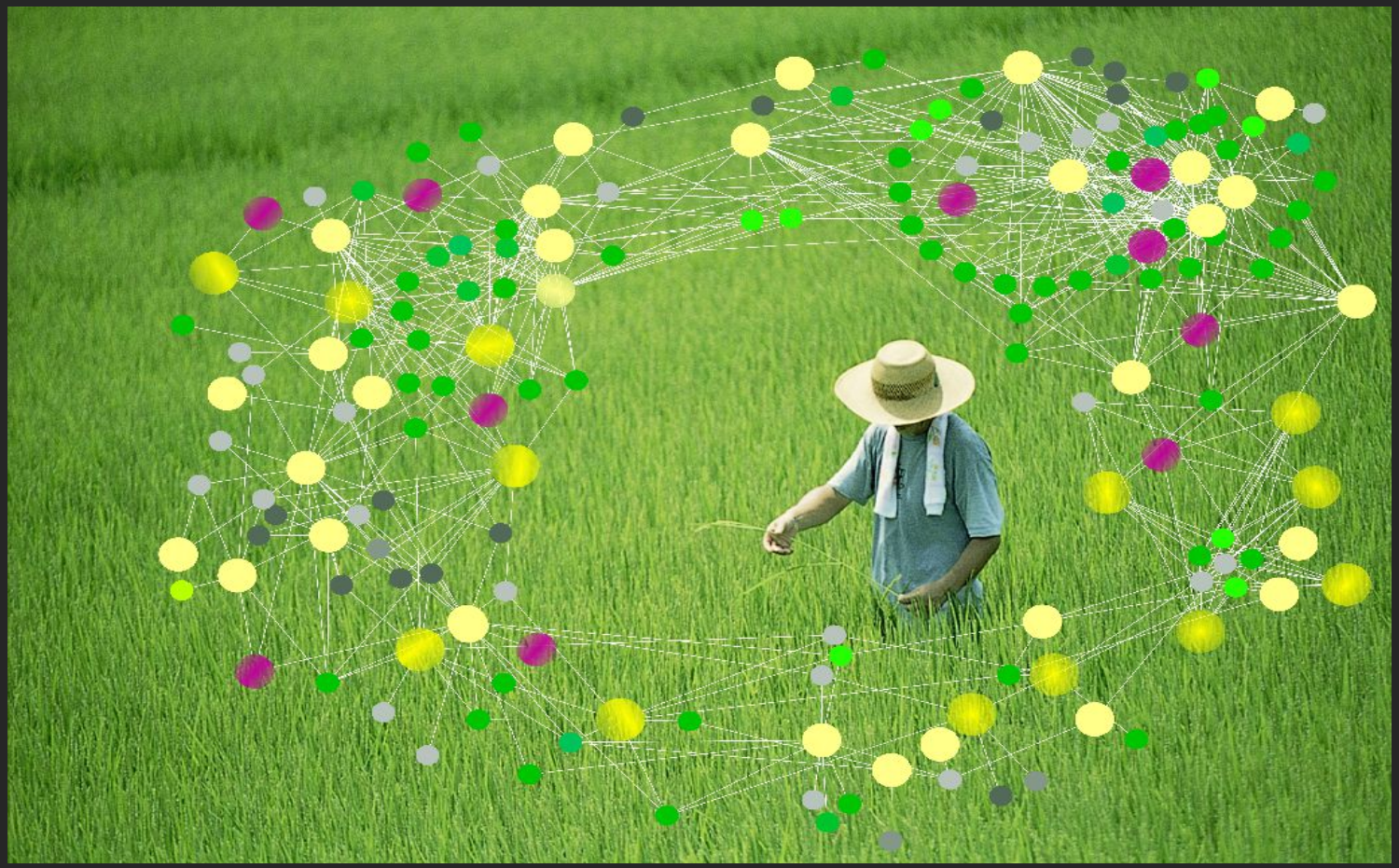
Linking the circadian clock to specialized metabolism using gene co-expression networks



2nd Training Workshop
ProCoGen 2014

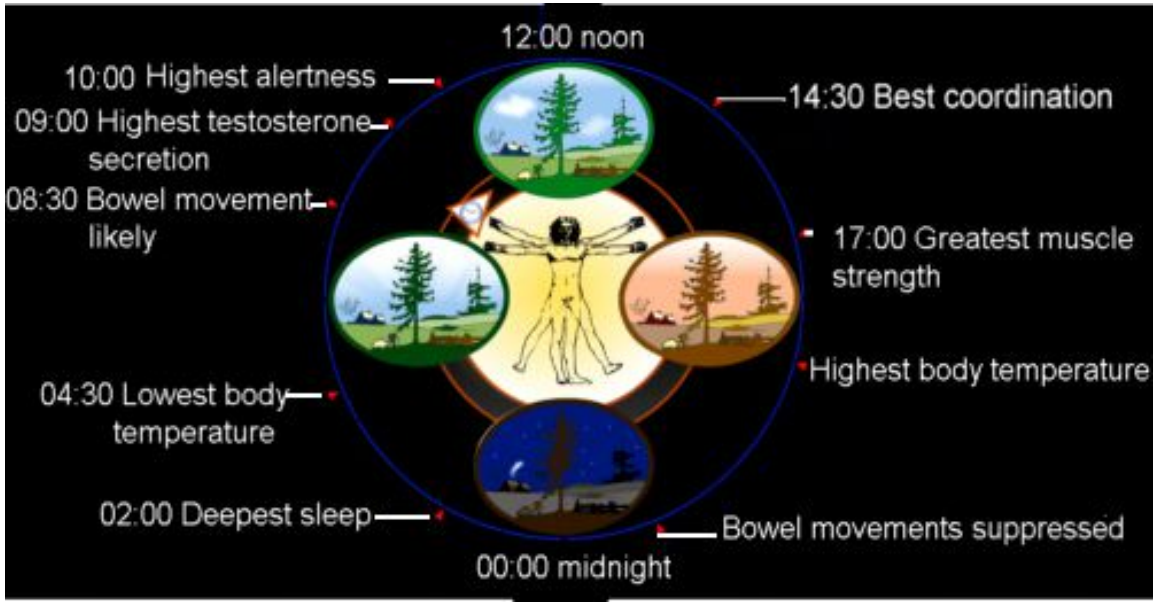
Diana Coman Schmid
ETH Zurich

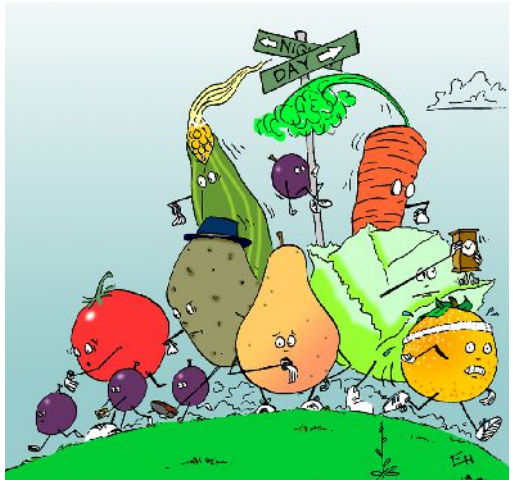
Outline

1. Gene co-expression networks reveal links between the circadian clock and isoprenoid biosynthesis

2. The *GGPPS* gene family at the branch point in the isoprenoid pathway

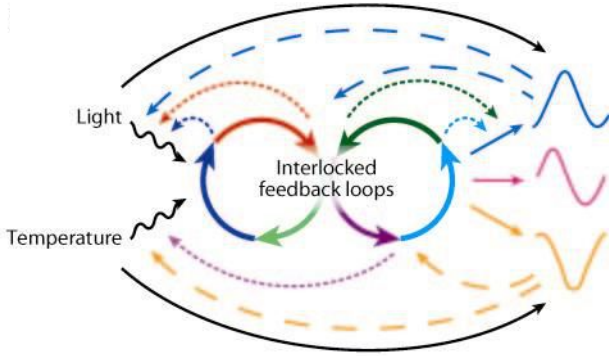
The circadian clock

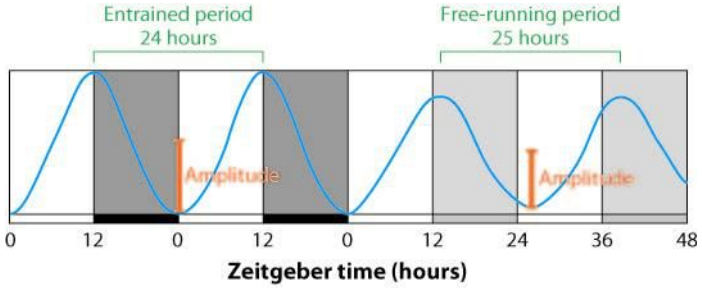




The circadian clock in plants

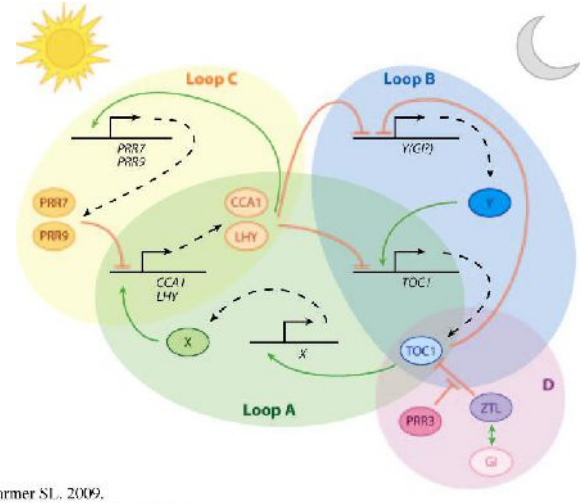
Concepts





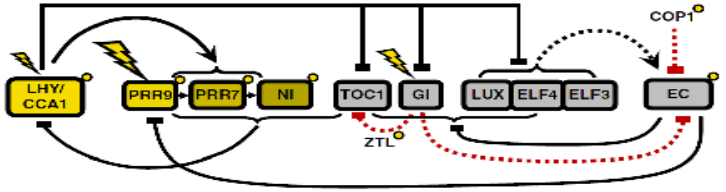
Harmer SL. 2009.
Annu. Rev. Plant Biol. 60:357–77

Molecular mechanism



Harmer SL. 2009.
Annu. Rev. Plant Biol. 60:357–77

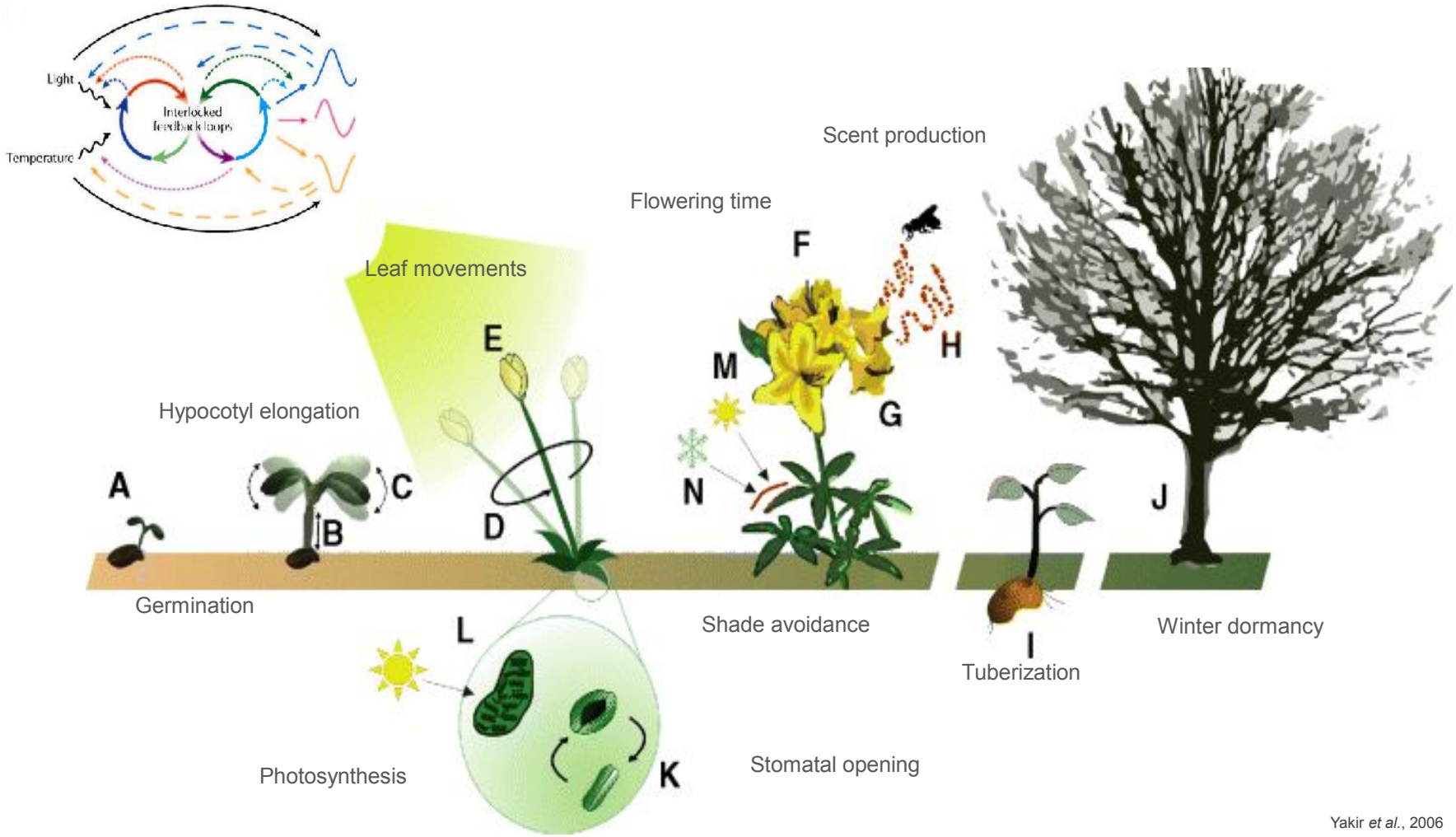
Repressilator



- Transcriptional regulation
- Protein complex formation
- Post-translational modification
- Light activation of transcription

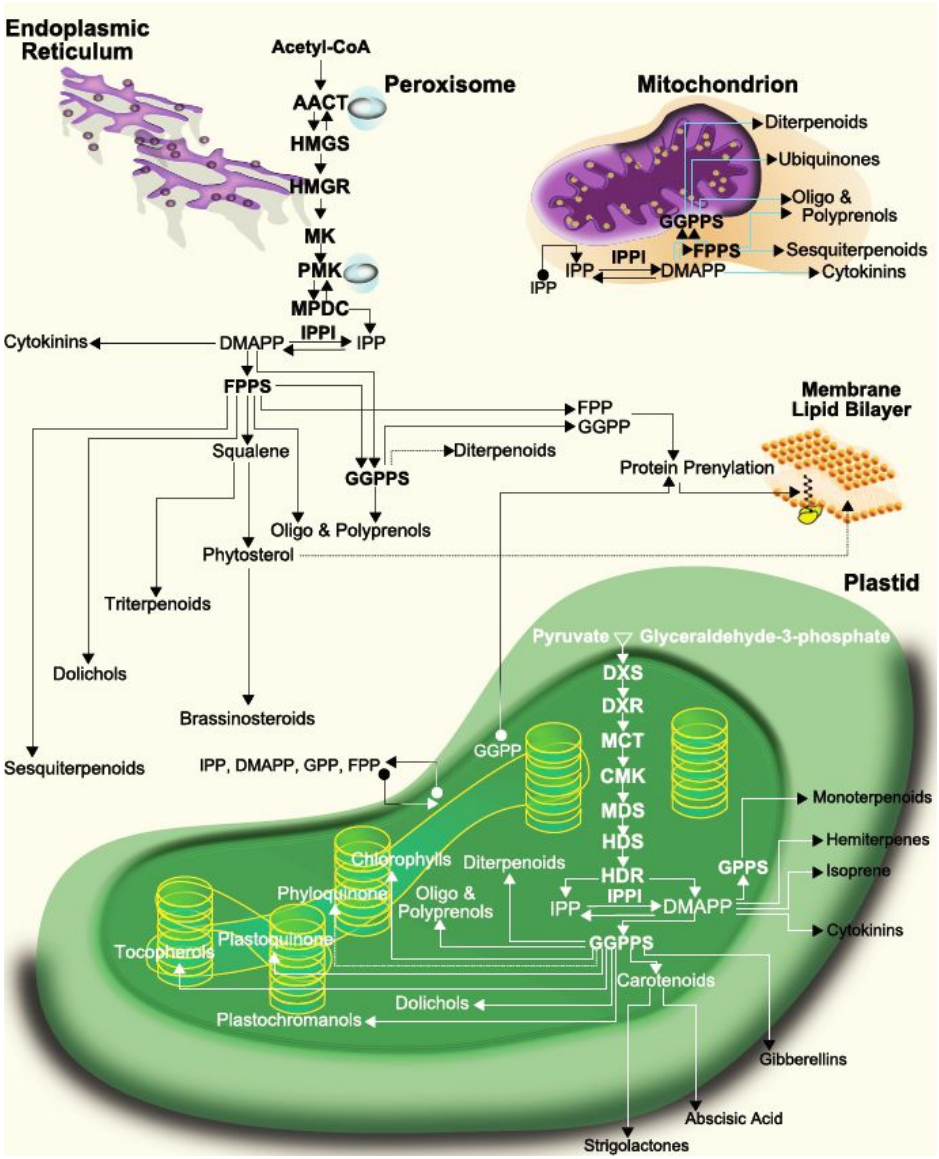
Pokhilko *et al.*, 2012

Outputs of the circadian clock in plants



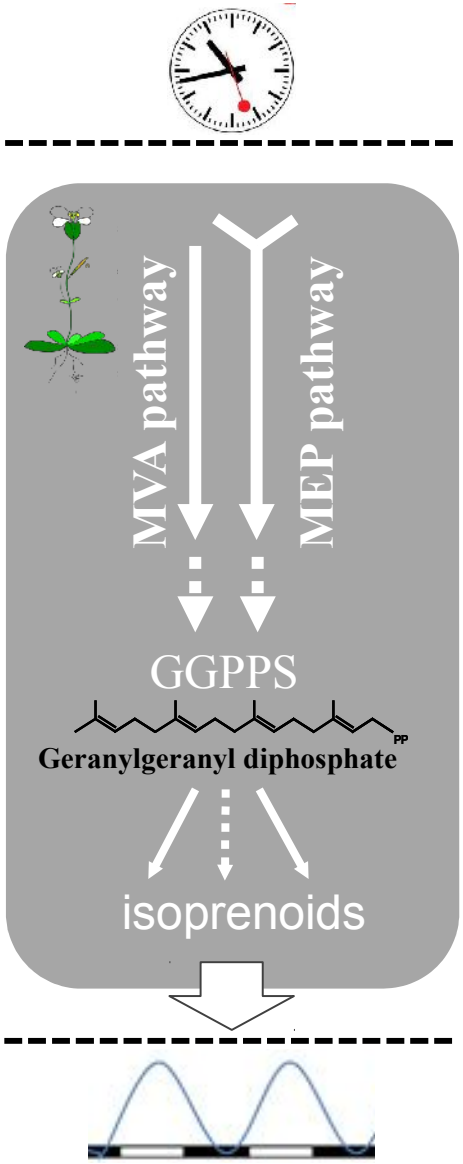
Yakir *et al.*, 2006

Isoprenoids (Terpenoids)



Vranová, Coman and Gruissem 2013
Annu. Rev. Plant Biol. 64:665–700

Part1: Linking the circadian clock to specialized metabolism



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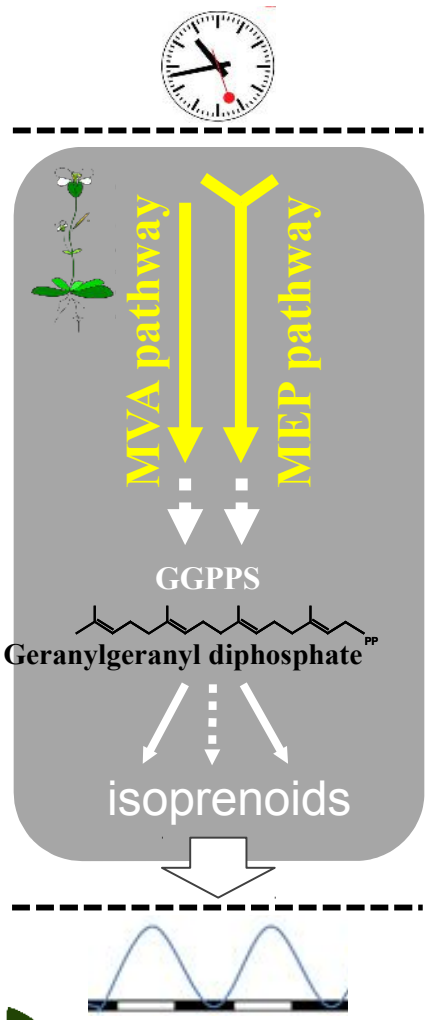
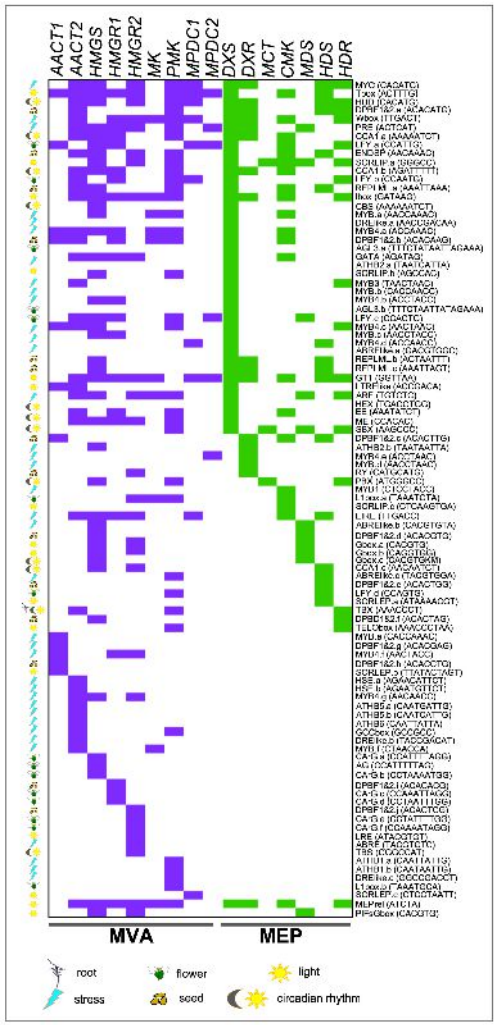
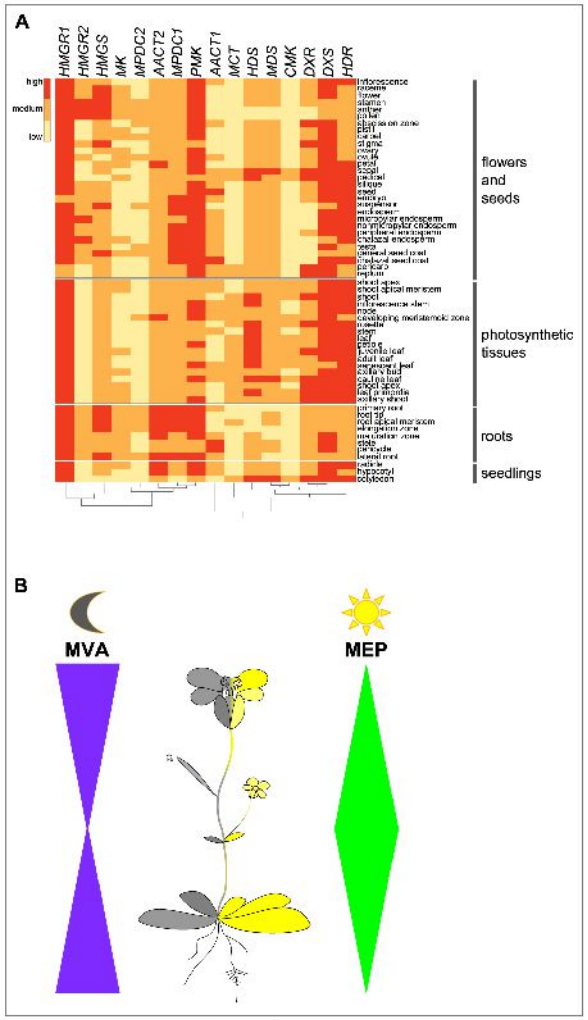
The circadian clock and the MVA- and MEP pathways (isoprenoids)



Cis-elements

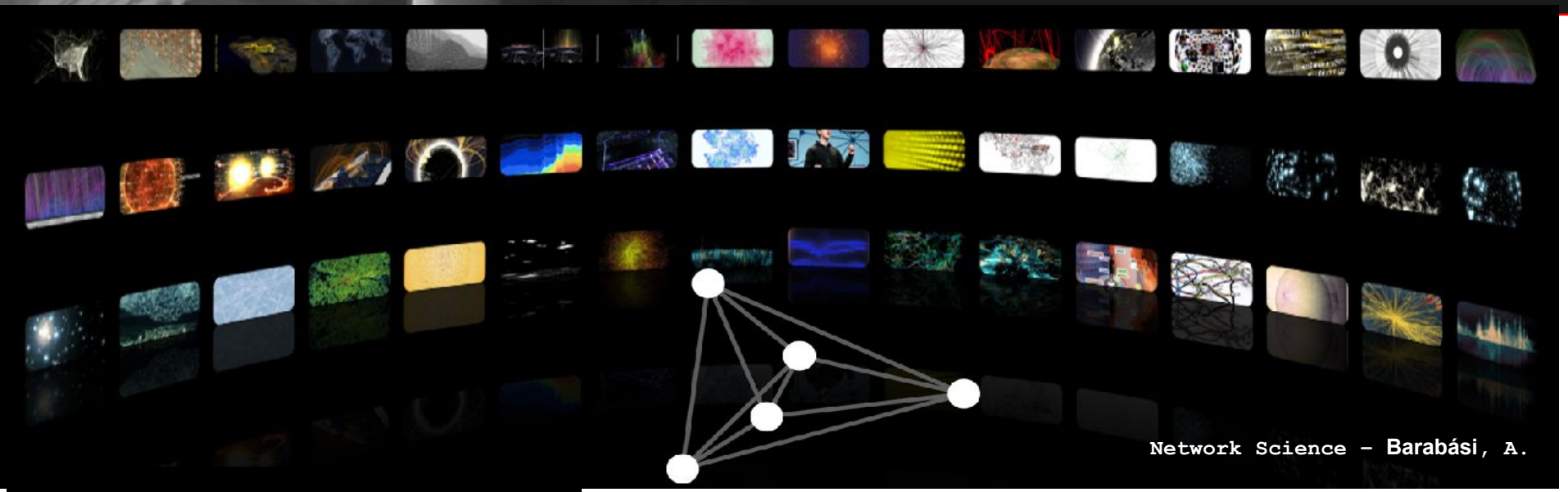


Transcriptional patterns



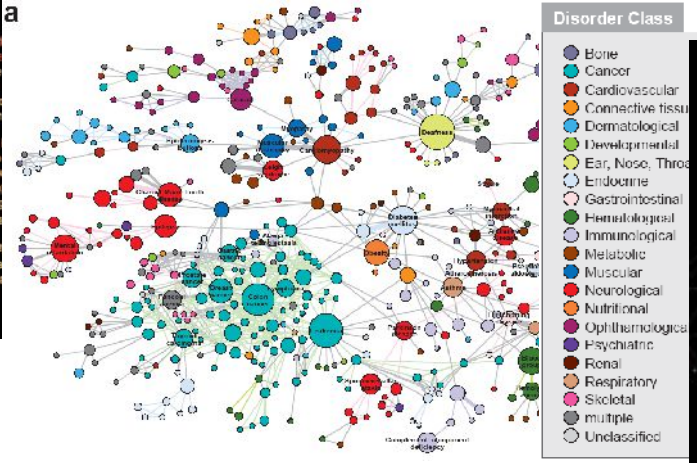
Vranová, Coman and Gruissem 2013
Annu. Rev. Plant Biol. 64:665–700

Biological Networks



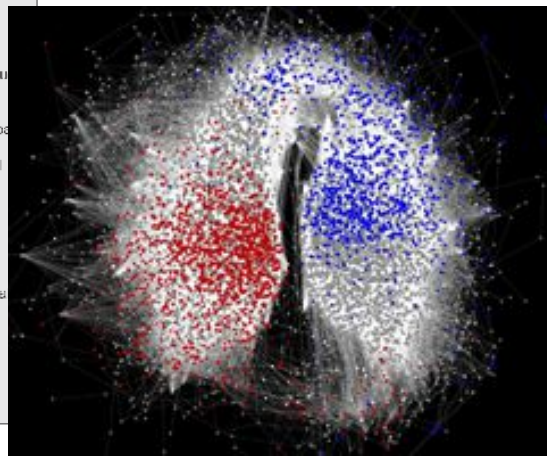
Predicting the H1N1 pandemic

HUMAN DISEASE NETWORK



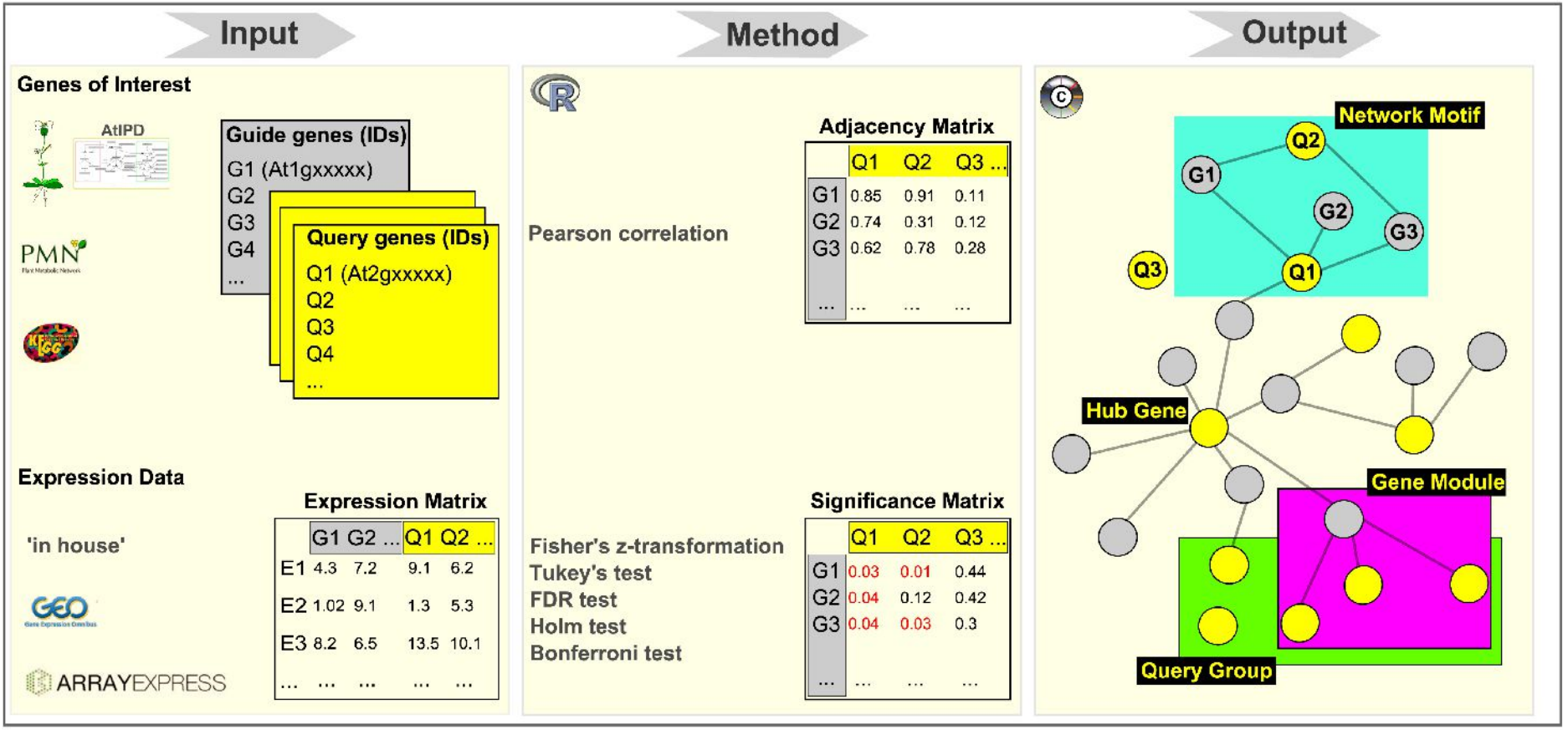
Goh *et al.*, 2007, PNAS

SeedNet(Arabidopsis)



Bassel *et al.*, 2011 *PNAS*

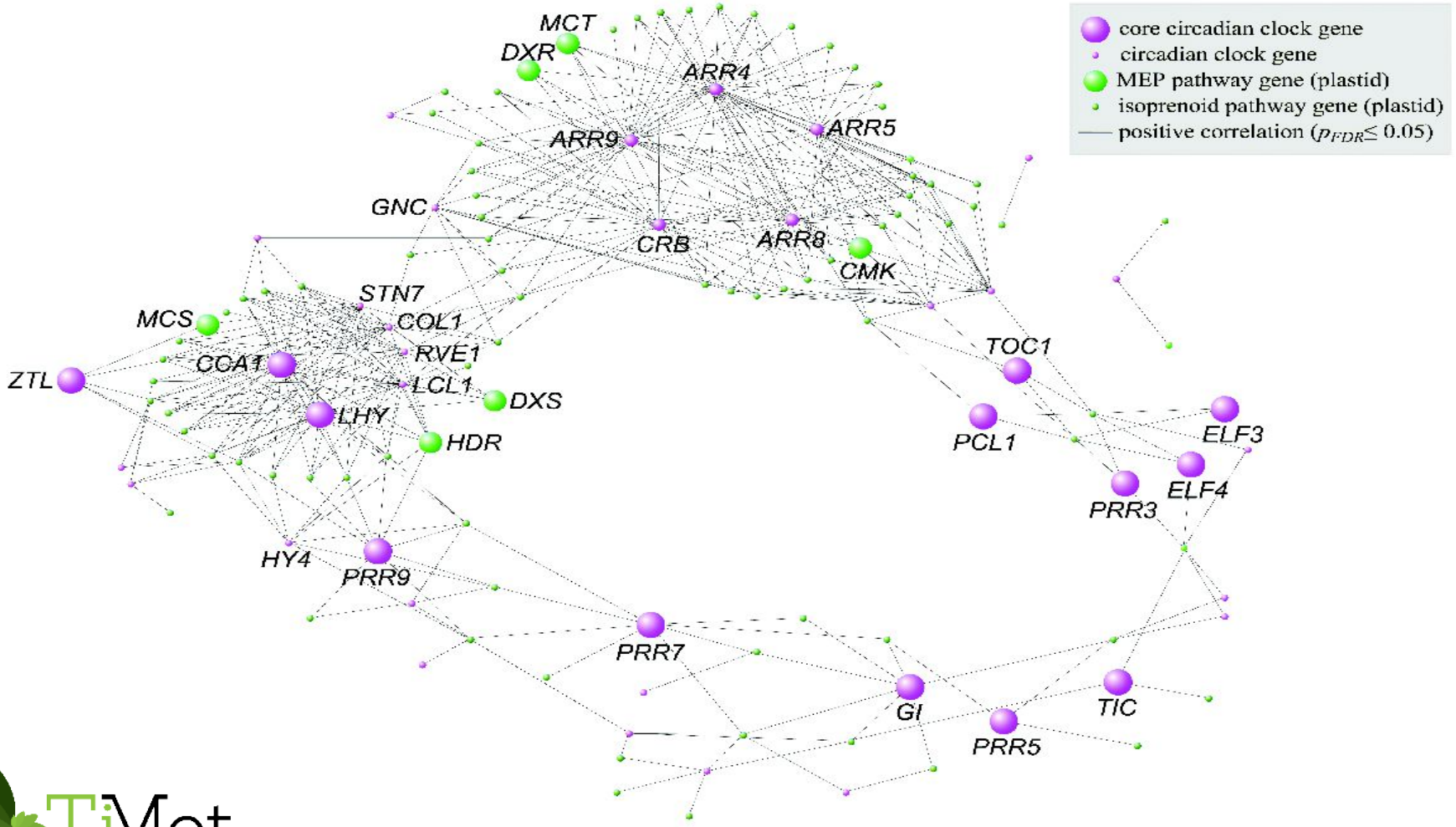
Gene Co-expression Networks (GCN)



Coman *et al.*, in press

Modular GCN of the circadian clock genes and isoprenoid pathway genes encoding enzymes localized in plastids

Except for *HDS*, all the MEP pathway genes correlate with the circadian clock



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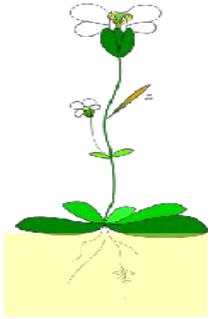
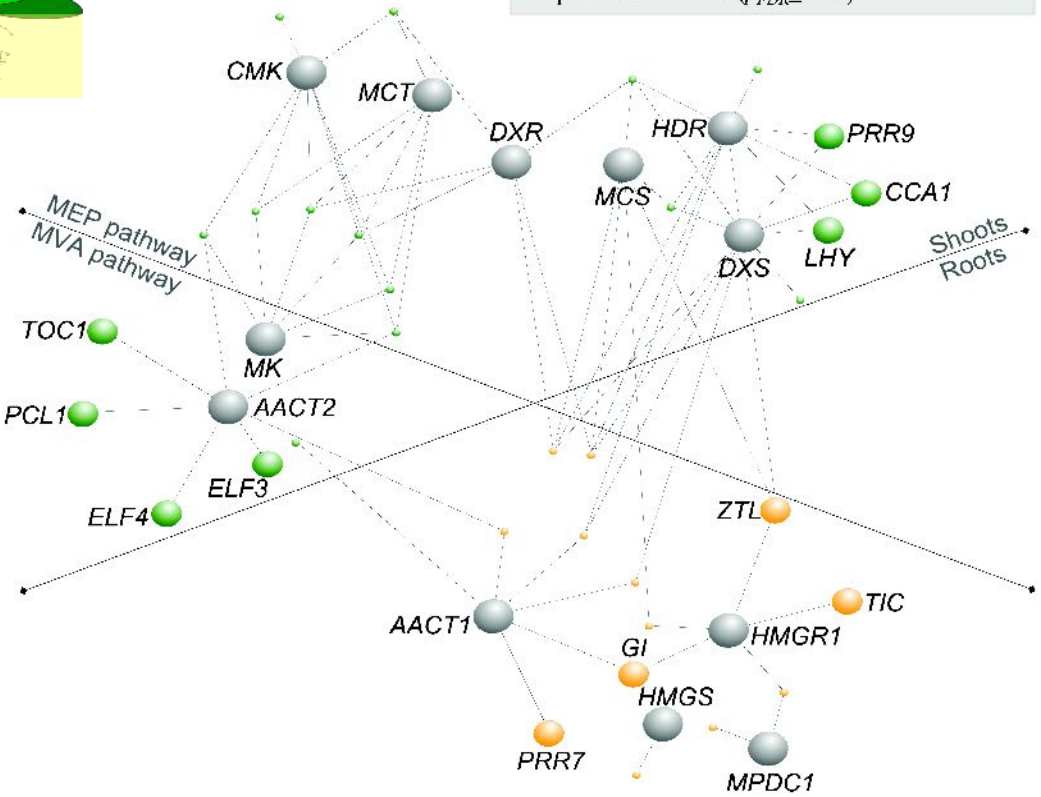
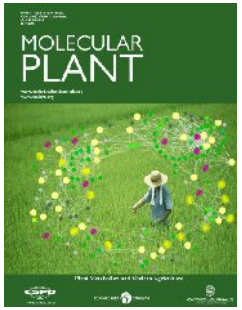
Vranová, Coman and Gruissem, 2012

Organ specific GCN of the circadian clock genes and MVA- and MEP pathway genes

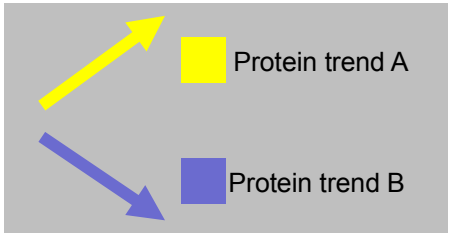


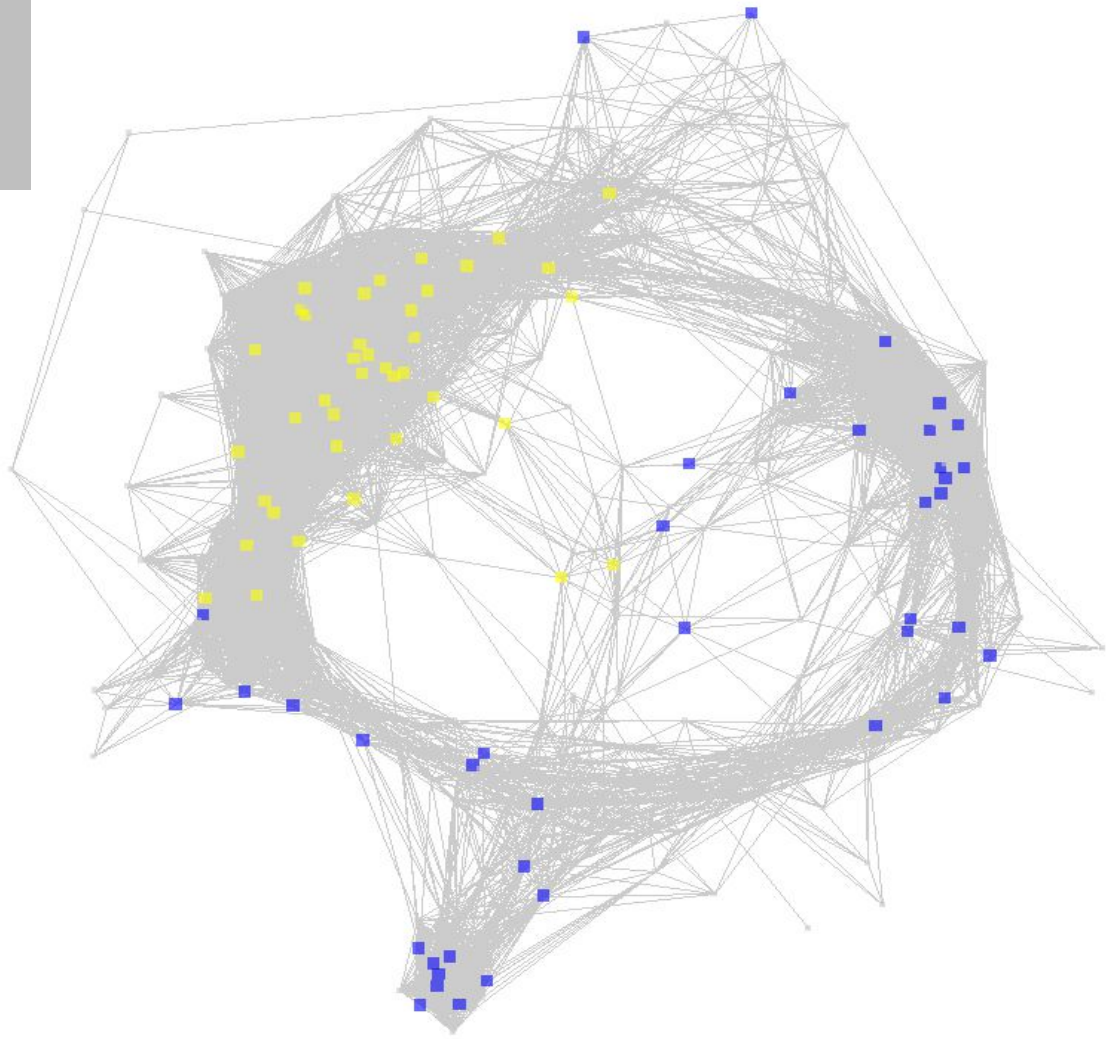




Vranová, Coman and Gruissem, 2012

Integrating additional levels: GCN, transcript & protein trends





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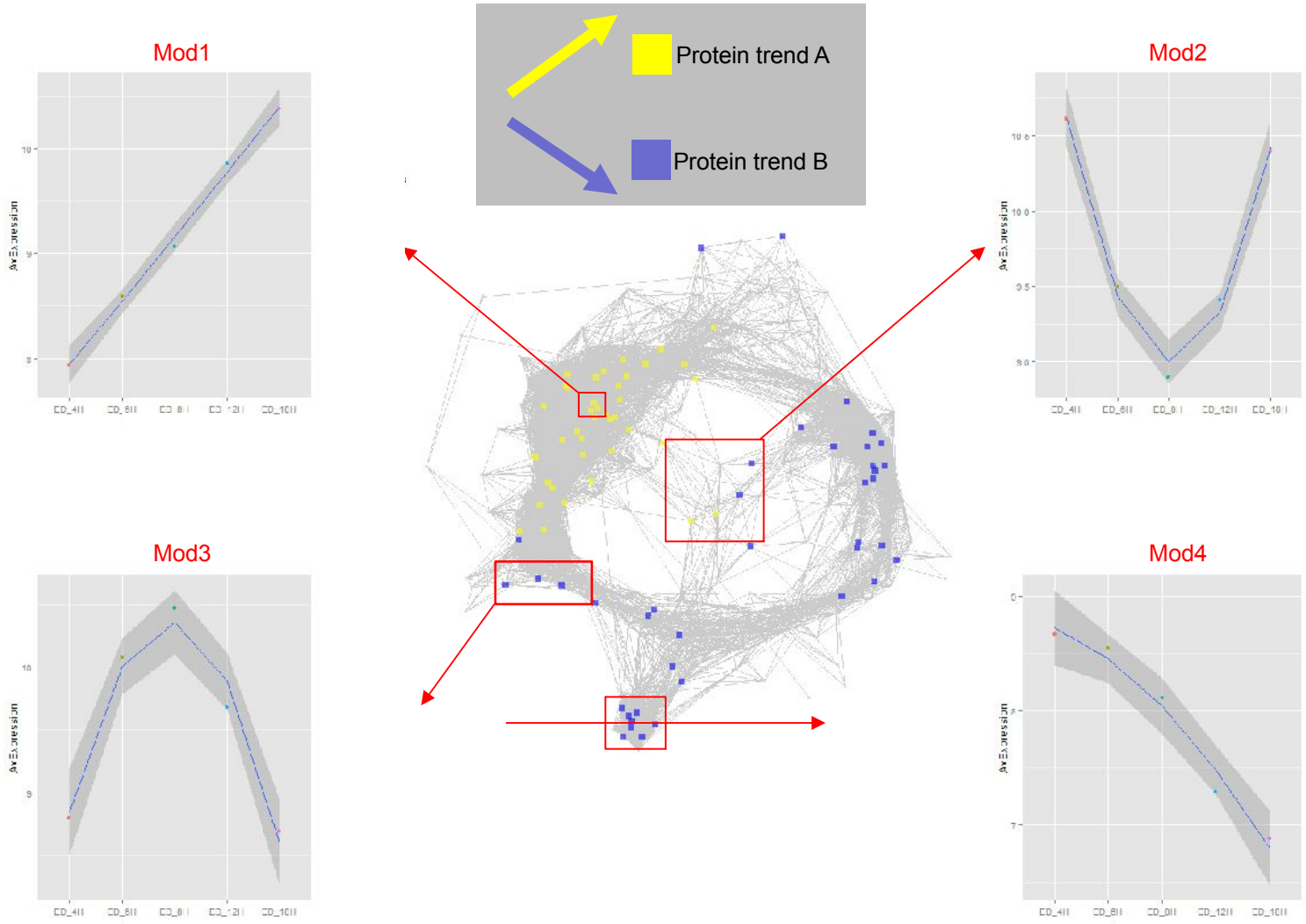
Integrating additional levels: GCN, transcript & protein trends



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Conclusions Part1

- The gene co-expression networks revealed the MVA and MEP pathway genes , which might link the circadian clock to the outputs
- The GCN identified a possible modular and organ specific regulation between the circadian clock and isoprenoids at transcript level

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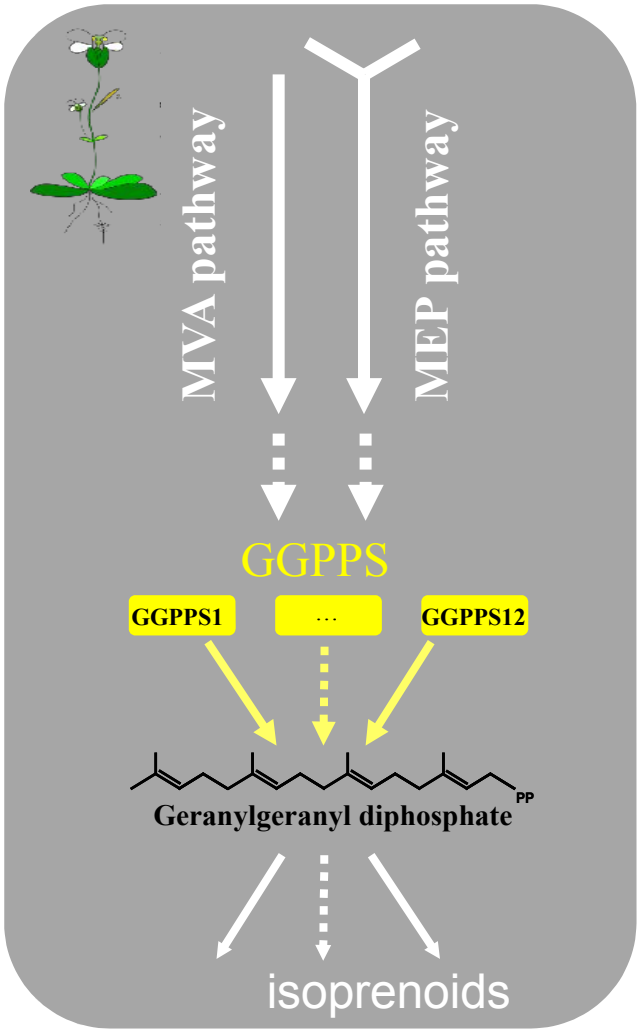
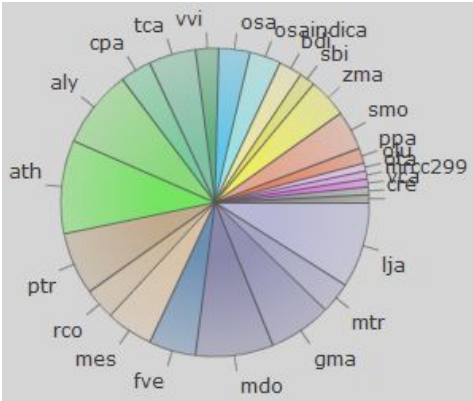
Part 2: The GGPPS branch point in the isoprenoid pathway

12 predicted GGPPS in *A. thaliana*: why? redundant or not?



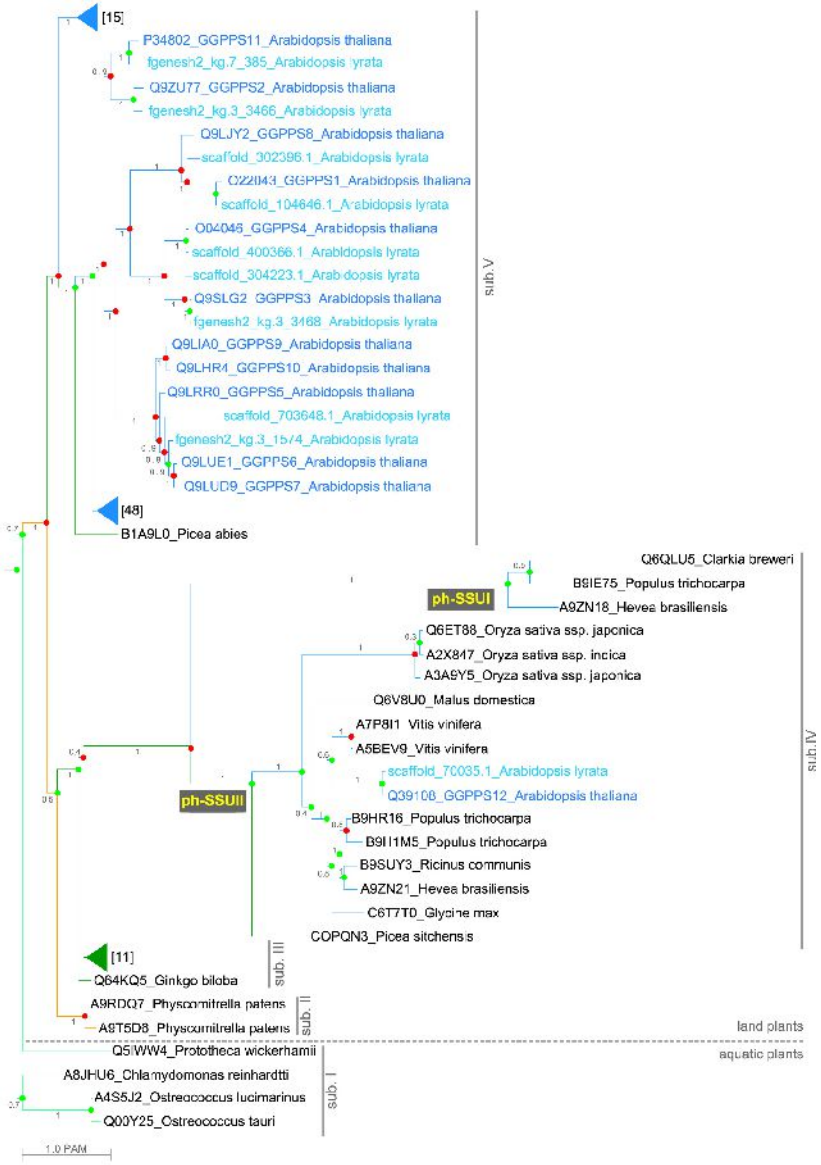
Multiple *GGPPS* gene paralogs exist in plants

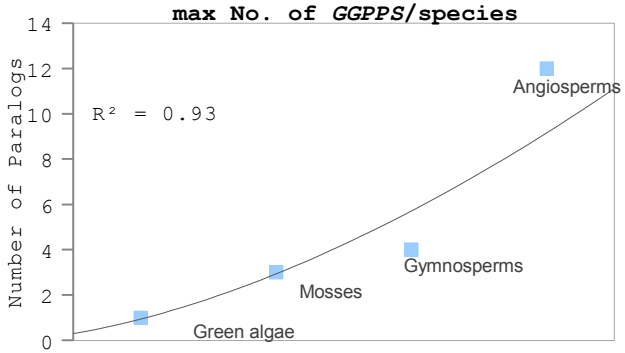


aly	Arabidopsis lyrata (10 genes)
ath	Arabidopsis thaliana (12 genes)
bdi	Brachypodium distachyon (3 genes)
cpa	Carica papaya (4 genes)
cre	Chlamydomonas reinhardtii (1 gene)
fve	Fragaria vesca (6 genes)
gma	Glycine max (8 genes)
lja	Lotus japonicus (11 genes)
mdo	Malus domestica (10 genes)
mes	Manihot esculenta (6 genes)
mrcc299	Micromonas sp. RCC299 (1 gene)
mtr	Medicago truncatula (4 genes)
olu	Ostreococcus lucimarinus (1 gene)
osa	Oryza sativa ssp. japonica (4 genes)
osaindica	Oryza sativa ssp. indica (4 genes)
ota	Ostreococcus tauri (1 gene)
ppa	Physcomitrella patens (2 genes)
ptr	Populus trichocarpa (8 genes)
rco	Ricinus communis (4 genes)
sbi	Sorghum bicolor (2 genes)
smo	Selaginella moellendorffii (5 genes)
tca	Theobroma cacao (6 genes)
vca	Volvox carteri (1 gene)
vvi	Vitis vinifera (3 genes)
zma	Zea mays (5 genes)

http://bioinformatics.psb.ugent.be/plaza/gene_families/view/HOM000909

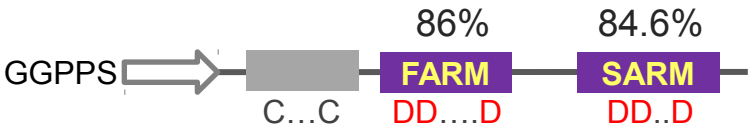
Increase of plant functional complexity, more *GGPPS* gene paralogs





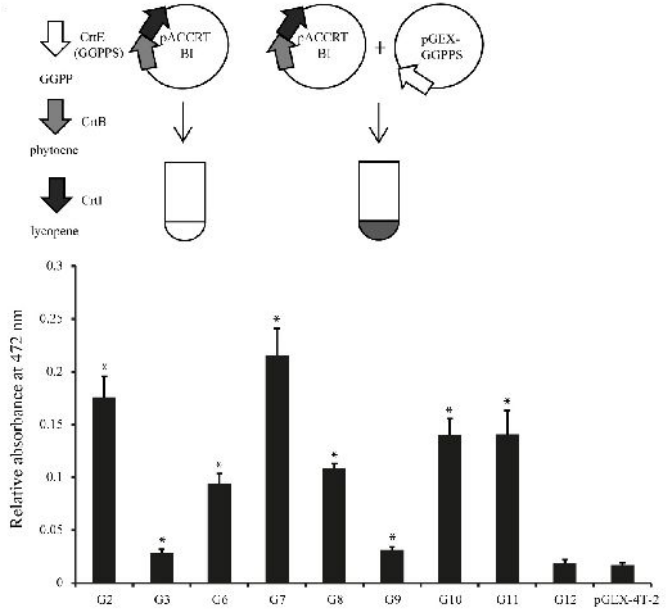
Coman *et al.*, in preparation

12 predicted GGPPS in *A. thaliana*: why? redundant or not?



100% FARM and SARM conservation in GGPPS1-11

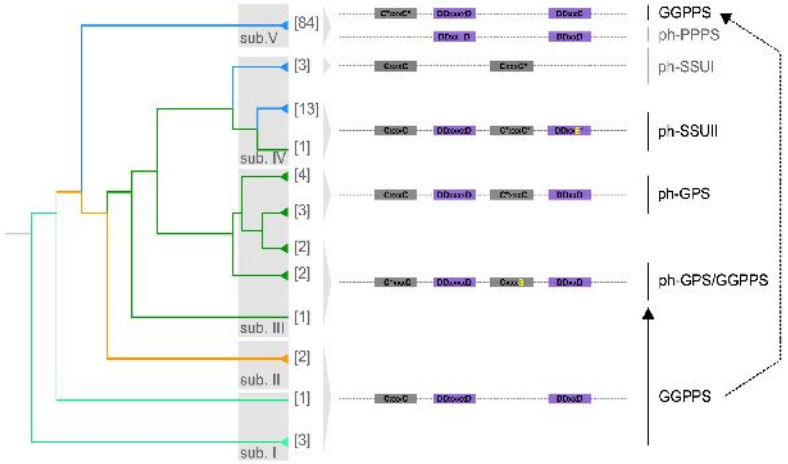
GGPPS1-4, 6-11 produce GGPP in *E. coli*



Beck* and Coman* *et al.*, 2013
** equal contribution*

The *GGPPS* paralogs: neofunctionalization

Evolution of the polyprenyl synthase domain in plants



Neofunctionalization -- Division of labor

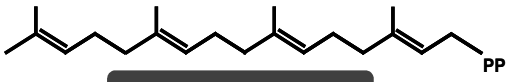
GGPPS12

ph-SSUII (! inactive)

\+

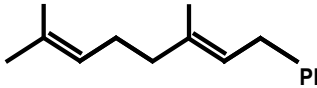
GGPPSx

GGPPS (C20)



"housekeeping"

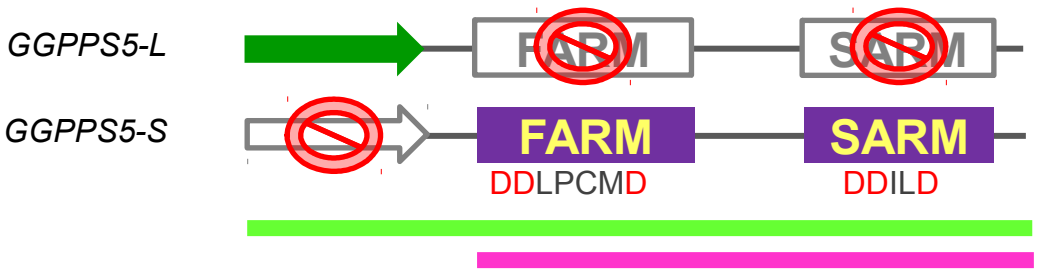
GPP (C10)

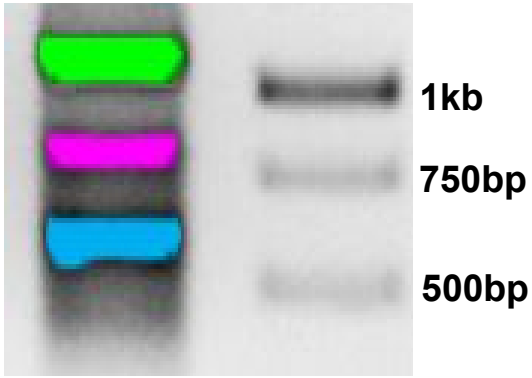


"defense"

Coman et al., in preparation

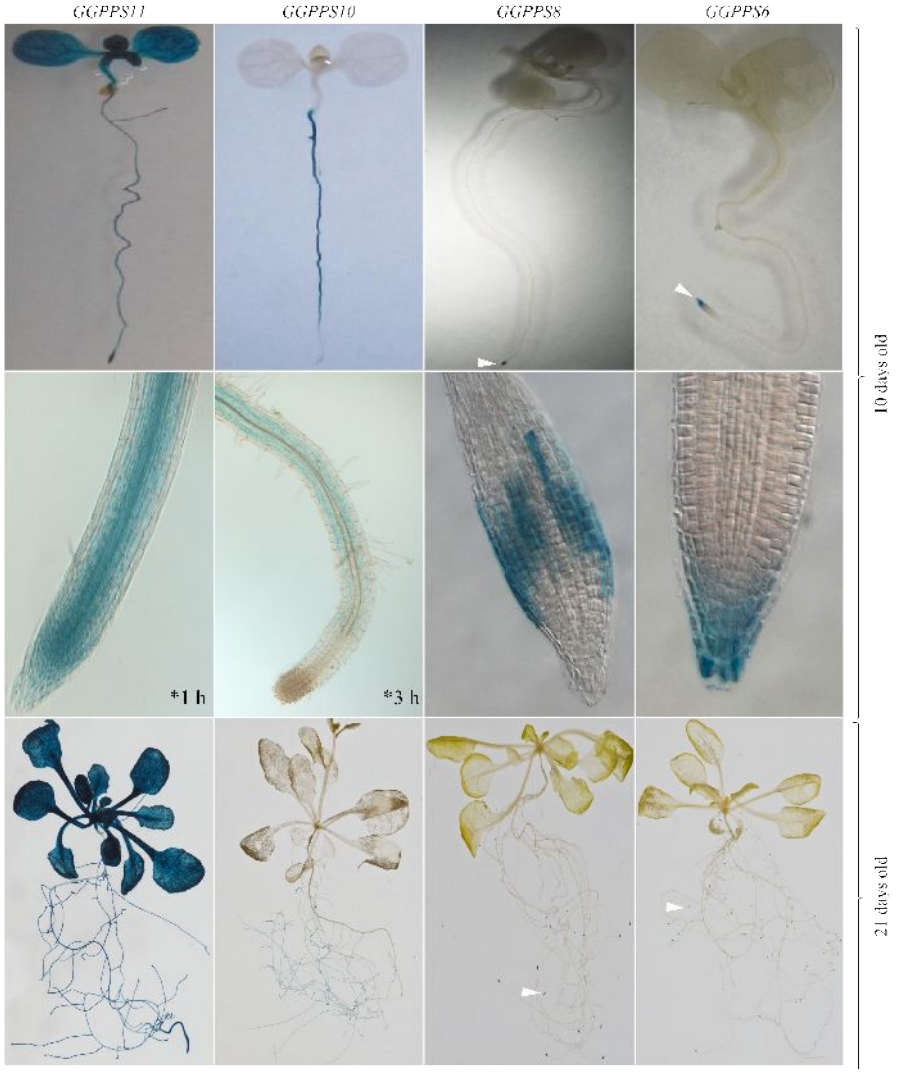
GGPPS5 is a ghost pseudogene

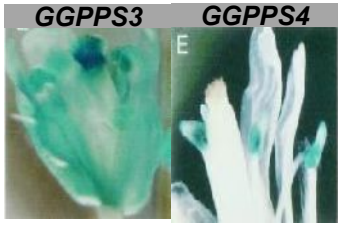


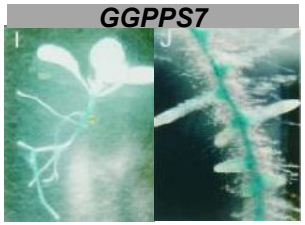


5' RACE, roots

The 10 *GGPPS* paralogs are differentially expressed during plant development



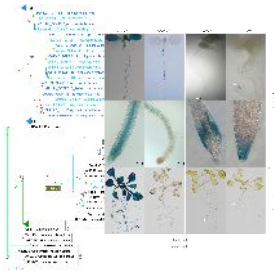


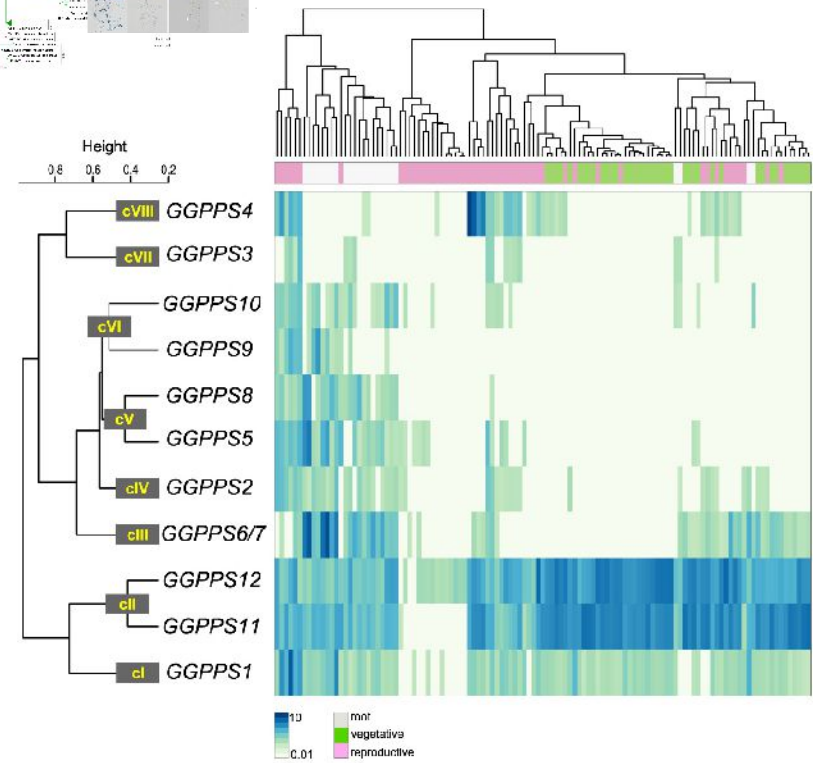


Okada *et al.*,2000

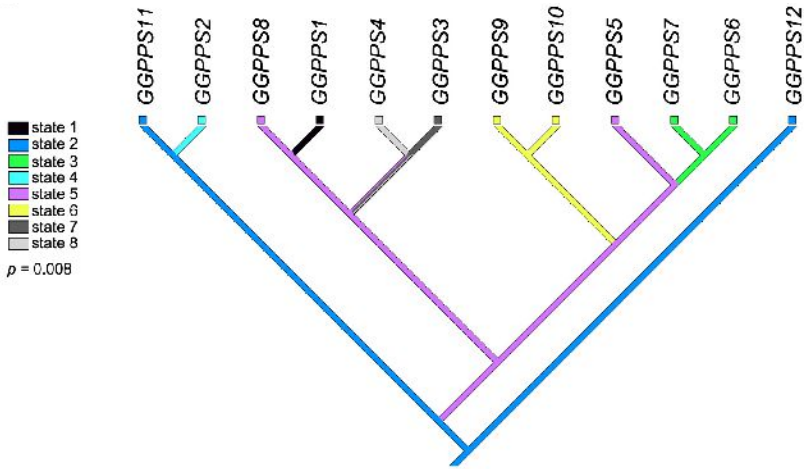
Beck* and Coman* *et al.*, 2013
** equal contribution*

GGPPS subfunctionalization is supported by the correlation of sequence and expression divergence



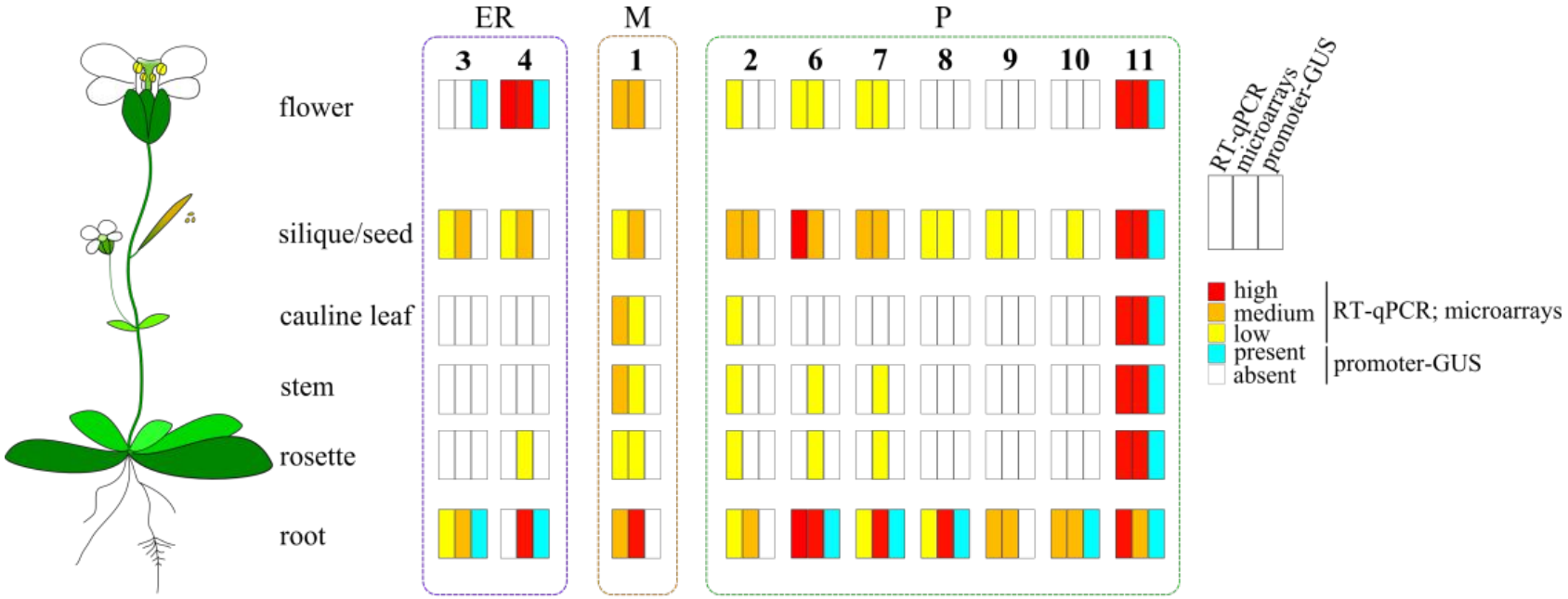


Ancestral state reconstruction



Coman *et al.*, in preparation

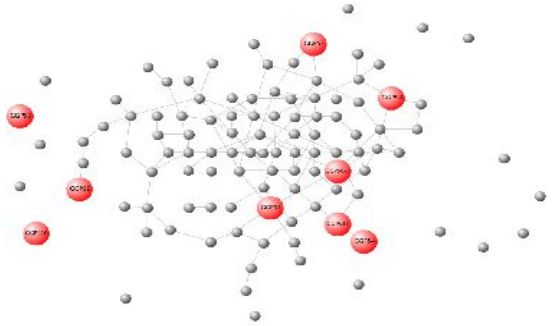
The 10 GGPPS paralogs have different subcellular localization and expression pattern



Beck* and Coman* *et al.*, 2013
** equal contribution*

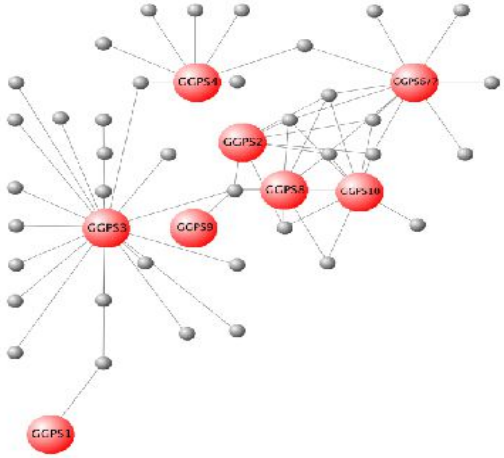
Being many is not enough: lethality vs. redundancy in the *GGPPS* gene family from Arabidopsis

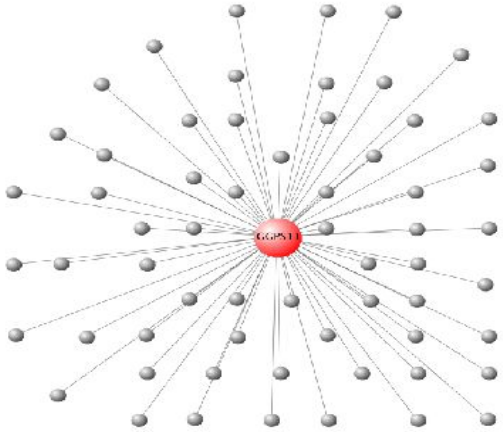
Simulated random network



vs.

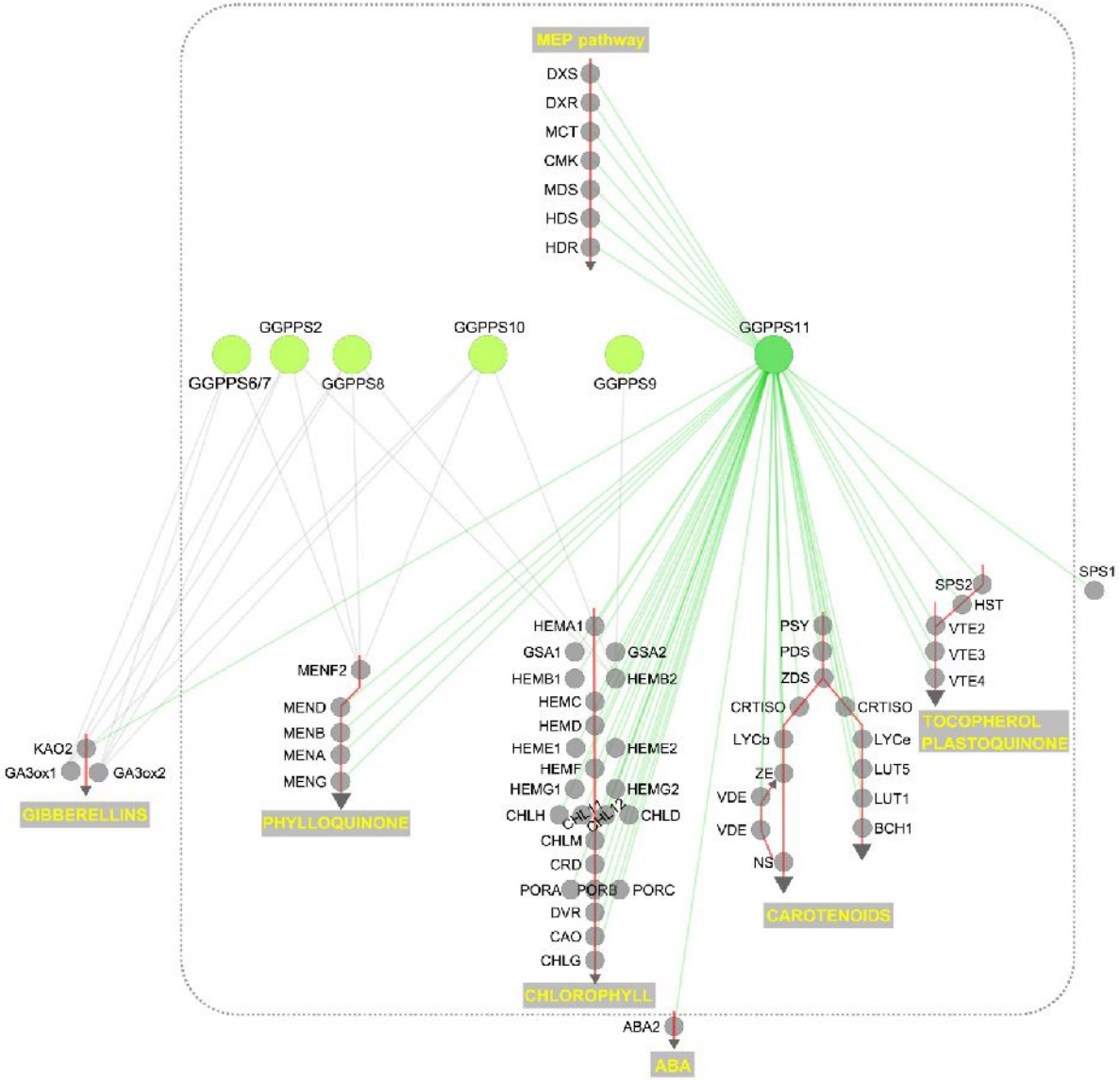
Modular gene co-expression network (*GGPPS*-isoprenoid pathway)





Coman *et al.*, under review

Being many is not enough: lethality versus redundancy of Arabidopsis plastid GGPP synthases reveals GGPPS11 as a major hub enzyme



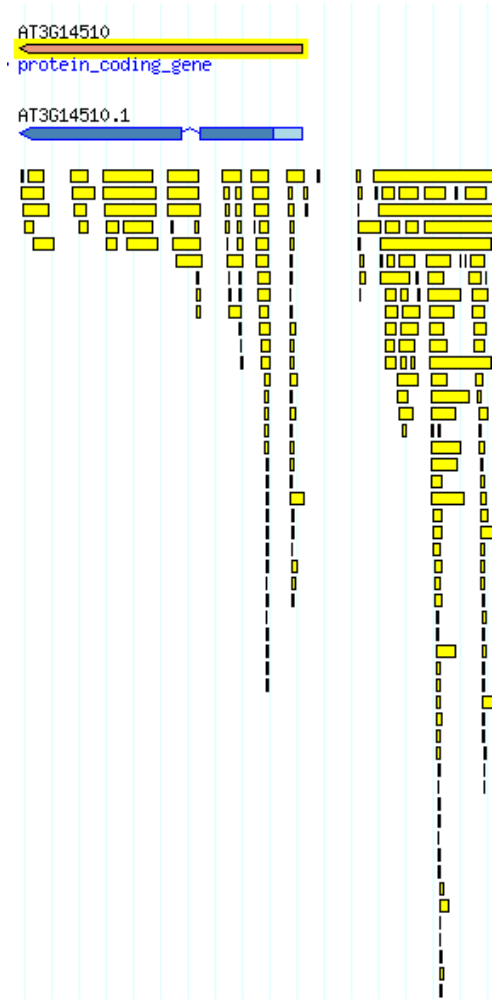
ggpps11

Coman *et al.*, under review

Continuing evolution of young *GGPPS*

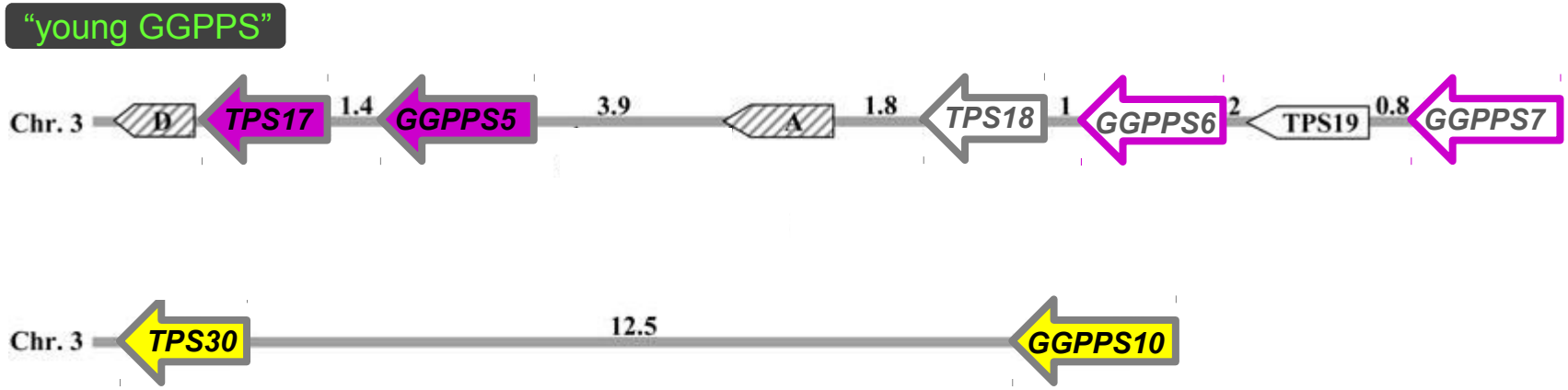
in *A. thaliana* accessions

1001 Genomes Data Center
A Catalog of *Arabidopsis thaliana* Genetic Variation



vs.

"Young GGPPS" paralogs: Operon-like gene clusters for specialized metabolic pathways



Final remarks

- The gene co-expression networks revealed MVA and MEP pathway genes that might link the circadian clock to the outputs
- The GCN identified a possible modular and organ specific regulation between the circadian clock and isoprenoids at transcript level
- GGPPS paralogs: being many is not enough; GGPPS11 is a hub paralog, conserved across plants and its function is essential; the “young GGPPS” might be required for particular developmental processes or environmental conditions
- GCN are species independent. GCN + Orthology => knowledge transfer and metabolic pathway evolution between species

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Acknowledgement

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Dr. Gilles Beck
Dr. Katja Bärenfaller
Dr. Alex Graf

TiMet