virtual liver network

CHARITÉ
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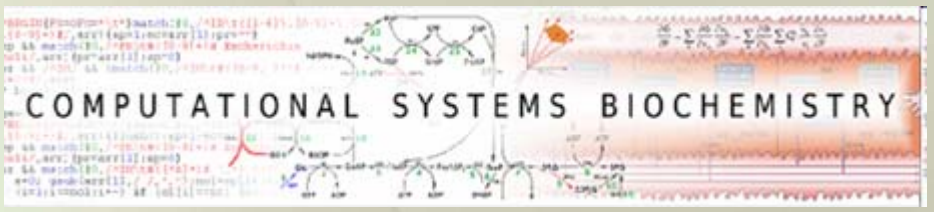
Effects of statin treatment

Steroltalk RNA data analyzed for metabolic regulation

Andreas Hoppe, Charité Universtitätsmedizin Berlin
Computational systems biochemistry group



virtual liver network

COMPUTATIONAL SYSTEMS BIOCHEMISTRY

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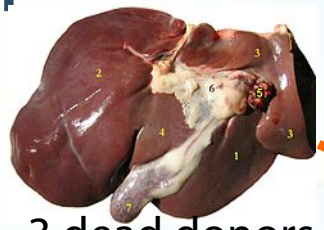
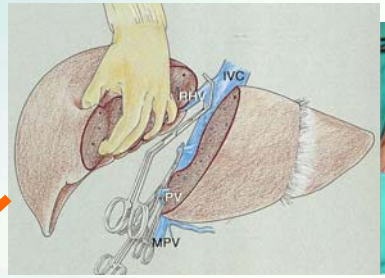
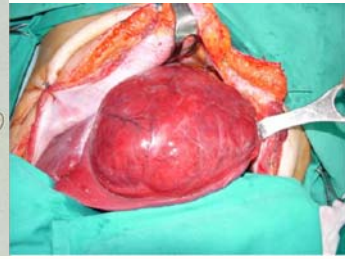
Experimental set-up



3 dead donors

A B C



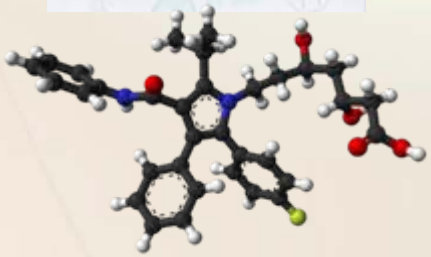


3 donors, lobectomy, liver cancer

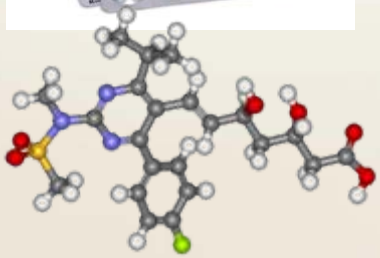
D E F

C

A



V



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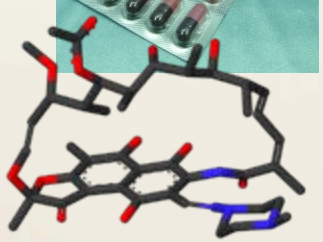
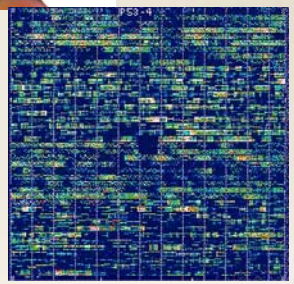


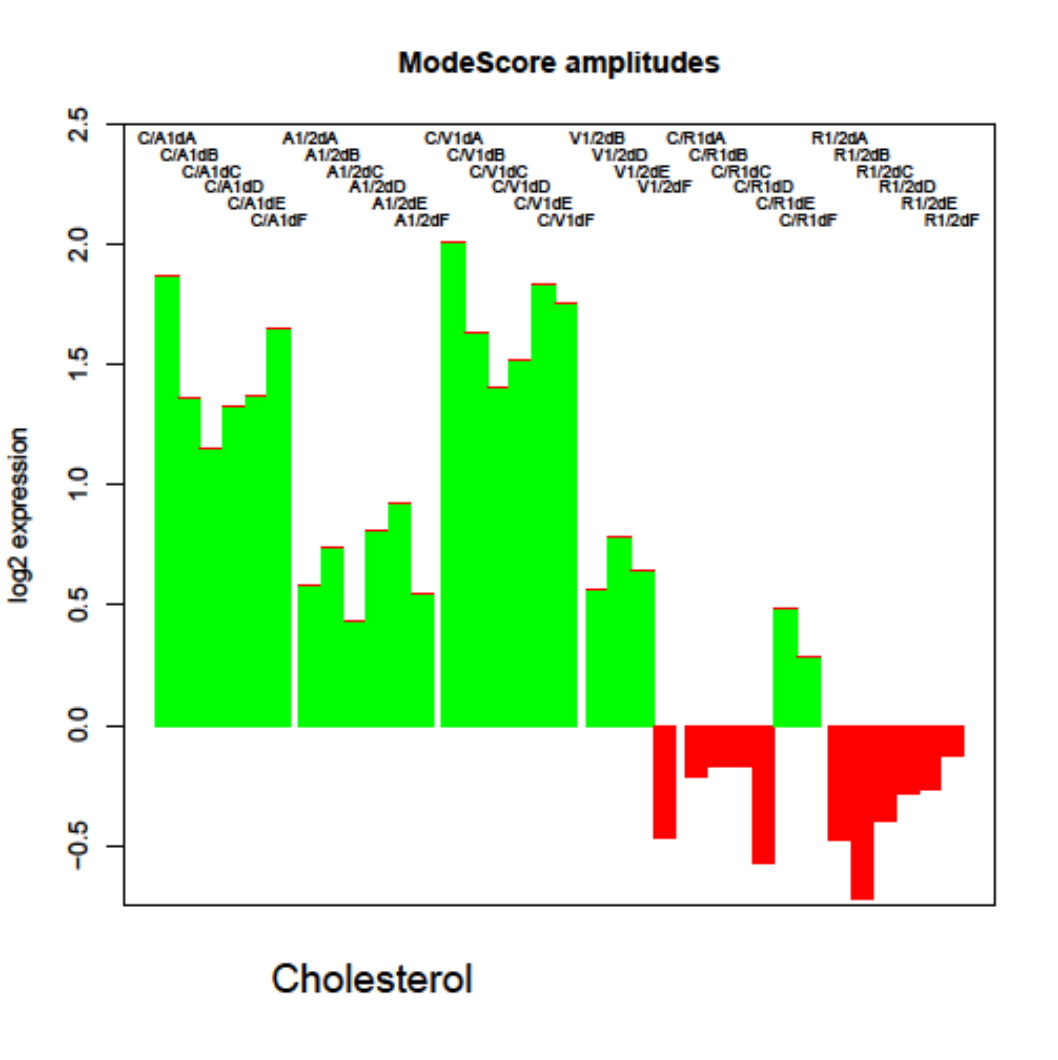


SterolTalk EU project
Budapest, Ljubljana

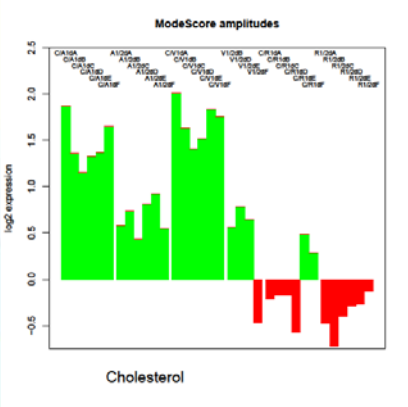
1d

2d

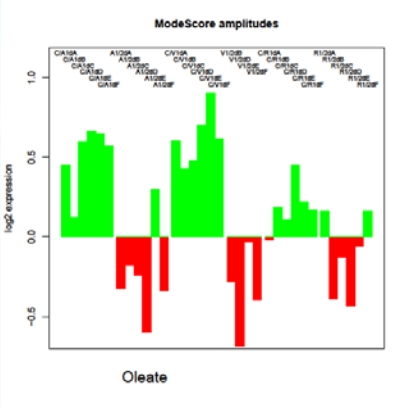
ModeScore analysis, top scorer



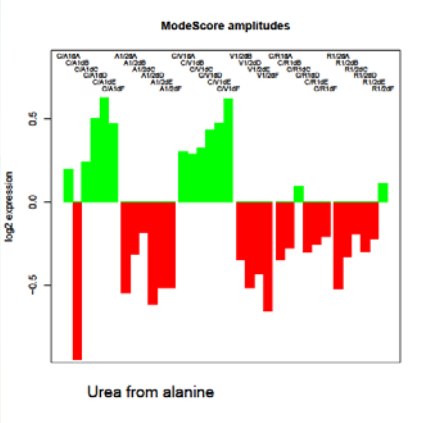
ModeScore analysis, areas of large changes



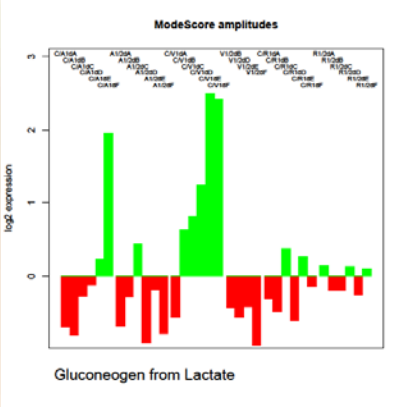
Cholesterol synthesis



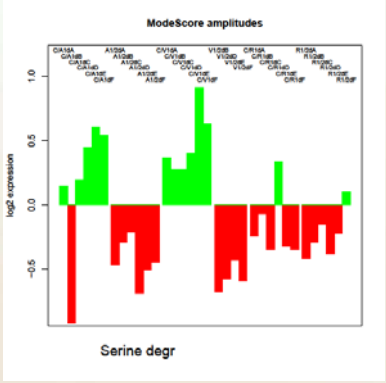
Fatty acid metabolism



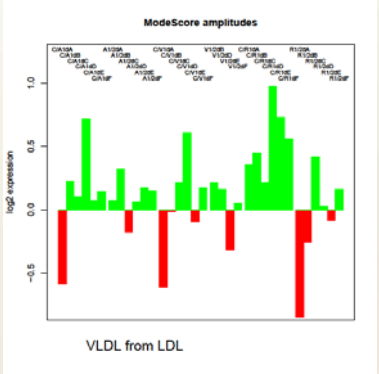
Urea synthesis



Sugar metabolism

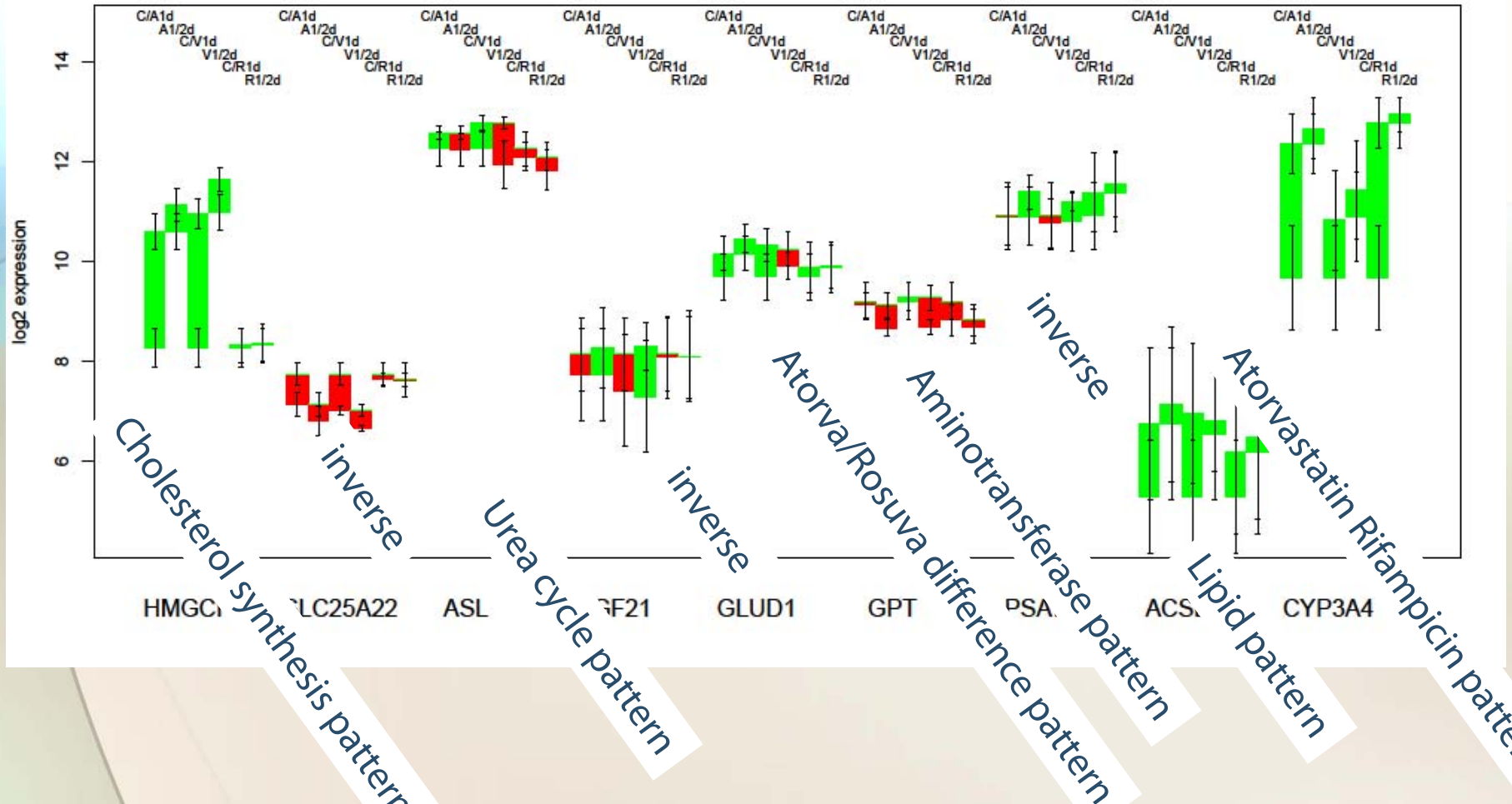


Transamination

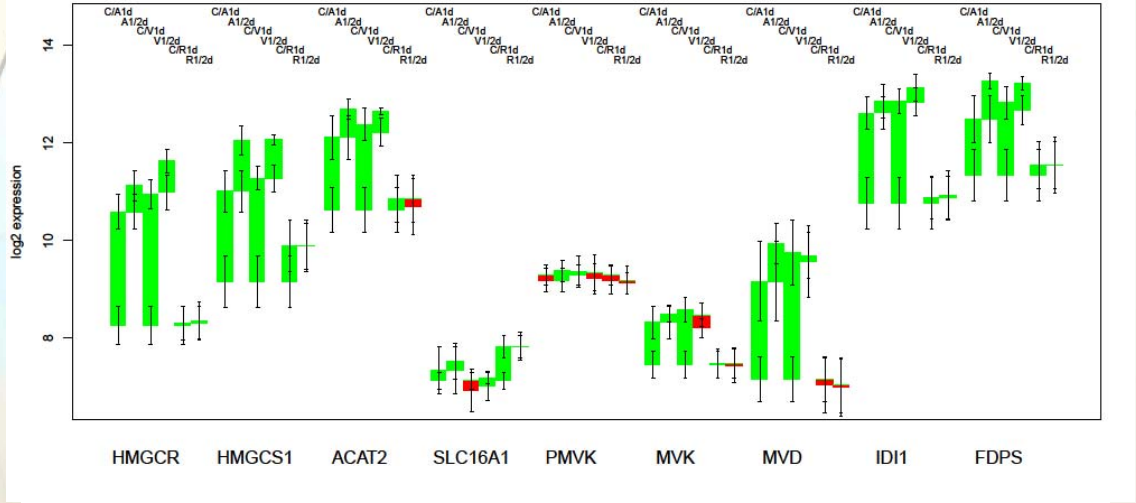


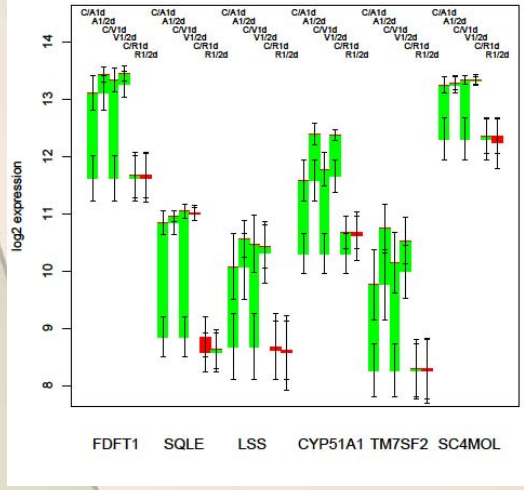
Lipoproteins

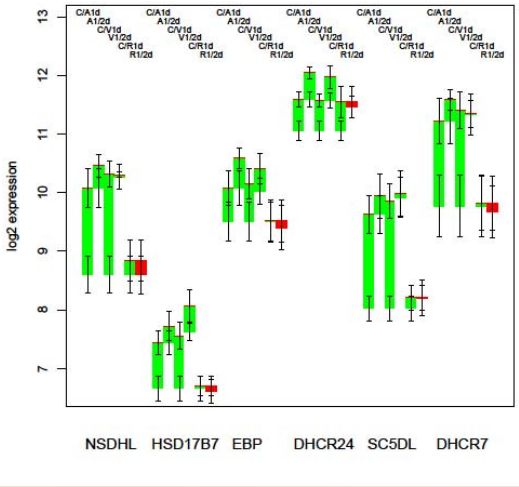
Patterns of gene changes



Cholesterol synthesis pattern







Very consistent

18/21 enyzmes of cholesterol synthesis

Large changes

Pattern definition

Statins:

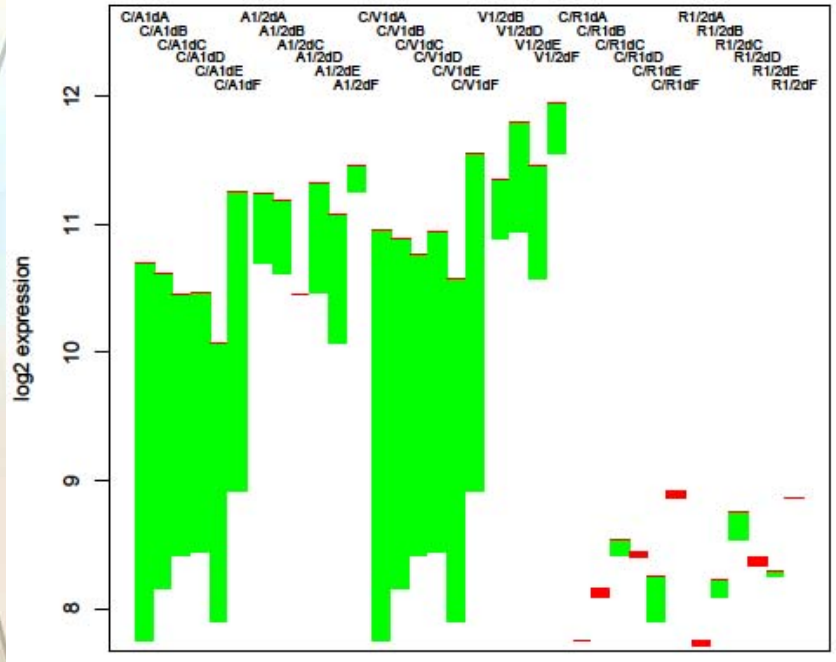
1d strong up

2d (slightly) up

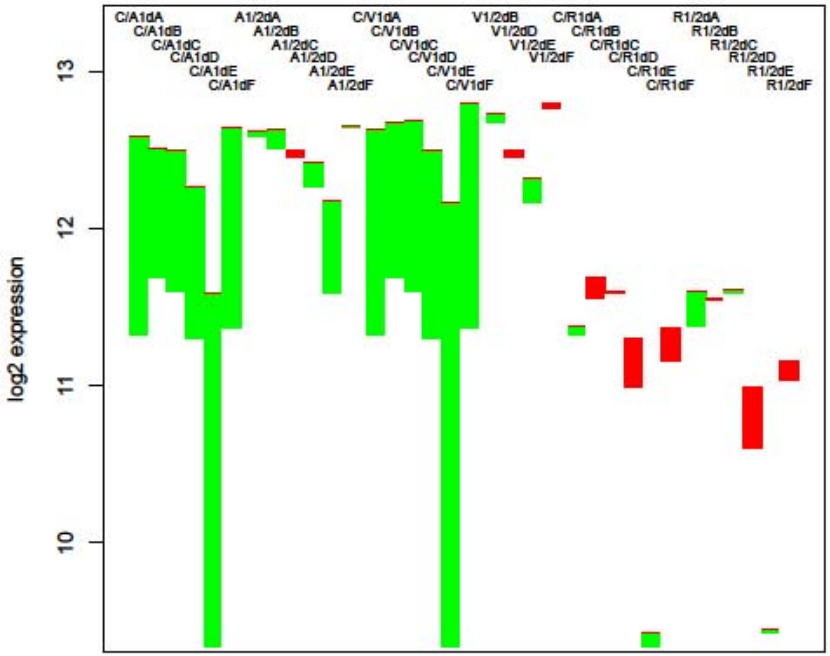
Rifampicin:

minor change

Cholesterol synthesis pattern



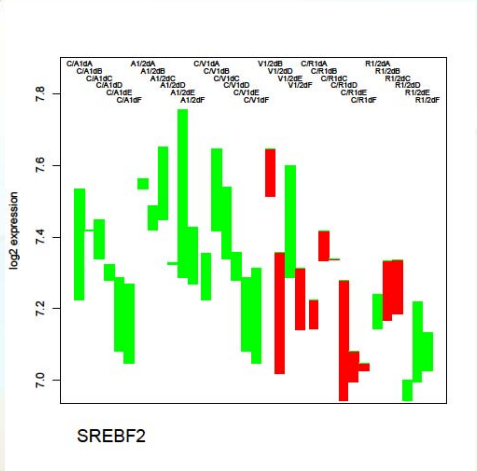
HMGCR HMG-CoA reductase

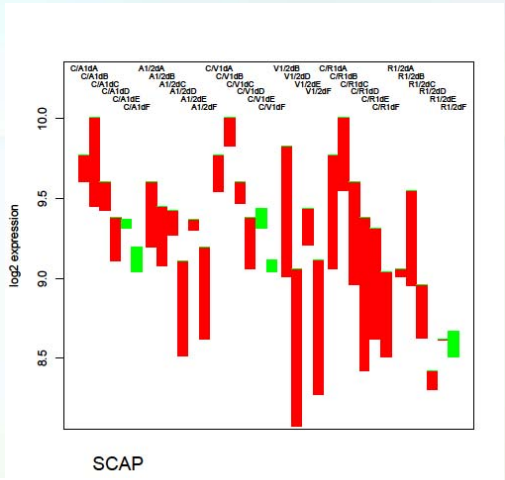


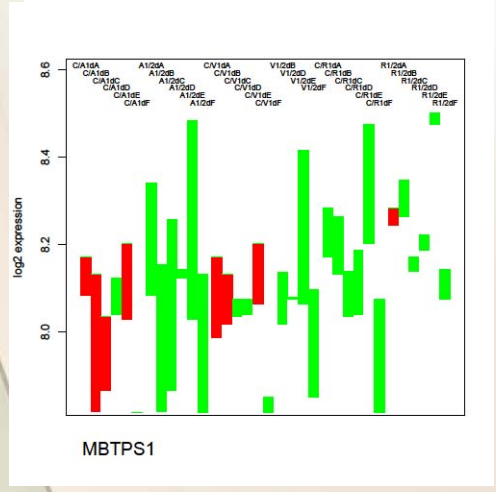
INSIG1 Insulin-induced gene

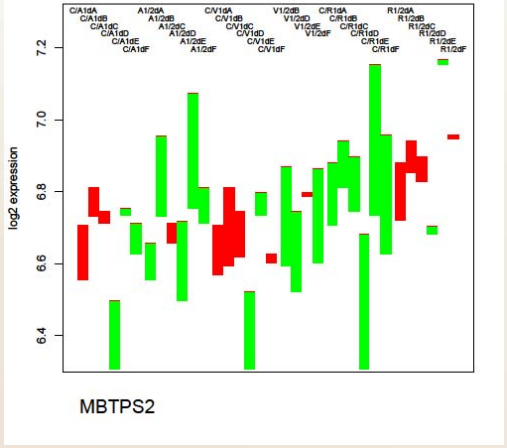
Other enzymes and genes: ACAT2, FABP1

Cholesterol synthesis pattern, how?



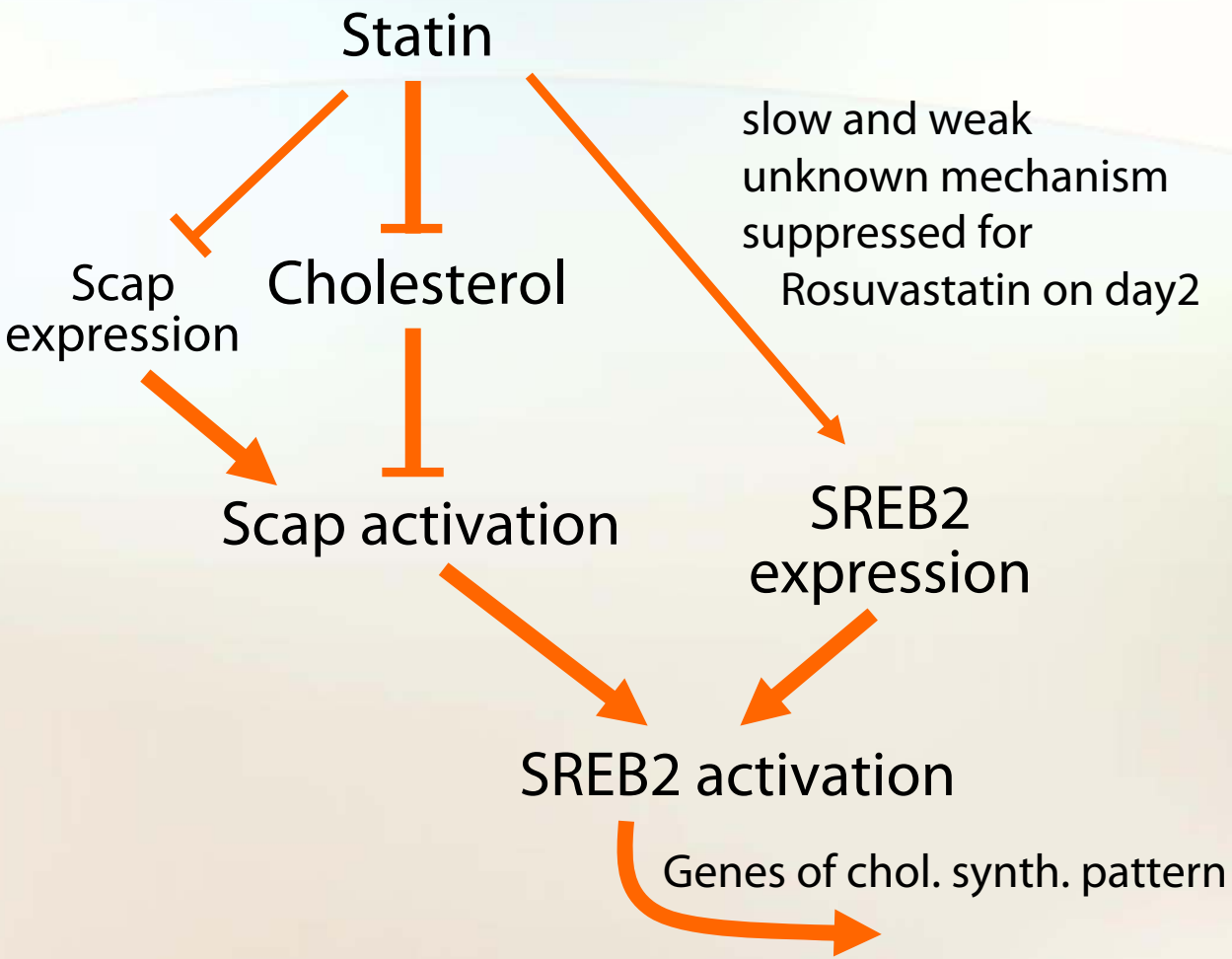




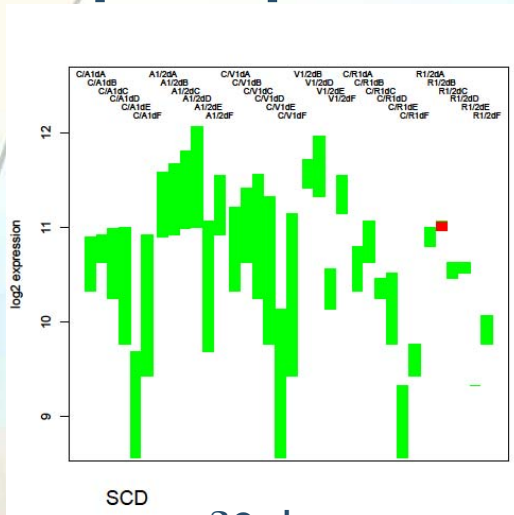


- Regulated by active SREB2
- Gene product of SREBF2
- Activated by Scap (sterol-sensing)
- cleaved by proteases

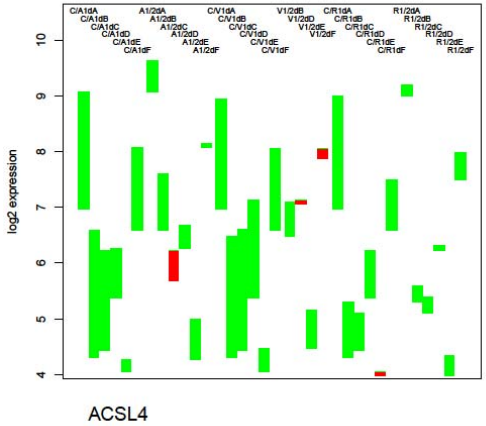
Sterol regulation



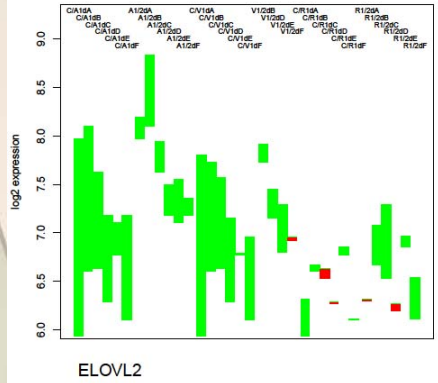
Lipid pattern

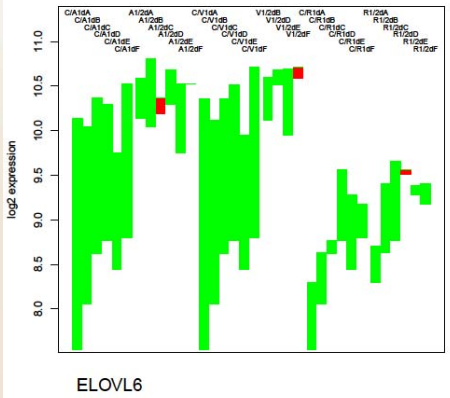


δ9 desaturase



acyl-CoA synthetase





FA elongases

Particular enzymes in lipid formation, FA synthesis and degradation

Specific isoforms

Pattern definition

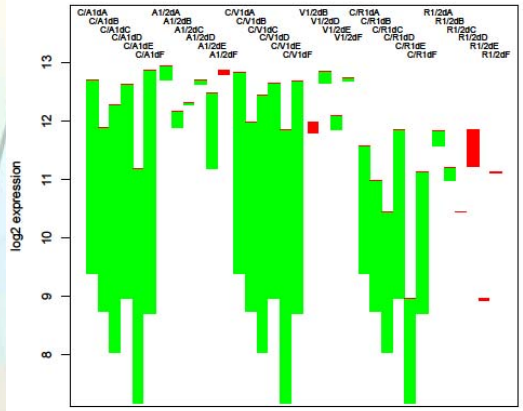
Statins:

- 1d up
- 2d up

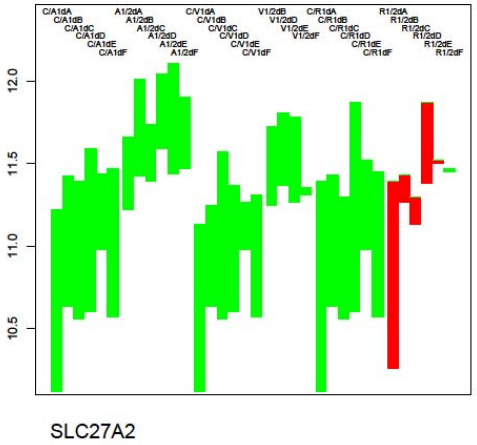
Rifampicin:

- up, less than statins

Lipid pattern

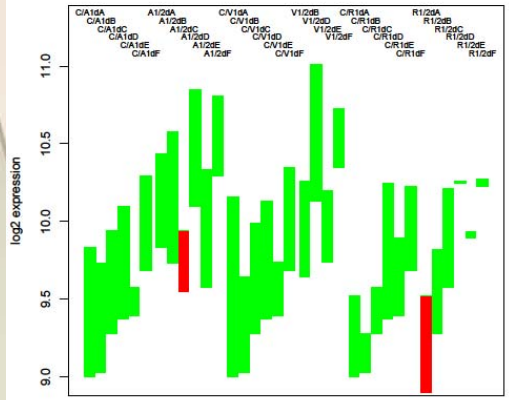


thyroid-hormone responsive

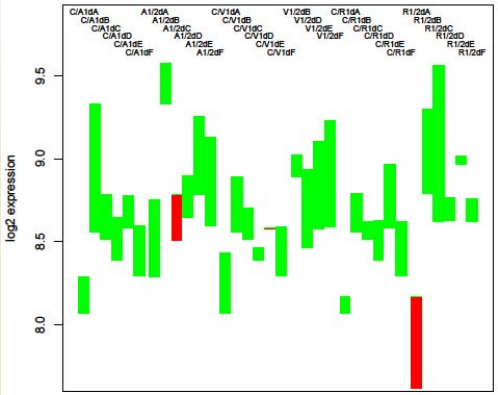


FA transporter

THRSP … known regulator of lipid metabolism



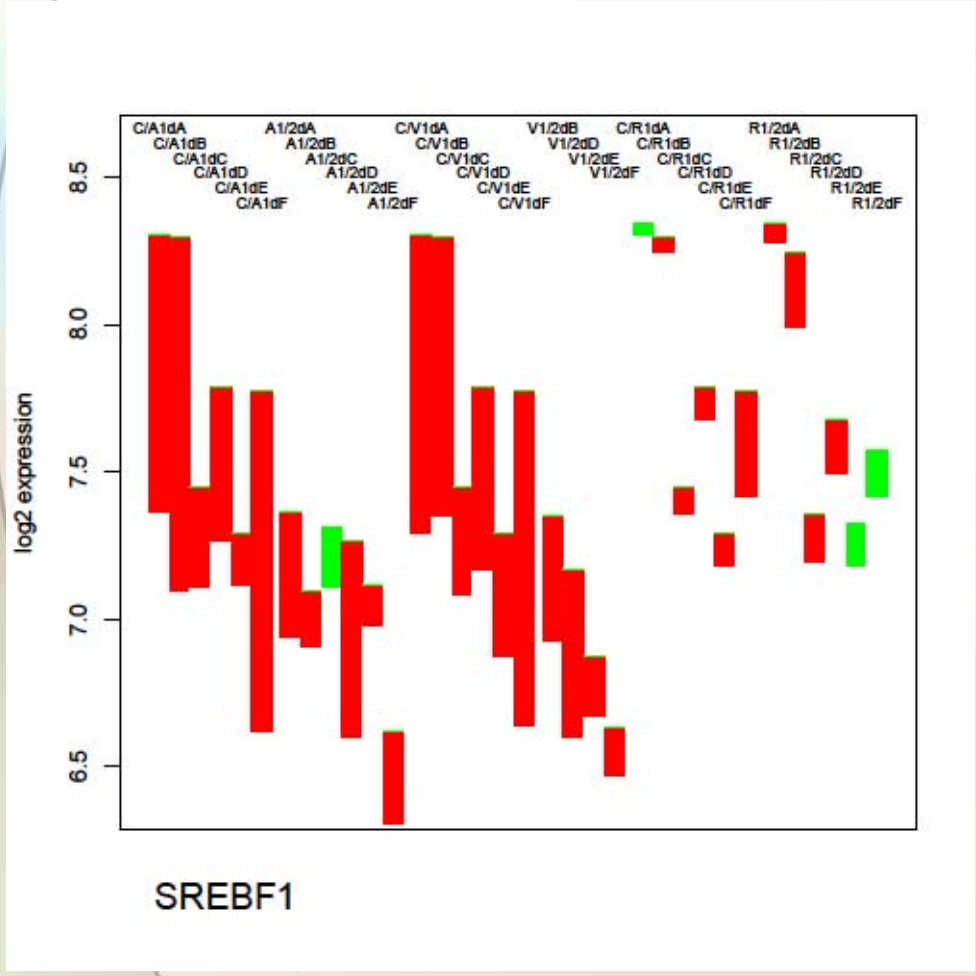
enoyl-CoA hydratase



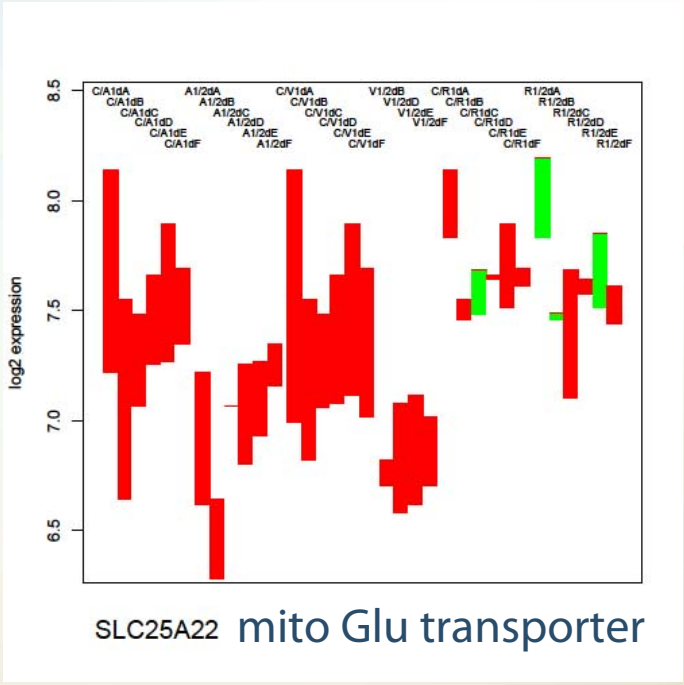
Insulin-induced gene

Inverse cholesterol synthesis pattern

Only few genes



SREBF1



SLC25A22 mito Glu transporter

Pattern definition

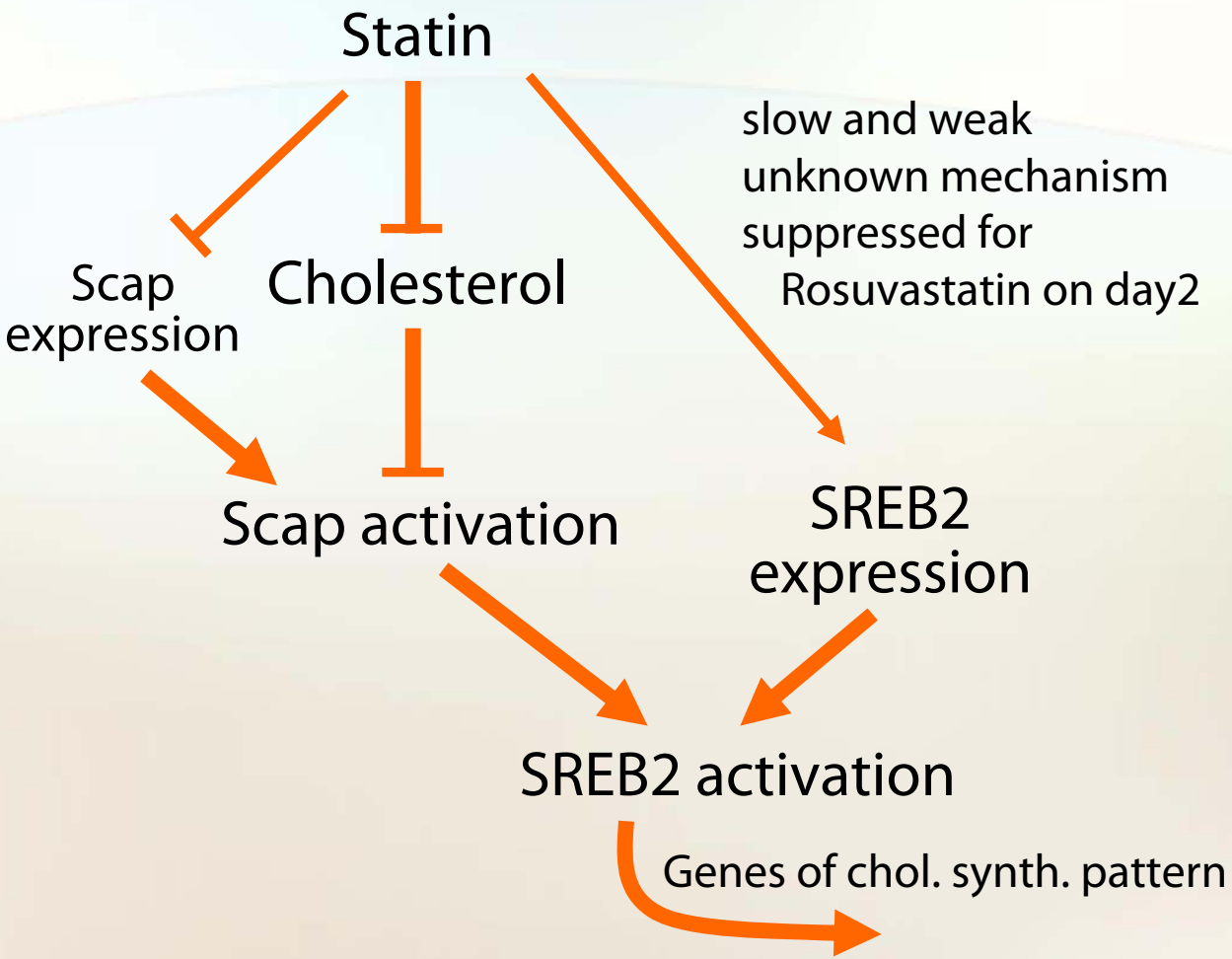
Statins:

- 1d strong down
- 2d (slightly) down

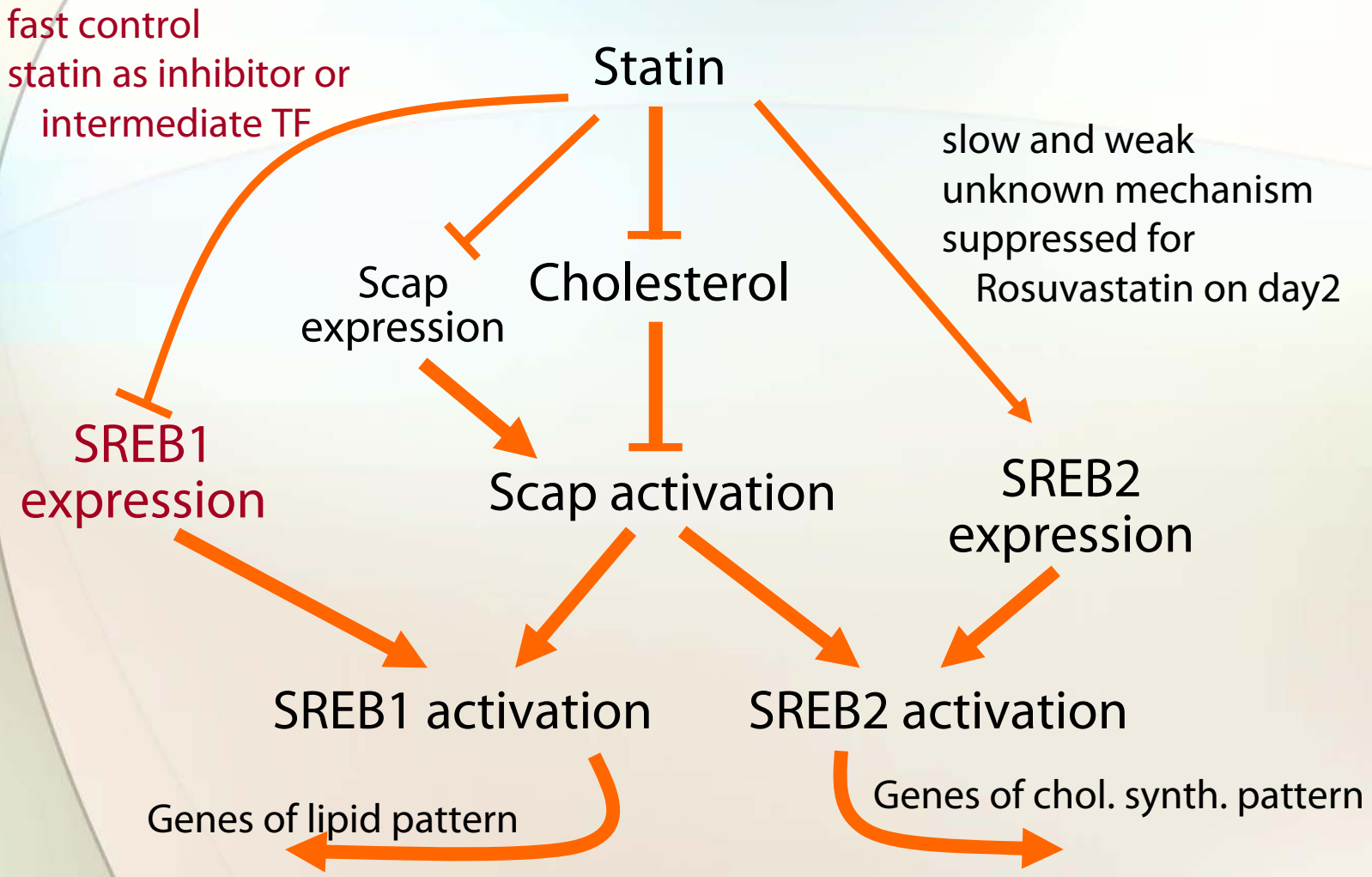
Rifampicin:

- minor change

Sterol regulation



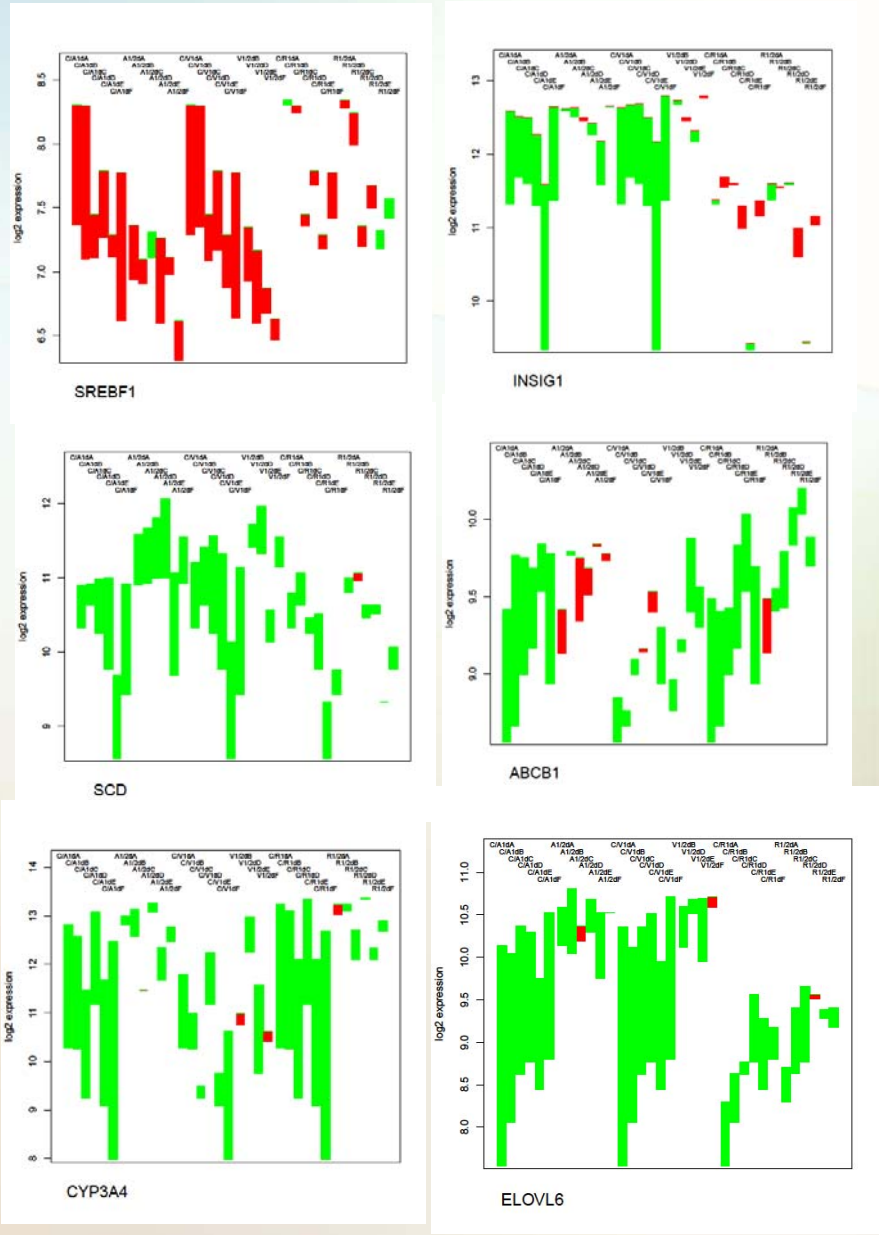
Link of sterol and lipid regulation



CAR/PXR

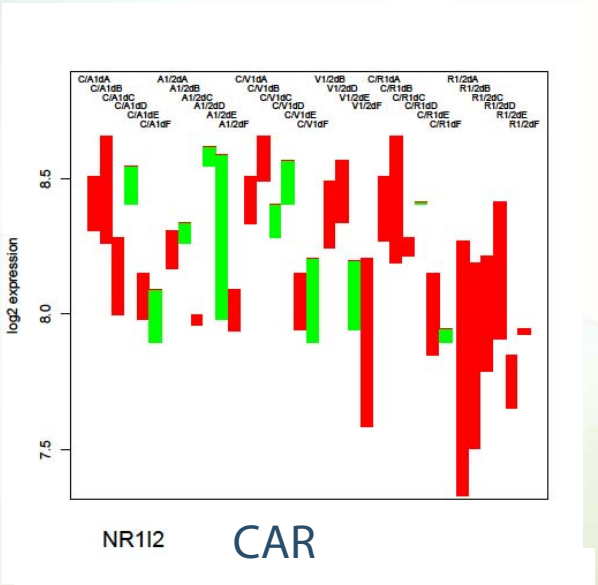
- SREBF1, INSIG1, SCD, ABCB1, CYP3A4, ELOVL6 are known to be activated by CAR/PXR
- Affected by both statins
- But: different patterns

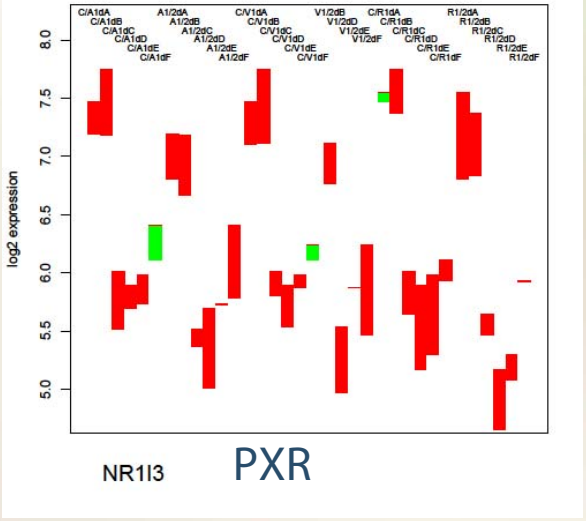
CAR … constituitive andrane receptor
PXR … pregnane X receptor
Hafner et al, 2011



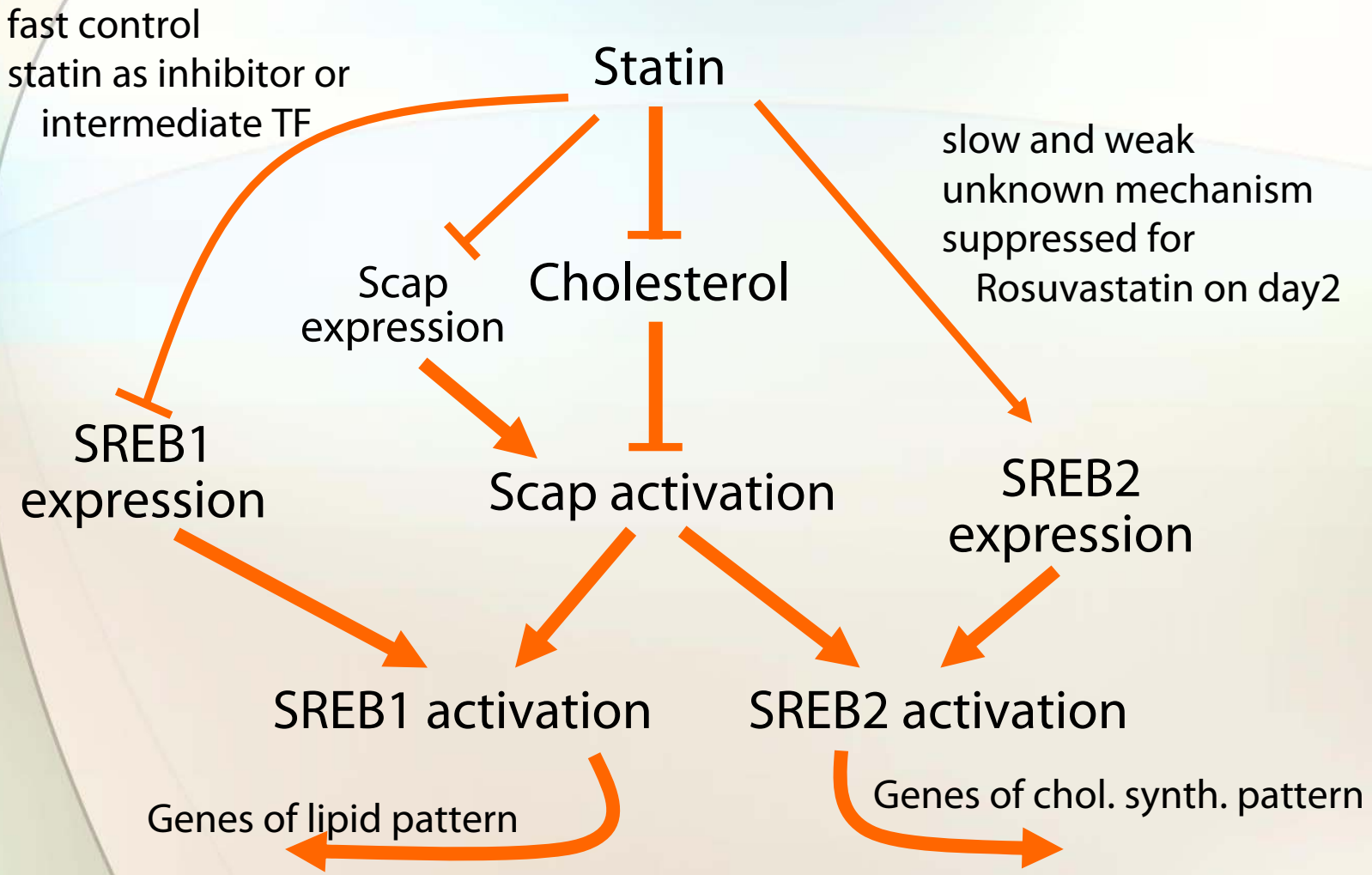
CAR/PXR

- De novo synthesis of receptors
  - CAR down by Rifmpicin
  - PXR slightly down by all
- May contribute statin regulation
  - decoupling of SREB1/SREB2

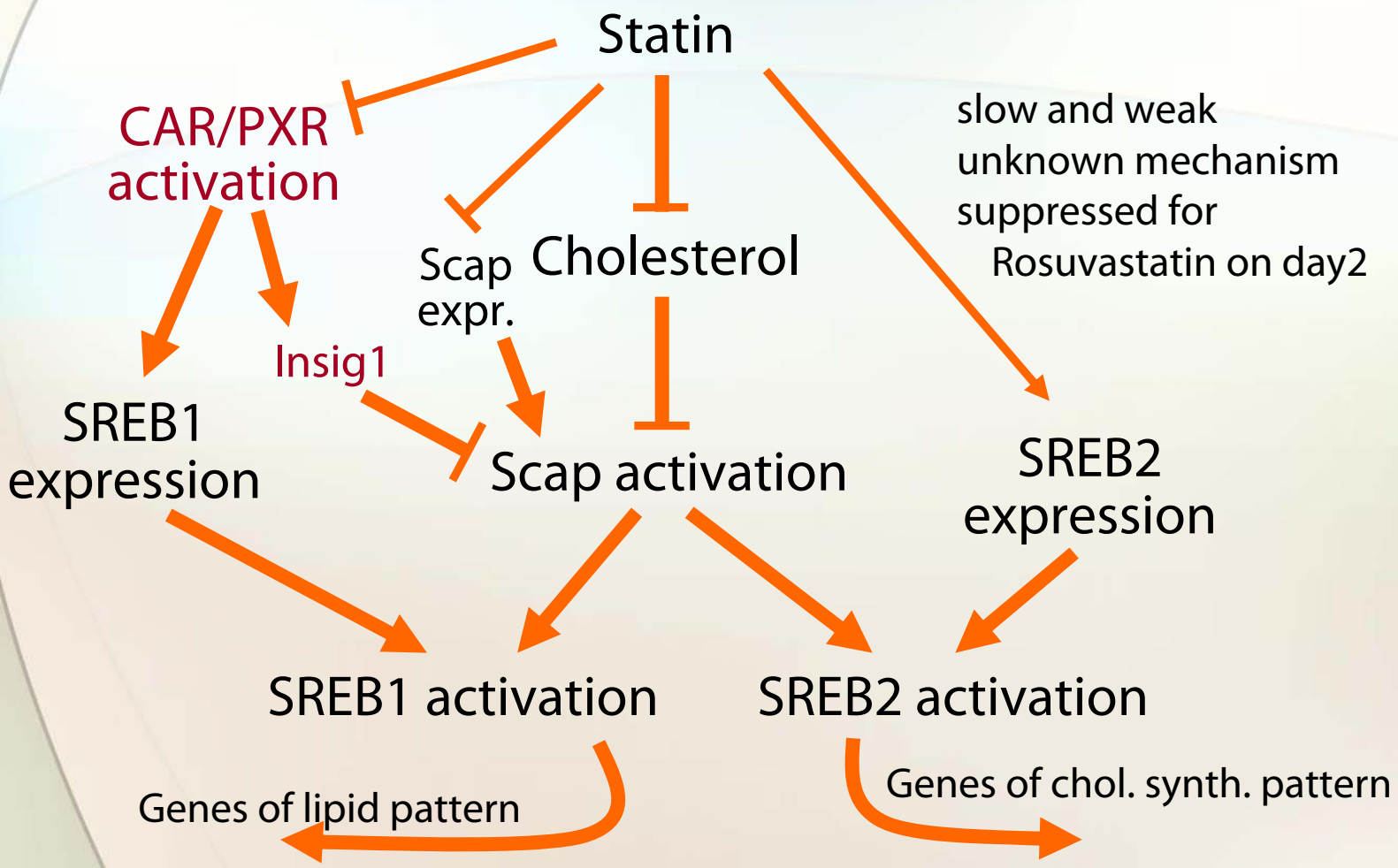




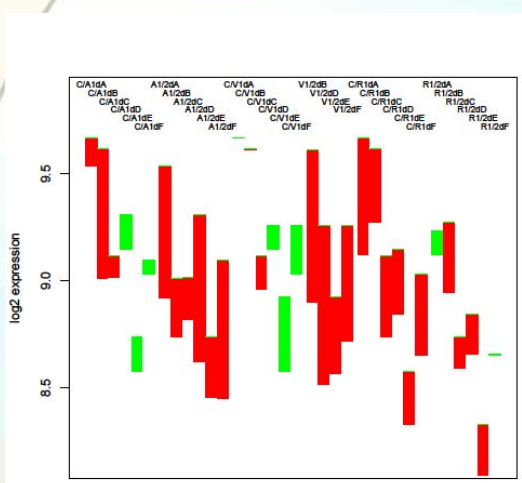
Link of sterol and lipid regulation



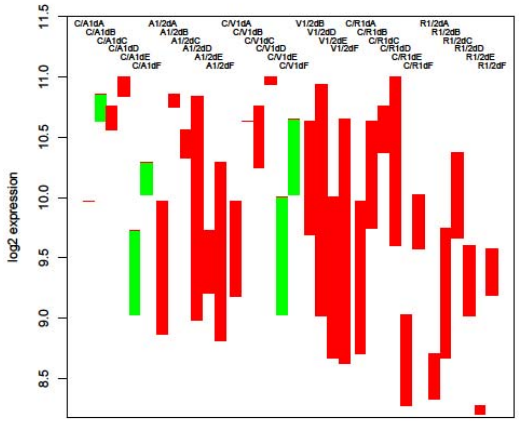
Link of sterol and lipid regulation



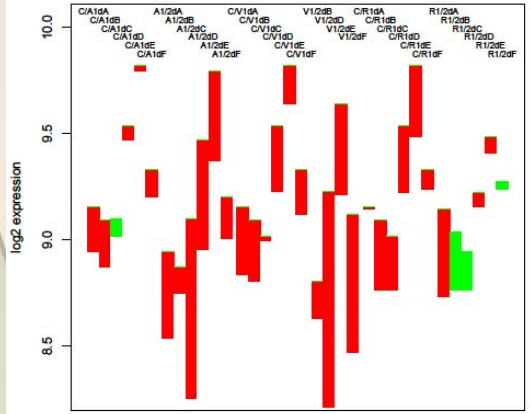
Aminotransferase pattern



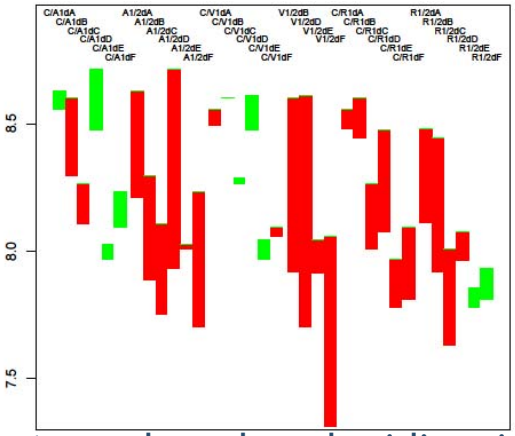
GPT
Alanine aminotransferase



SDS
Serine dehydratase



GNPNAT1 glucosamine-phosphate N-acetyltransferase



AGPAT1 lysophosphatidic acid acyltransferase

Several amino-acid enzymes

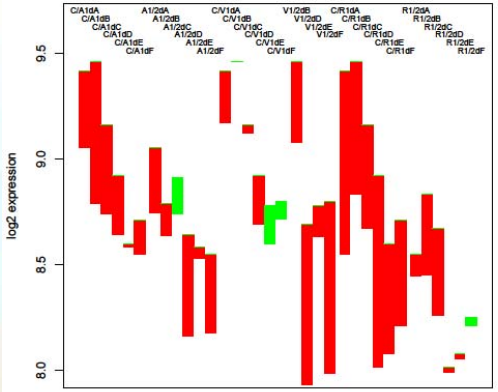
But also other enzymes TPI1 PCCB ALDH4A1 APOC2 CYP8B1

Pattern definition

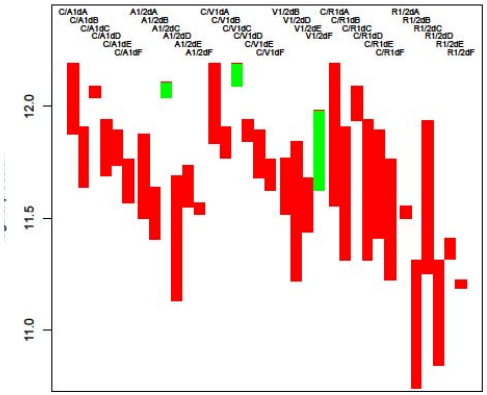
Statins:
- 1d minor change
- 2d down

Rifampicin:
- 1d down
- 2d minor change

Aminotransferase pattern, how?

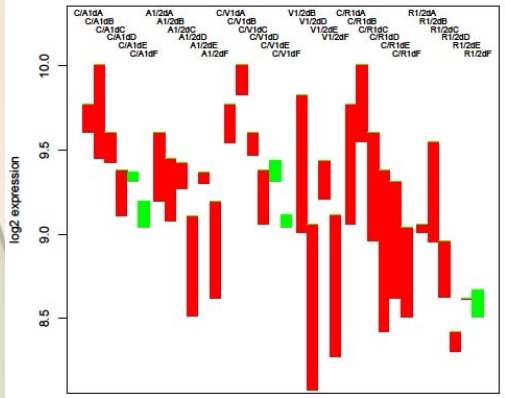


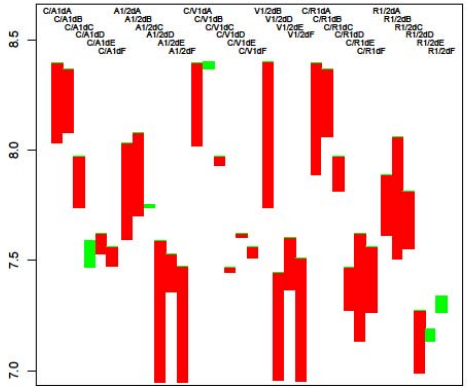
retinoid-X-receptor α



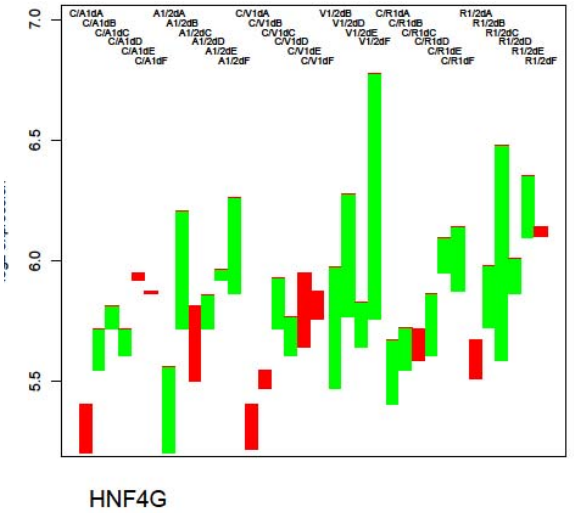
Interlinked with SREB activation

Nuclear factors





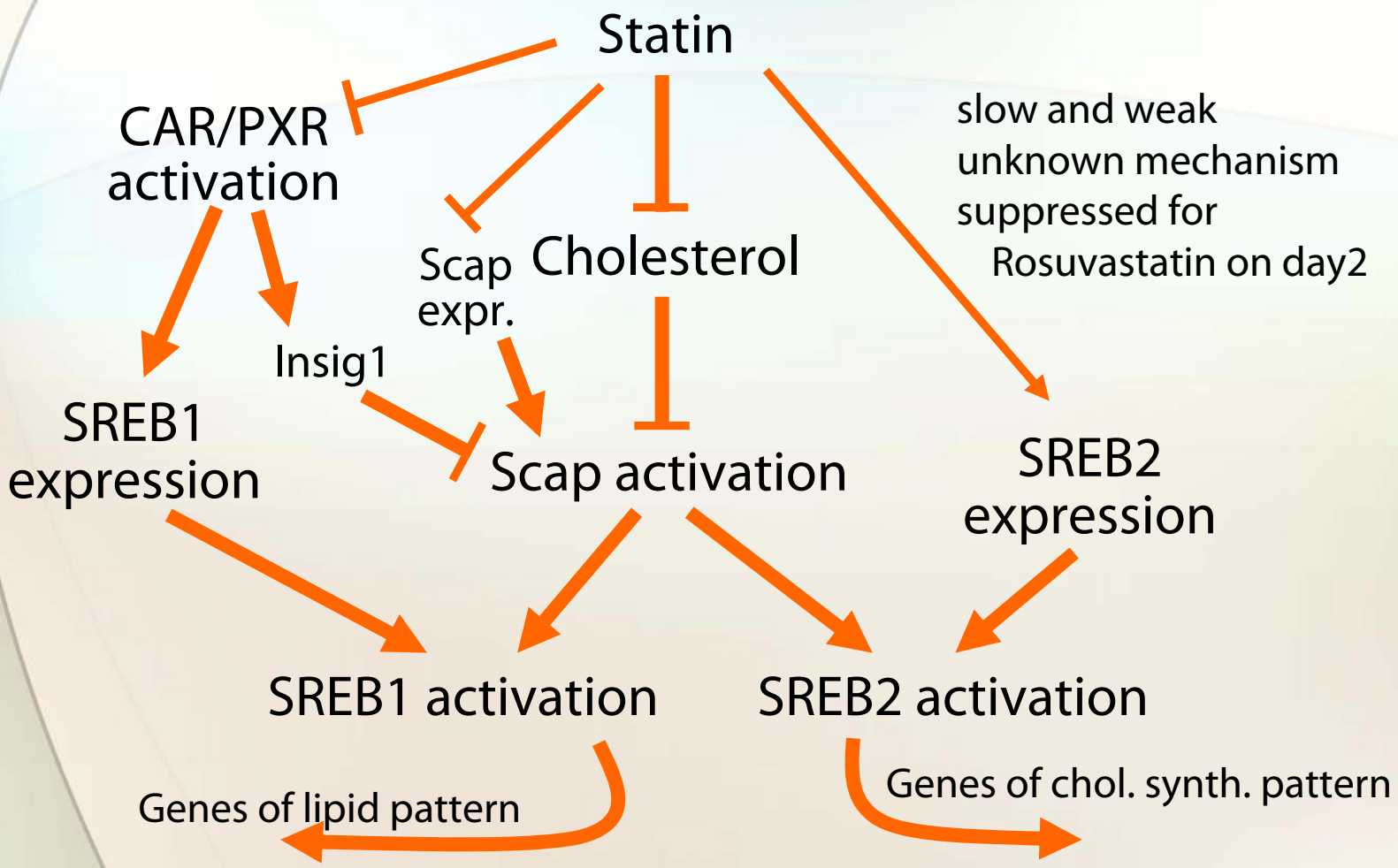
hepatocyte nuclear factor α



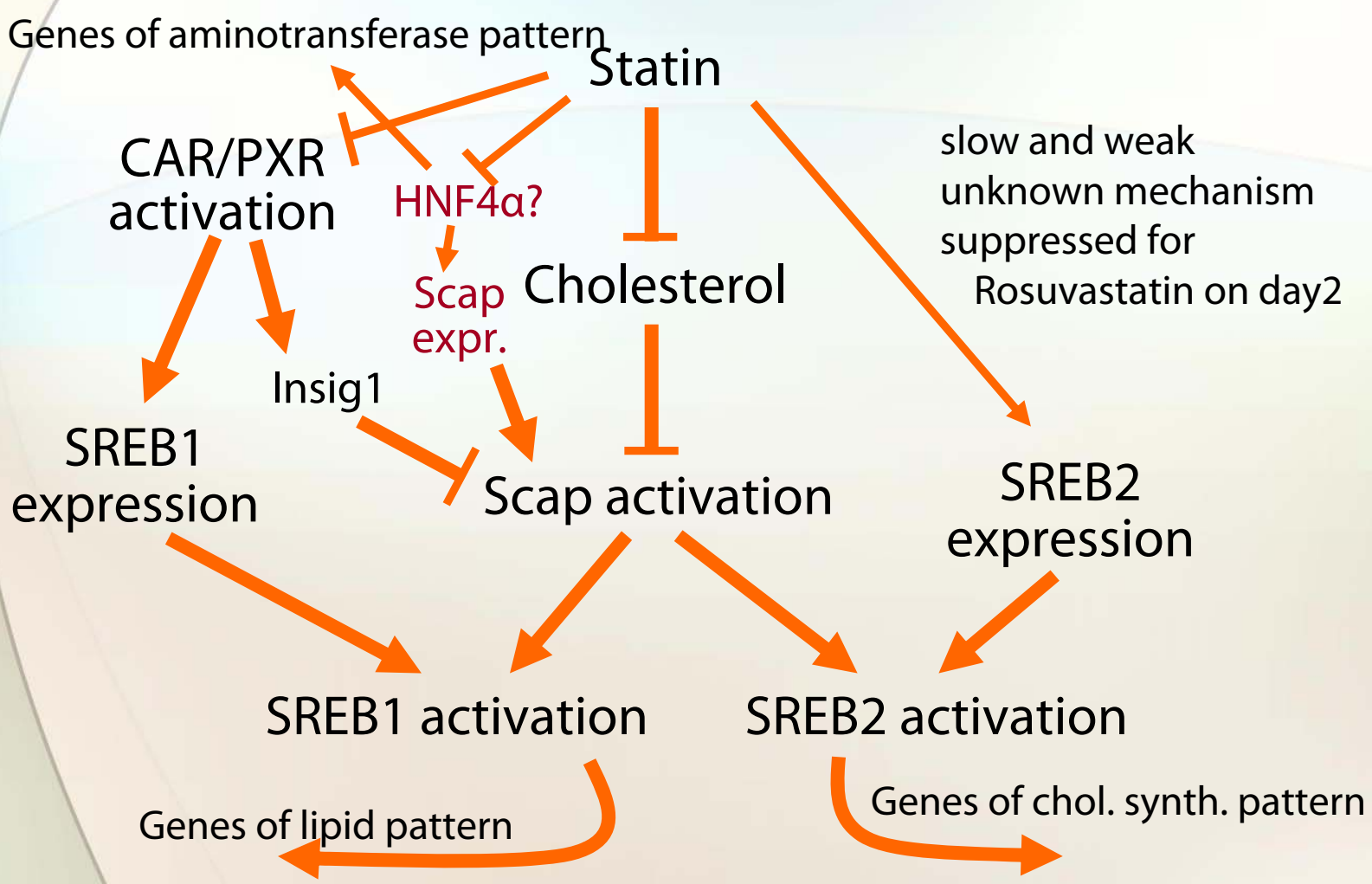
hepatocyte nuclear factor γ

inverse pattern

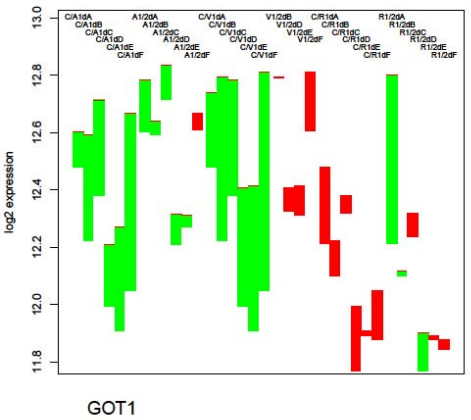
Link of sterol and lipid regulation



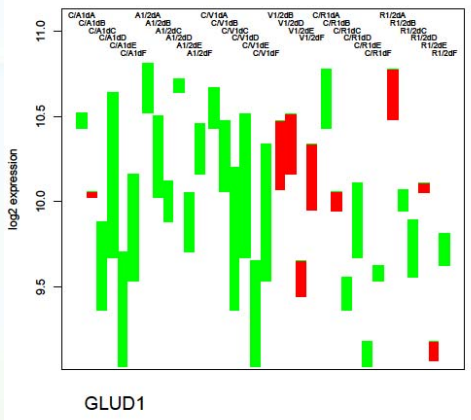
Link of sterol and lipid regulation



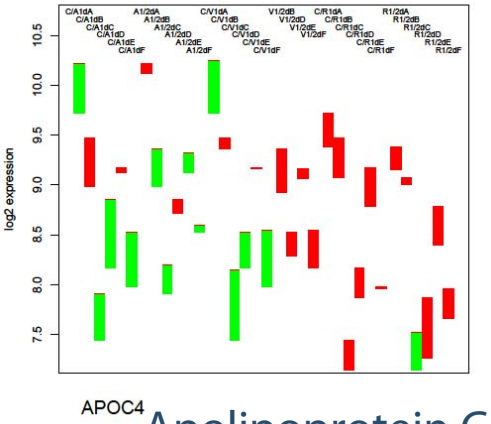
Atorva/Rosuvastatin difference



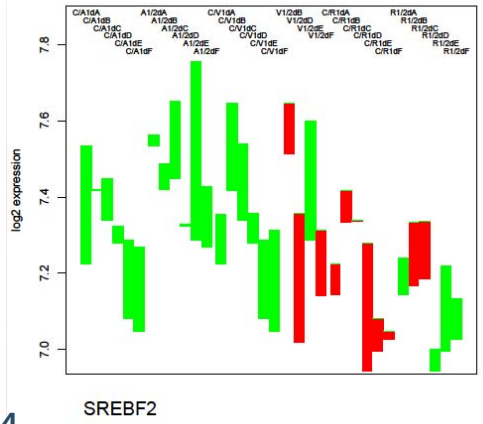
Aspartate aminotransferase



Glutamatedehydrogenase



Apolipoprotein C4



Several amino-acid enzymes

Some nuclear factors

Pattern definition

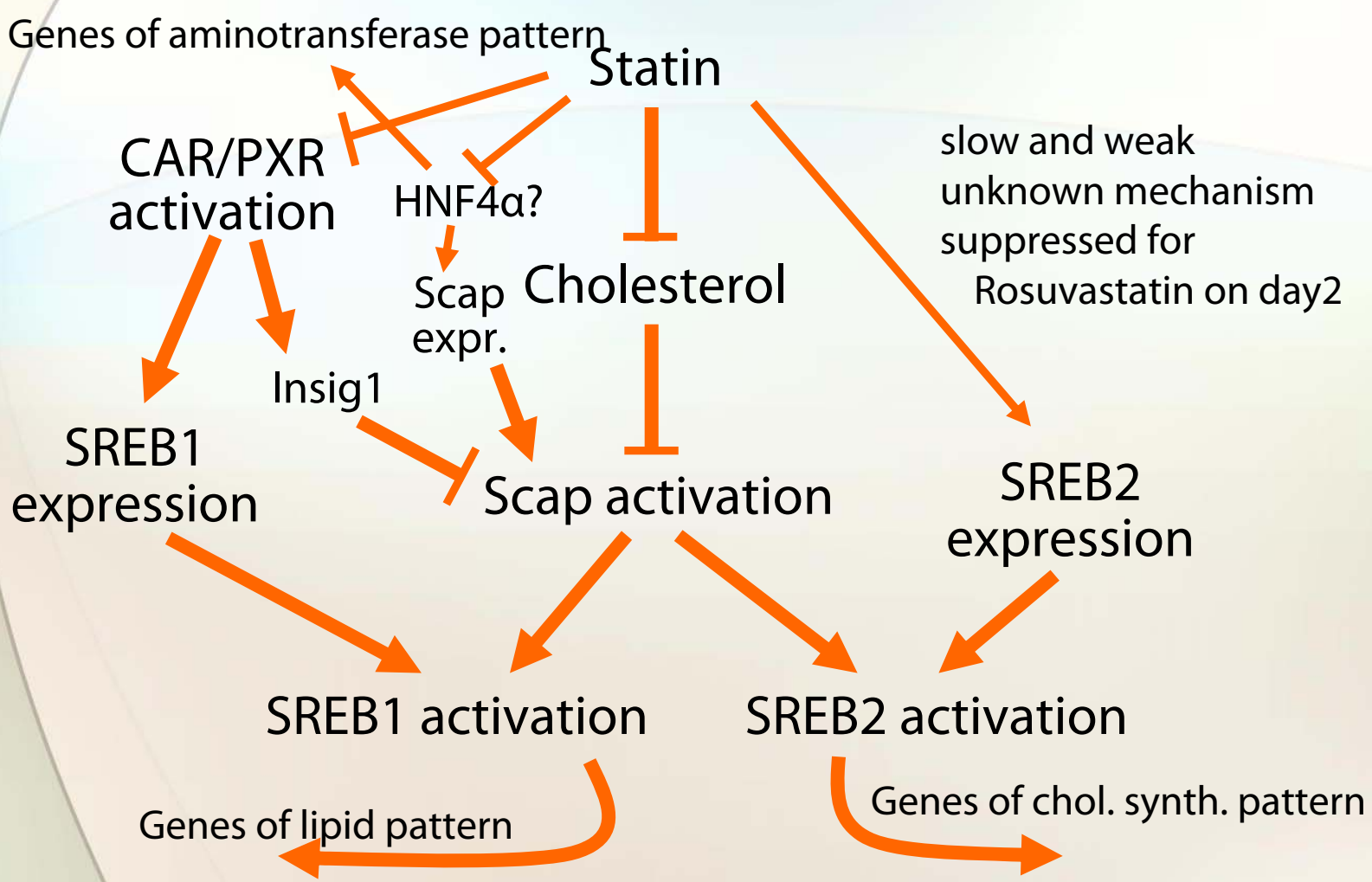
Both statins:
1d up

Atorvastatin: 2d up

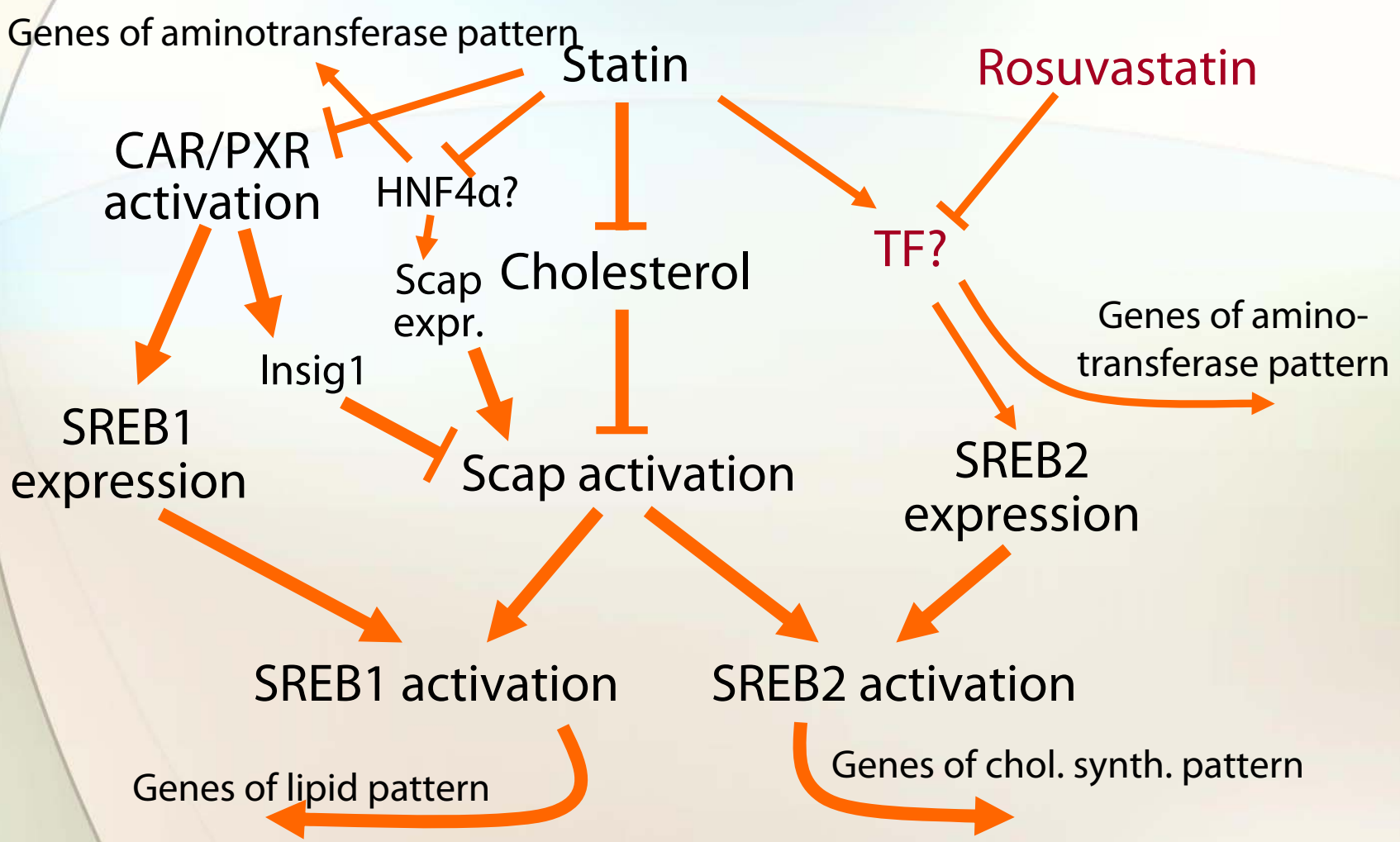
Rosuvastatin: 2d down

Rifampicin:
minor change

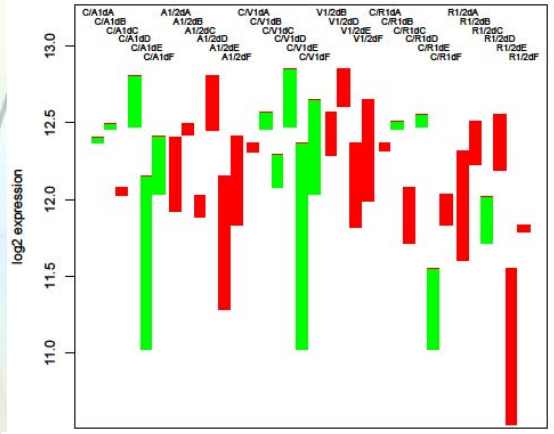
Link of sterol and lipid regulation



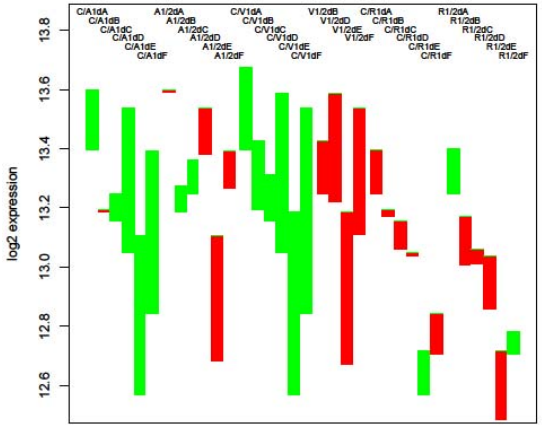
Link of sterol and lipid regulation



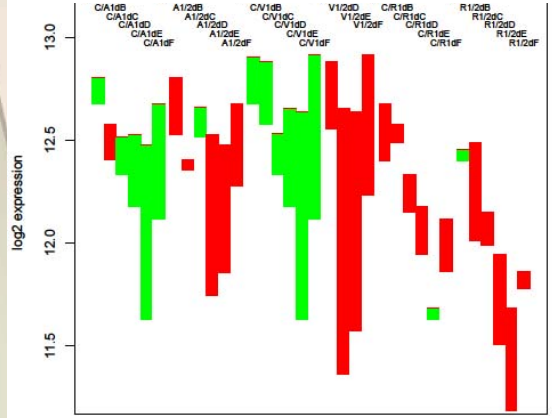
Urea cycle pattern



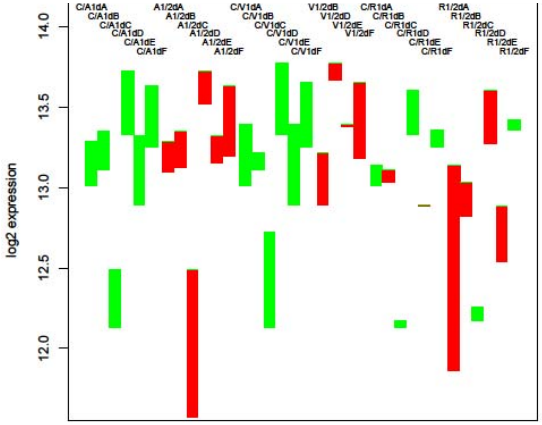
CPS1 Carbamoyl-P synth



ASS1 Arginosucc synth



ASL Arginosucc lyase



ARG1 Arginase

Urea cycle except OTC

Pattern definition

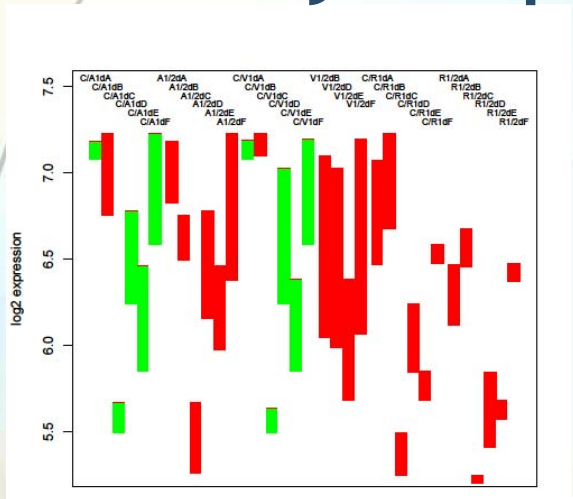
Statins:

- 1d up
- 2d down

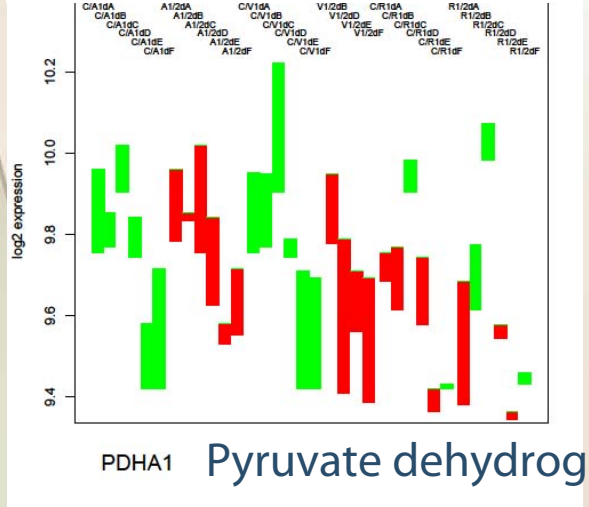
Rifampicin:

- minor change

Urea cycle pattern



GLS2 Glutaminase 2



PDHA1 Pyruvate dehydrogenase

Enzymes cooperating with urea cycle

Urea cycle pattern, how?

Statin

SREB1?

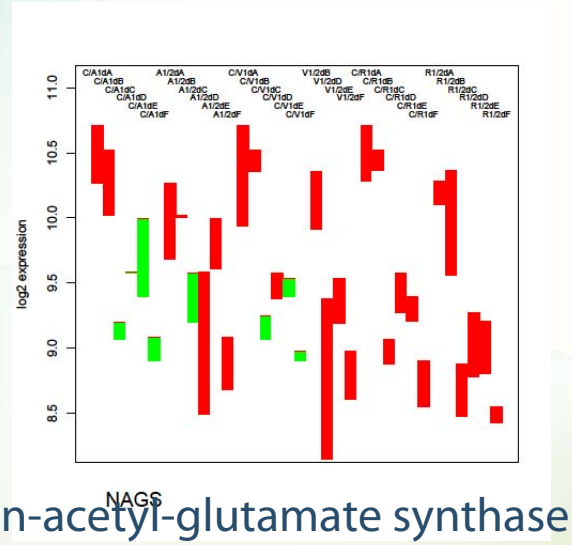
fast

PXR?

slow

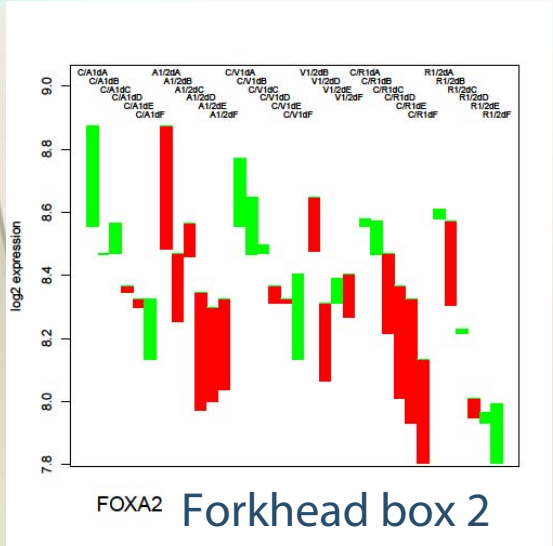
TF

Genes of urea cycle pattern



n-acetyl-glutamate synthase

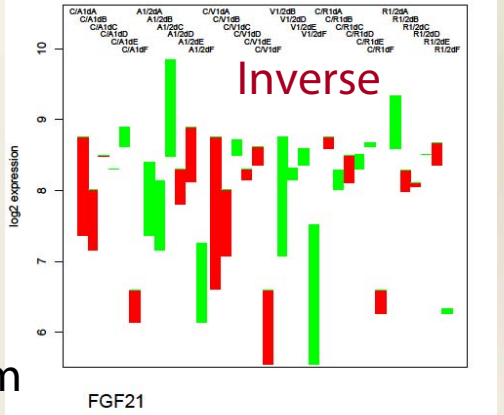
n-acetyl-glutamate known to control CPS-I



Forkhead box 2

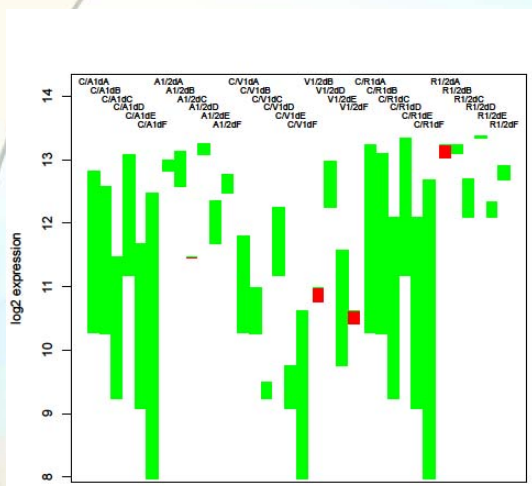
Small amplitude
Probably downstream

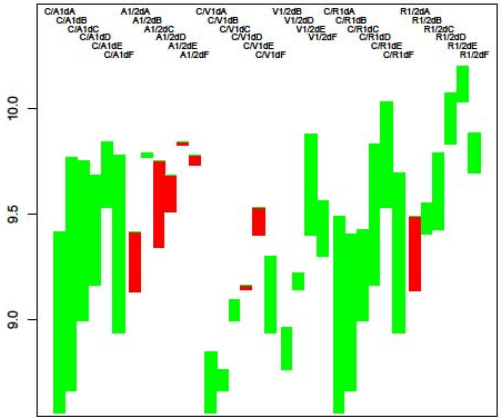
Inverse pattern
Possibly downstream



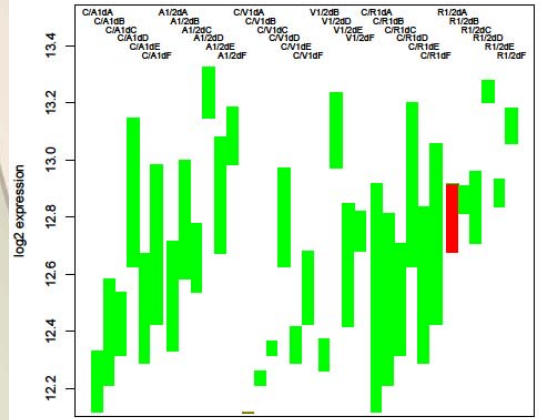
Fibroblast growth factor

Atorvastatin Rifampicin pattern

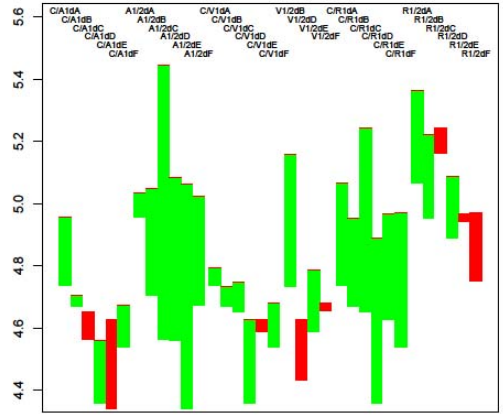




MDR/TAP binding



UDP-glucuronosyl transf.



Apolipoprotein D

CYP 3A4 … oxidizing all 3 molecules

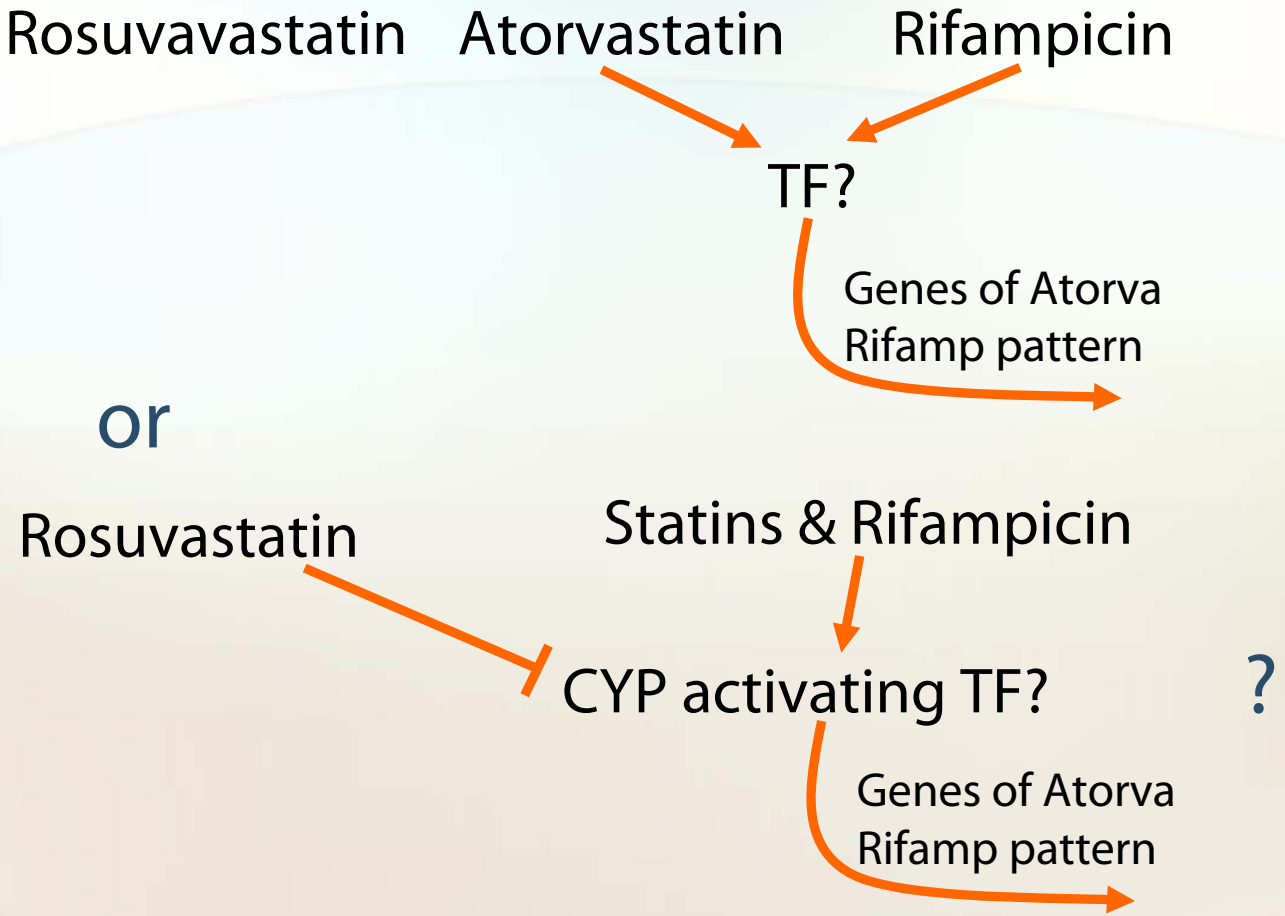
Rosuvastatin suppresses its own degradation

Pattern definition

Atorvastatin & Rifampicin
- 2d up

Rosuvastatin:
- minor change

Atorvastatin Rifampicin pattern



Other patterns

- Donor specific response: sugar metabolism
- Donation type difference
  - Acute serum response proteins — cancer donors
- Gluconeogenesis
  - G6P controlled by SREB1
  - Down-regulation of glucose transporter SLC2A2

Summary

- ModeScore ranking focus on parts of metabolism
- Specific patterns of gene regulation
  - Strong cholesterol synthesis up-regulation
    - mechanism known: Scap→SREB2
  - Selective regulation of FA metabolism
    - several mechanisms: SREB1, CAR/PXR, Insig1
  - Aminotransferase pattern
    - affecting Scap desensitizing Cholesterol regulation
  - Urea cycle regulation (unclear how)
- Patterns suggest regulation cascade
  - new mechanisms proposed
    - Strong effect of Rosuvastatin by inhibition of transcription factor

virtual liver network

COMPUTATIONAL SYSTEMS BIOCHEMISTRY

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