.14
p<0.21
p<0.65
p<0.51
p<0.16
p<0.32
p<0.64
p<0.066
p<0.083
p<0.34


Phenylalanine degr, gene Hpd
log2 expression
10
9
8
7
6
5
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I8h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI8h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
I/HI4h
I/HI8h
I/HI16h
I/HI24h
I/HI32h
p<0.83
p<0.0026
p<0.019
p<0.028
p<0.012
p<0.057
p<0.041
p<0.41
p<0.038
p<0.026
p<0.14
p<0.016
p<0.038
p<0.71
p<0.24
p<0.15
p<0.0025
p<0.59
p<0.038
p<0.064
p<0.11
p<0.84
p<0.0077
p<0.26
p<0.69
p<0.038
p<0.67
p<0.98
p<0.51
p<0.89
p<0.95
p<0.013
p<0.27
p<0.84
p<0.81
p<0.36
p<0.12
p<0.68
p<0.52
p<0.042
p<0.69
p<0.46
Treatment accelerates/enhances down-regulation

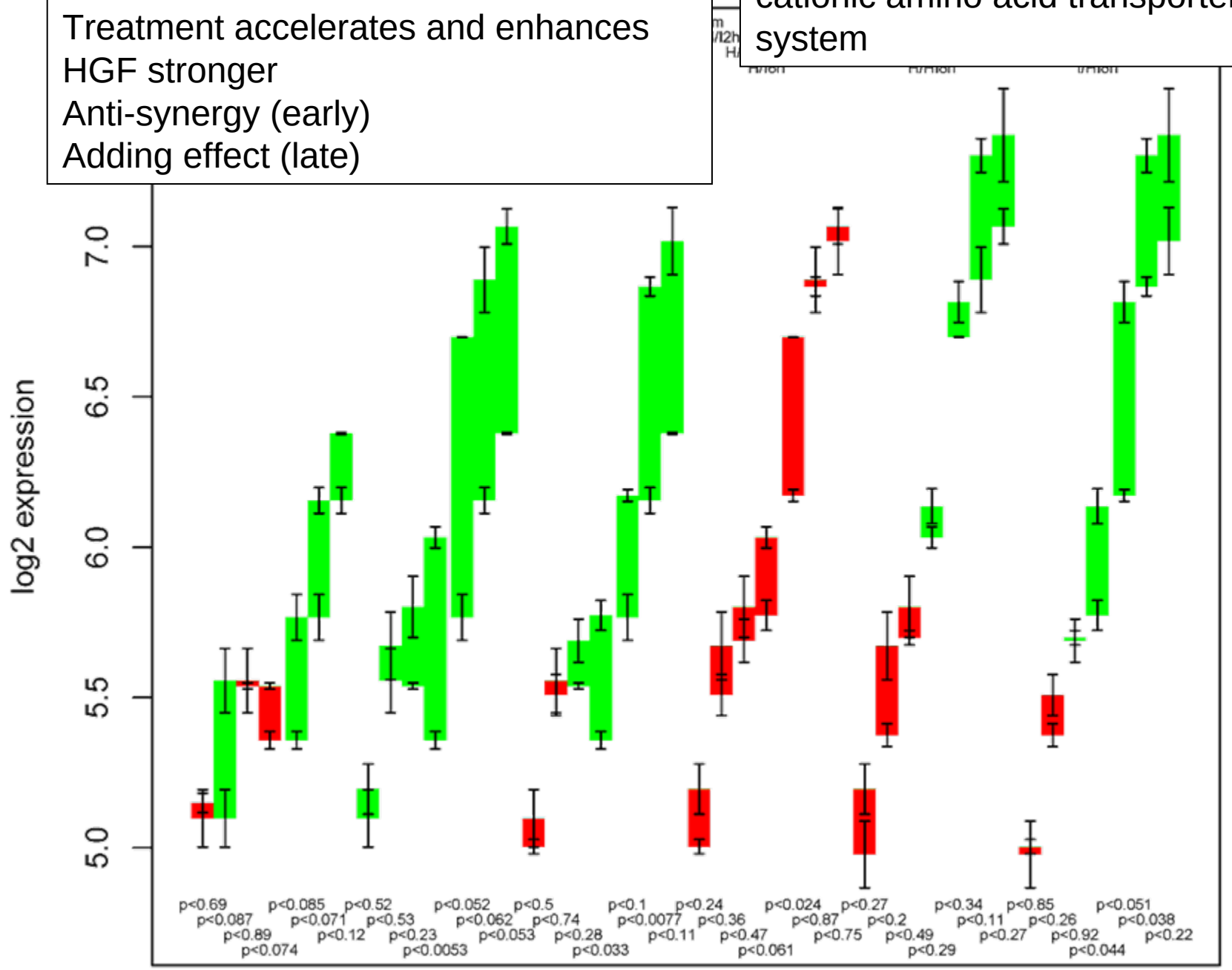

Phenylalanine degr, gene Hgd
Treatment accelerates down-regulation
HGF much stronger
Median of effects (late)
log2 expression
9
8
7
6
5
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
p<0.74
p<0.96
p<0.12
p<0.095
p<0.027
p<0.016
p<0.037
p<0.44
p<0.22
p<0.18
p<0.034
p<0.042
p<0.011
p<0.0004
p<0.48
p<0.19
p<0.19
p<0.09
p<0.16
p<0.11
p<0.33
p<0.88
p<0.06
p<0.21
p<0.72
p<0.079
p<0.039
p<0.077
p<0.54
p<0.19
p<0.69
p<0.17
p<0.48
p<0.18
p<0.15
p<0.42
p<0.035
p<0.12
p<0.23
p<0.26
p<0.12
p<0.81

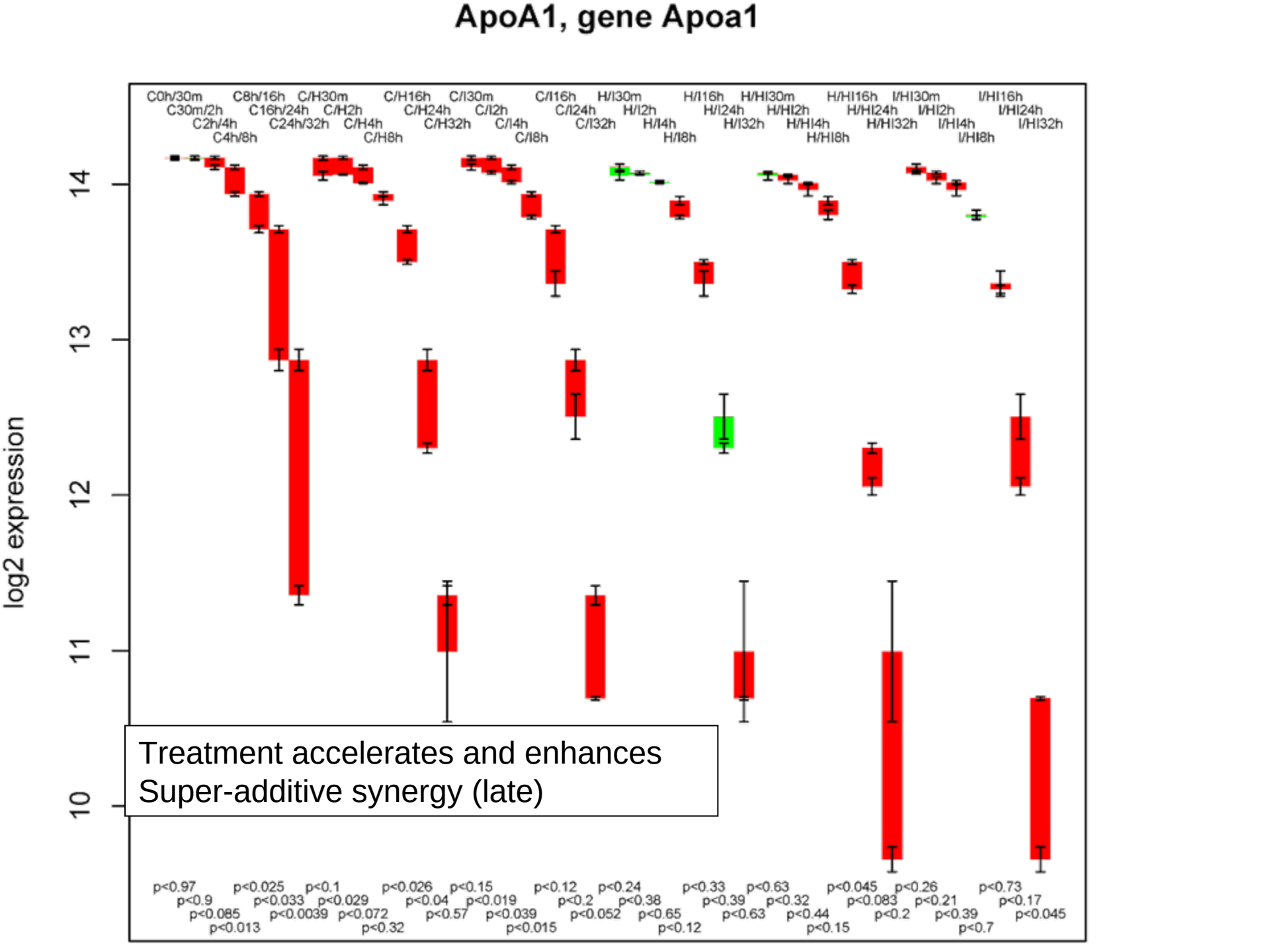

Saccharopine, gene Aass
Aminoadipate-semialdehyde synthase
N6-(L-1,3-Dicarboxypropyl)-L-lysine:NADP+ oxidoreductase
log2 expression
11
10
9
8
7
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
p<0.07
p<0.036
p<0.054
p<0.097
p<0.012
p<0.29
p<0.1
p<0.92
p<0.079
p<0.036
p<0.17
p<0.34
p<0.0022
p<0.42
p<0.43
p<0.17
p<0.055
p<0.27
p<0.28
p<0.093
p<0.2
p<0.17
p<0.27
p<0.26
p<0.022
p<0.16
p<0.21
Treatment accelerates and enhances HGF stronger
Median of effects (early)
Adding of treatment effect (late)

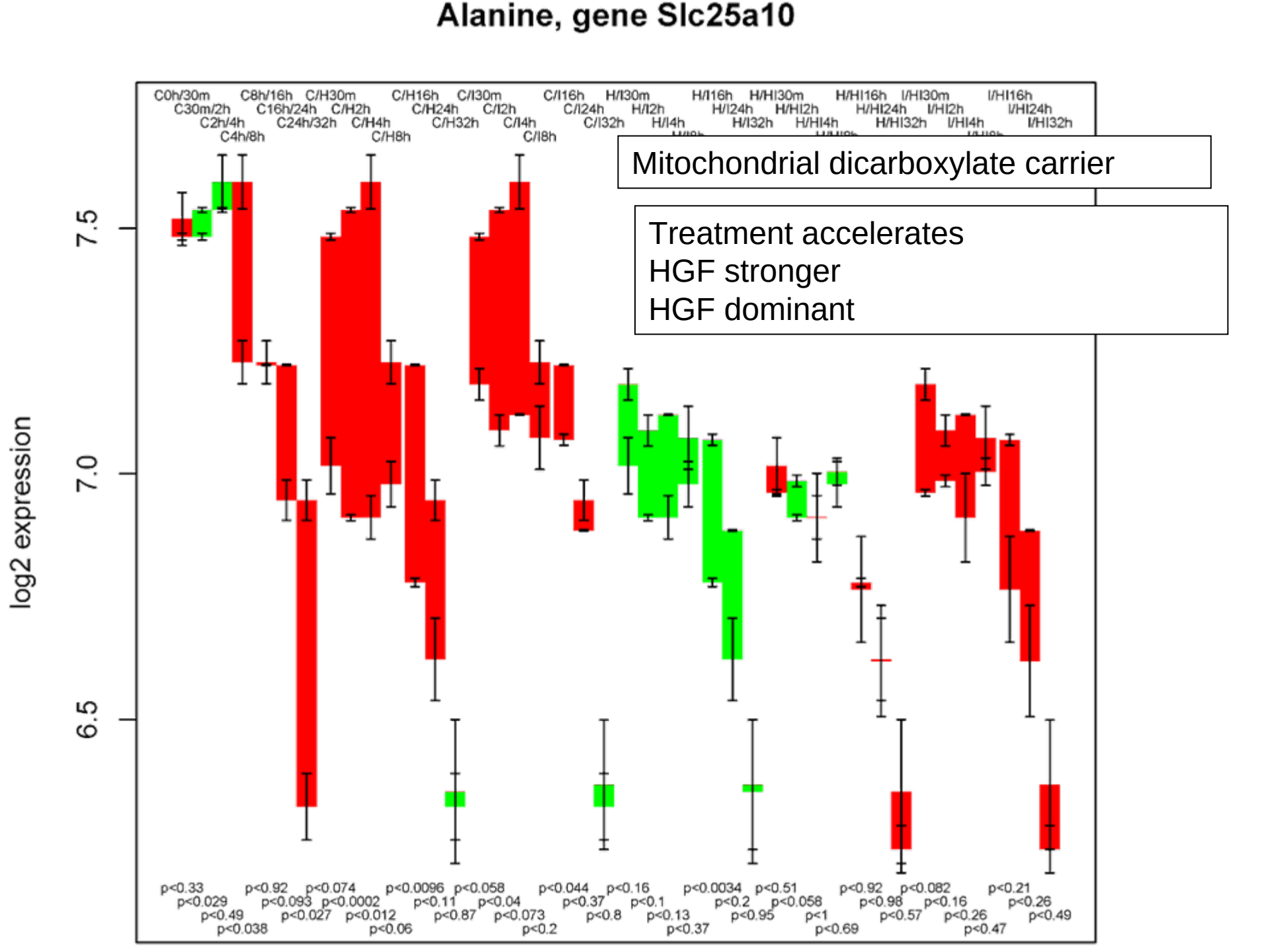
Saccharopine, gene Slc7a6

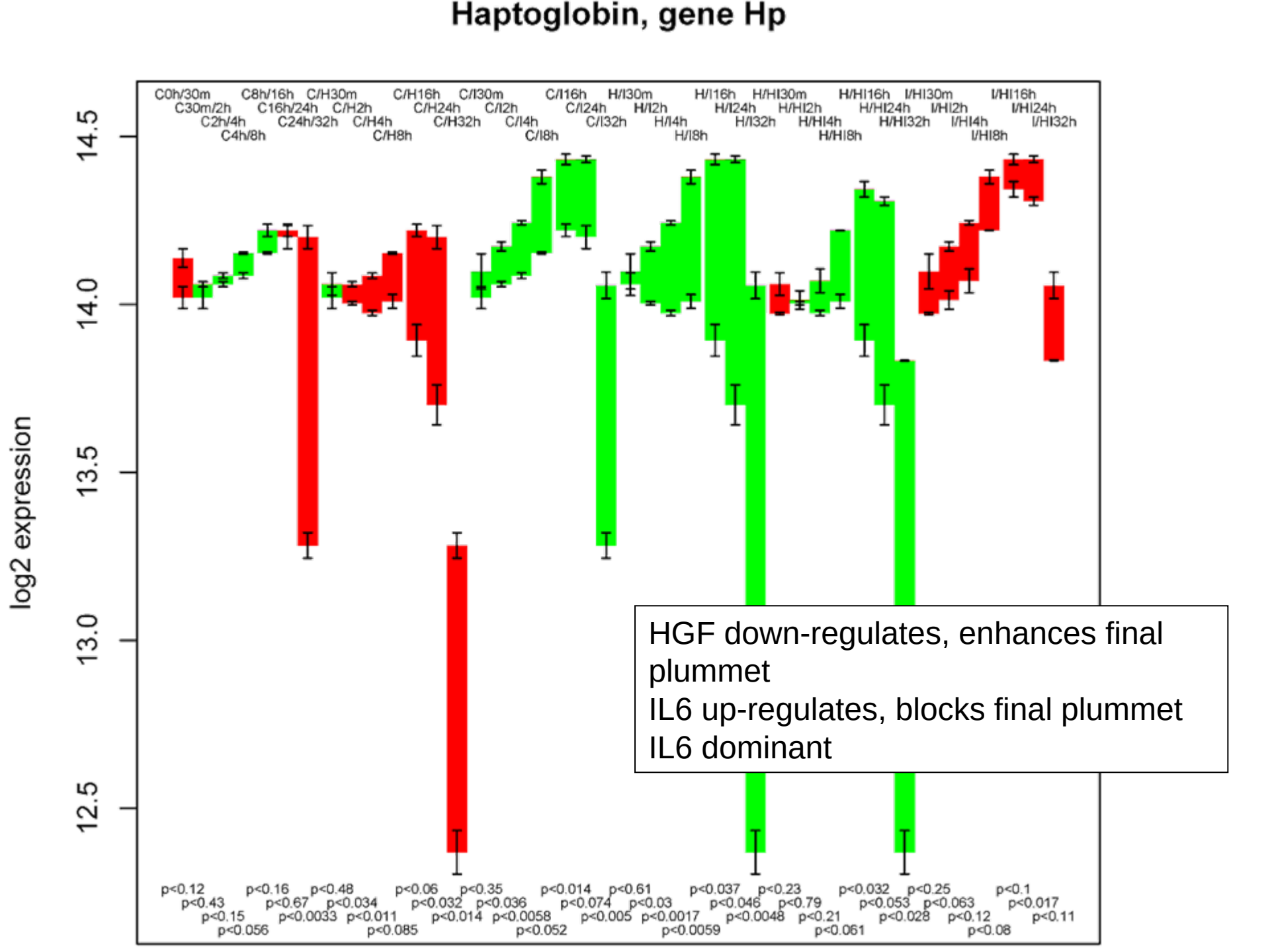
Treatment accelerates and enhances
HGF stronger
Anti-synergy (early)
Adding effect (late)

cationic amino acid transporter, y+ system




ApoA1, gene Apoa1
log2 expression
14
13
12
11
10
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I8h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI8h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
I/HI4h
I/HI8h
I/HI16h
I/HI24h
I/HI32h
p<0.97
p<0.9
p<0.085
p<0.013
p<0.025
p<0.033
p<0.0039
p<0.1
p<0.029
p<0.072
p<0.32
p<0.026
p<0.04
p<0.57
p<0.15
p<0.019
p<0.039
p<0.015
p<0.12
p<0.2
p<0.052
p<0.24
p<0.38
p<0.65
p<0.12
p<0.33
p<0.39
p<0.63
p<0.63
p<0.32
p<0.44
p<0.15
p<0.045
p<0.083
p<0.2
p<0.26
p<0.21
p<0.39
p<0.7
p<0.73
p<0.17
p<0.045
Treatment accelerates and enhances
Super-additive synergy (late)


Alanine, gene Slc25a10
Mitochondrial dicarboxylate carrier
Treatment accelerates
HGF stronger
HGF dominant
log2 expression
7.5
7.0
6.5
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
I/HI4h
I/HI16h
I/HI24h
I/HI32h
p<0.33
p<0.029
p<0.49
p<0.038
p<0.92
p<0.093
p<0.027
p<0.074
p<0.0002
p<0.012
p<0.06
p<0.0096
p<0.11
p<0.87
p<0.058
p<0.04
p<0.073
p<0.2
p<0.044
p<0.37
p<0.8
p<0.16
p<0.1
p<0.13
p<0.37
p<0.0034
p<0.2
p<0.95
p<0.51
p<0.058
p<1
p<0.69
p<0.92
p<0.98
p<0.57
p<0.082
p<0.16
p<0.26
p<0.47
p<0.21
p<0.26
p<0.49


Haptoglobin, gene Hp
log2 expression
14.5
14.0
13.5
13.0
12.5
C0h/30m
C30m/2h
C2h/4h
C4h/8h
C8h/16h
C16h/24h
C24h/32h
C/H30m
C/H2h
C/H4h
C/H8h
C/H16h
C/H24h
C/H32h
C/I30m
C/I2h
C/I4h
C/I8h
C/I16h
C/I24h
C/I32h
H/I30m
H/I2h
H/I4h
H/I8h
H/I16h
H/I24h
H/I32h
H/HI30m
H/HI2h
H/HI4h
H/HI8h
H/HI16h
H/HI24h
H/HI32h
I/HI30m
I/HI2h
I/HI4h
I/HI8h
I/HI16h
I/HI24h
I/HI32h
p<0.12
p<0.43
p<0.15
p<0.056
p<0.16
p<0.67
p<0.0033
p<0.48
p<0.034
p<0.011
p<0.085
p<0.06
p<0.032
p<0.014
p<0.35
p<0.036
p<0.0058
p<0.052
p<0.014
p<0.074
p<0.005
p<0.61
p<0.03
p<0.0017
p<0.0059
p<0.037
p<0.046
p<0.0048
p<0.23
p<0.79
p<0.21
p<0.061
p<0.032
p<0.053
p<0.028
p<0.25
p<0.063
p<0.12
p<0.08
p<0.1
p<0.017
p<0.11
HGF down-regulates, enhances final plummet
IL6 up-regulates, blocks final plummet
IL6 dominant

Types of treatment effect

Effect of a single treatment

- plain regulation
- acceleration
- block of development

Combined effect of treatments

- additive in regulation
- additive in acceleration
- synergistic
- anti-synergistic (factors block each other)
- median of diverging effects
- dominance of one