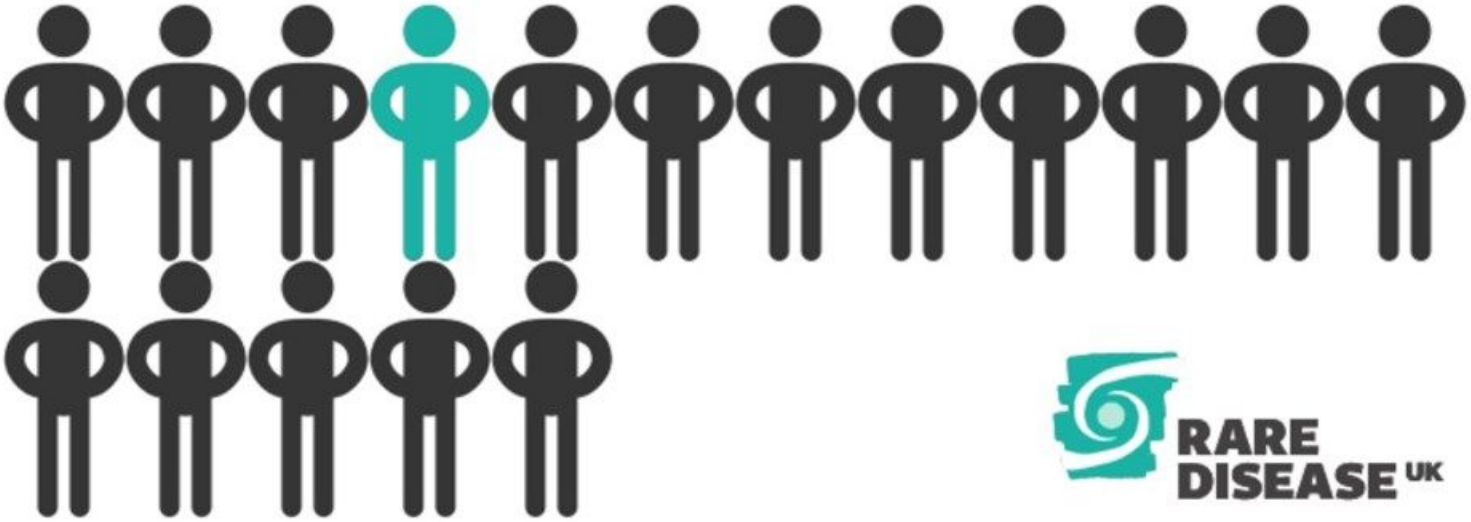
Chris Evelo, Friederike Ehrhart

Science café 28.02.2019


RARE
DISEASE
DAY®

1 in 17 people will be affected by a rare disease at some point in their life.



RARE DISEASE UK

Objectives (our summary ;-))

- Better diagnosis and better treatments through better research

IRDiRC goals 2017 – 2027

- Patients are **diagnosed within one year** if their disorder is known in the medical literature;
- Undiagnosable individuals will enter a globally coordinated **diagnostic and research pipeline**;
- **1000 new therapies** for rare diseases will be approved, the majority of which will focus on diseases without approved options;
- **Methodologies will be developed to assess** the impact of diagnoses and therapies on rare disease patients.

EUROPEAN JOINT PROGRAMME ON RARE DISEASES

Coordinated by Inserm
La science pour la santé | From science to health

Some numbers:
85 partners
33 participating countries
about 100 Mio budget
Started January 2019
Duration 5 years

COORDINATION & TRANSVERSAL ACTIVITIES

INTEGRATIVE RESEARCH STRATEGY

SUSTAINABILITY

ETHICAL, LEGAL, REGULATORY & IPR ISSUES

COMMUNICATION & DISSEMINATION

1 RESEARCH FUNDING

2 COORDINATED ACCESS TO DATA & SERVICES

3 CAPACITY BUILDING & EMPOWERMENT

4 ACCELERATING TRANSLATION

WP1 COORDINATION & MANAGEMENT

WP2 STRATEGY	WP3 SUSTAINABILITY	WP4 ETHICS, LEGAL, REGULATORY & IPR	WP5 COMMUNICATION & DISSEMINATION

- WP6 Joint Transnational Calls
- WP7 Networking scheme
- WP8 RDR Challenges
- WP9 Monitoring of funded projects

- WP 10 User-driven strategic planning for P2
- WP 11 Virtual Platfform for data & resources
- WP 12 Enabling sustainable FAIRness
- WP 13 Holistic approaches for rare disease diagnostics and therapeutics

- WP 14 Training on data management & quality
- WP 15 Capacity building and training of patients and researchers
- WP 16 Online Academic education course
- WP 17 ERN RD training and support programme
- WP 18 Development and adaptation of training activities

- WP 19 Facilitating partnerships and accelerating translation
- WP 20 Validation , use and development of innovative methodologies for clinical studies

Maastricht University
Bioinformatics

Coordinated by

Inserm
La science pour la santé
From science to health

Infrastructural work around the analysis of -omics data - Pillar 2

WP10: User-driven strategic planning and transversal activities for Pillar 2 data ecosystem

Annual strategic meetings with users (ERNs) & developers to define the priorities – coordination of outputs & needs – technical GDPR implementation – quality, sustainability and scaling up

WP11: Common virtual platform for discoverable data and resources for RD research

Metadata & ontological models – FAIR compliance – data deposition & access to data infrastructure – online tools

WP12: Enabling sustainable FAIRness and Federation at the record for RD data, patients and samples

Alignment of core interoperability standards – software for FAIR ecosystem – FAIRification support

WP13: Enabling multidisciplinary, holistic approaches for rare diseases diagnostics and therapeutics

System biology approaches for RD – biological pathways – variants to function – environmental toxicology – treatment drugs - proof of principle studies

That's WP13

Sub task leaders

Peter-Bram 't Hoen (Radboud University Medical Centre, Nijmegen)

member

ELIXIR and EMBL-EBI

FUNDACIO CENTRE DE REGULACIO GENOMICA

Marco Roos (Leiden University Medical Centre)

WP13 lead

Chris Evelo (Maastricht University) and Franz Schäfer (University Hospital Heidelberg)

UNIVERSITÄT TÜBINGEN

UNIVERSITAETS-KLINIKUM FREIBURG

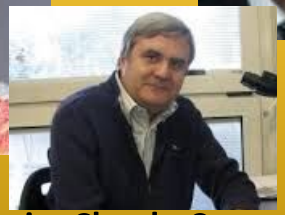
Instituto de Salud Carlos III

Anaïs Baudot (INSERM-AMU)

Acibadem University

University hospital Groningen

Ludwig Boltzmann Gesellschaft GmbH



Domenica Taruscio, Claudo Carta and Alberto Mantovani (Instituto Superiore di Sanita, Rome)

EJP RD

Funded by the European Union GA n°825575

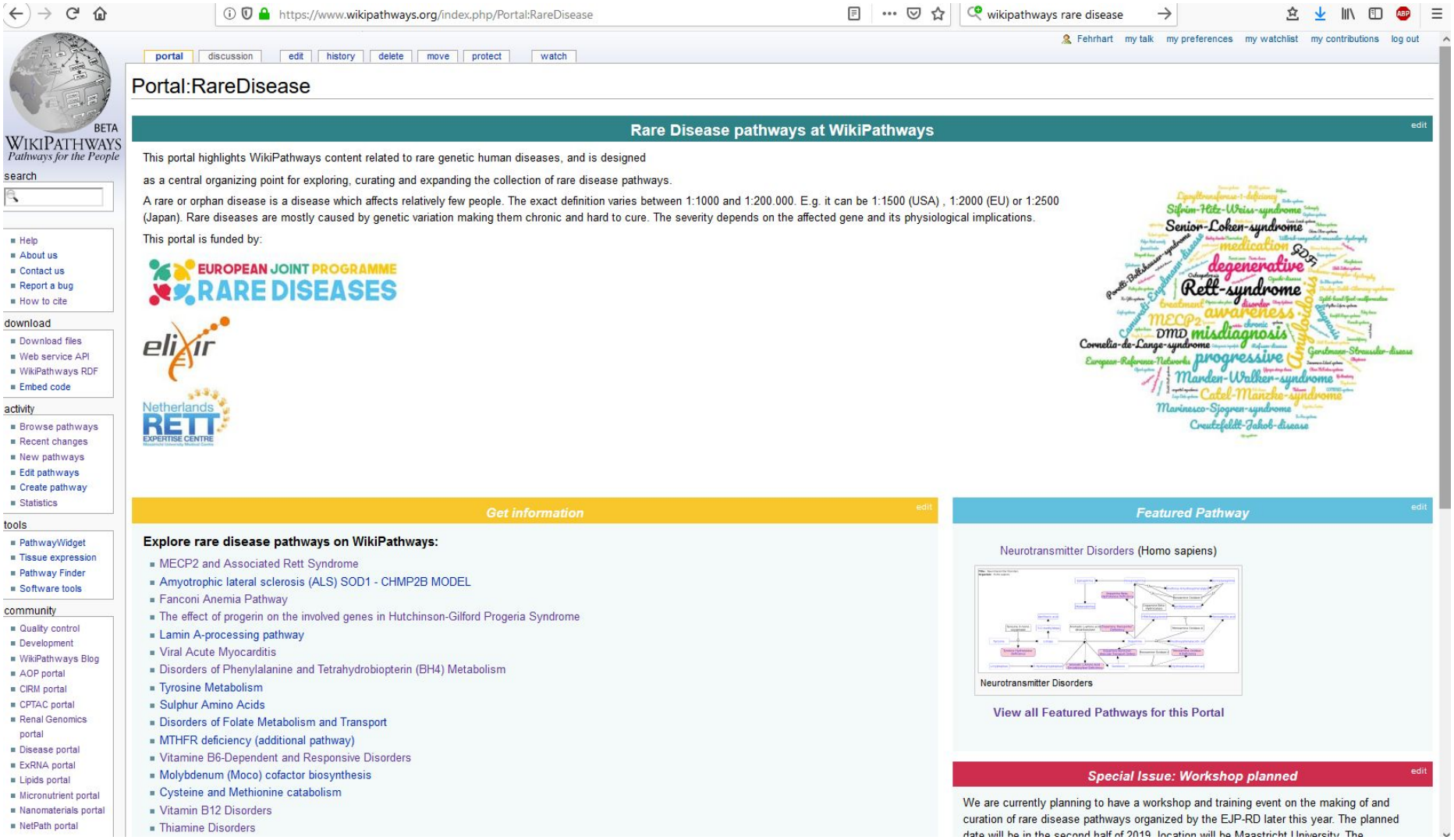
WP13 - objectives

- WikiPathways rare disease portal (see http:///raredisease.wikipathways.org
- **Evaluate omics and other relevant data-availability** e.g. from ERN partners
- **Combine affected pathways into data and knowledge supported rare disease networks**, evaluate these for things like active nodes and make them available on NDEX.
- Allow **extension of these networks with relevant regulatory information** (e.g. transcription factors and miRNAs) and where available evaluate data on such regulatory factors.
- Use the networks to **evaluate drug targets** and thus come up with ideas for drug repurposing with some special interest in orphan drugs (building on our IMI collaborations).
- Evaluate the network for **intrinsic lifestyle factors** (e.g. micronutrients present in or known to affect the networks) or processes known to be affected by exercise (building on our NuGO and other nutrition-related collaborations).
- Allow extension with **external environmental factors** like chemical exposure (toxicology) and evaluate overlap with so-called adverse outcome pathways (building on toxicology collaborations).
- **Create complete workflows and make these available**, including component containers and specific networks resulting from the analysis.

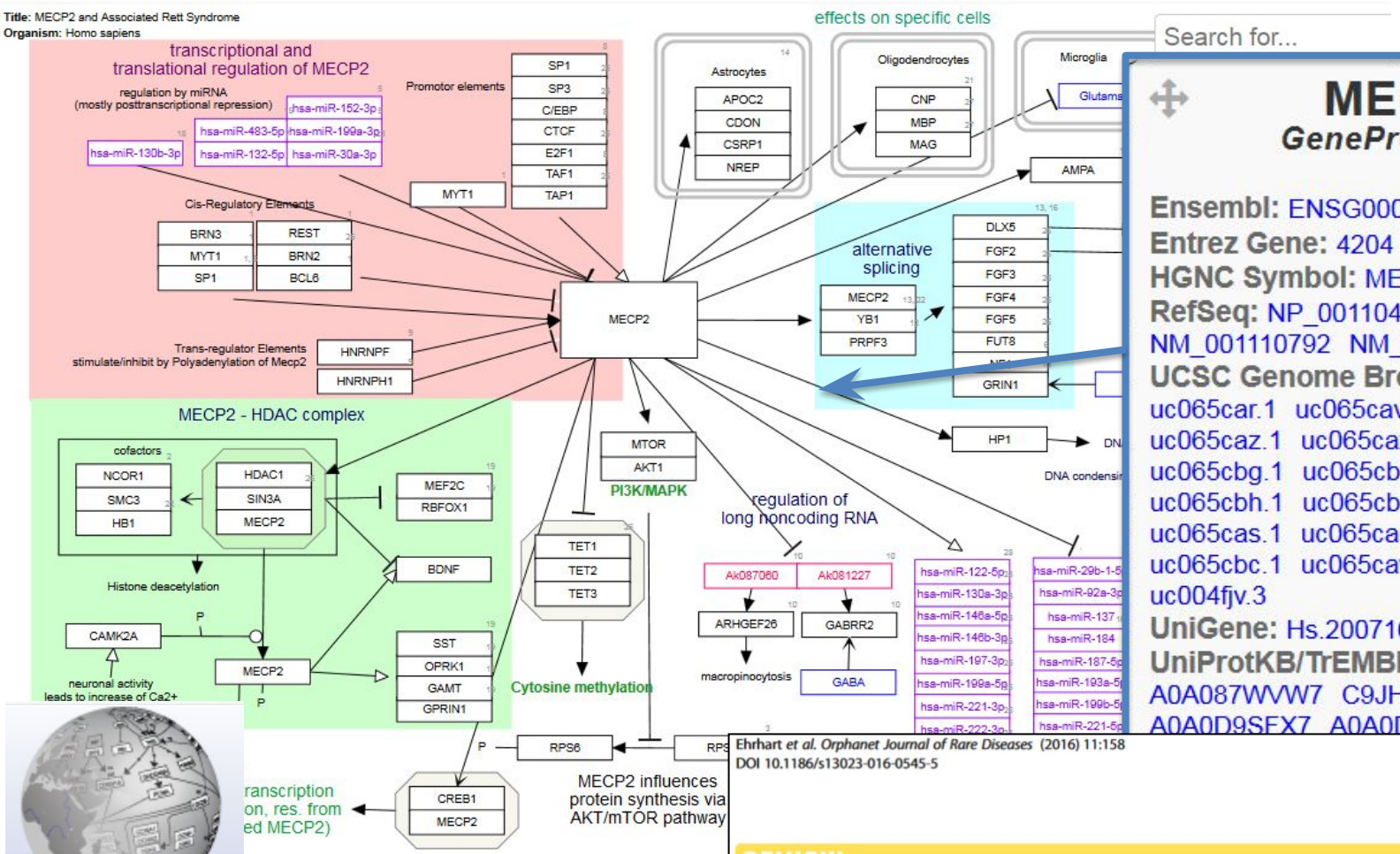
WP13 Holistic approaches

Task 13.1: Gap filling
13.1.1: Pathways created and expert curated.
13.1.2: Mapping to genes.
13.1.3: Mapping genes to function.
13.1.4: Link to external FAIR data.
13.1.5: Network repository.
13.1.6: Environmental lifestyle
13.1.7: Treatment drugs
13.1.8: Environmental toxicology
13.1.9: Workflow leading to understanding of disease mechanisms and diagnosis
13.1.10: Link to Adverse Outcome Pathway approach
13.2 Organise proof of principle studies

13.1.1: Pathways created and expert curated.



Maastricht University



Search for...

MECP2

GeneProduct

Ensembl: ENSG00000169057
Entrez Gene: 4204
HGNC Symbol: MECP2
RefSeq: NP_001104262 NP_004983 NM_001110792 NM_004992
UCSC Genome Browser: uc065cbb.1 uc065car.1 uc065cav.1 uc065cat.1 uc065caz.1 uc065cax.1 uc004fjw.3 uc065cbg.1 uc065cbf.1 uc065cbe.1 uc065cbh.1 uc065cba.1 uc065cbi.1 uc065cas.1 uc065cau.1 uc065cay.1 uc065cbc.1 uc065caw.1 uc065cbd.1 uc004fjv.3
UniGene: Hs.200716
UniProtKB/TrEMBL: D3YJ43 B5MCB4 A0A087WVW7 C9JH89 H7BY72 A0A0D9SEX7 A0A0D9SEX1

BETA
WIKIPATHWAYS
Pathways for the People

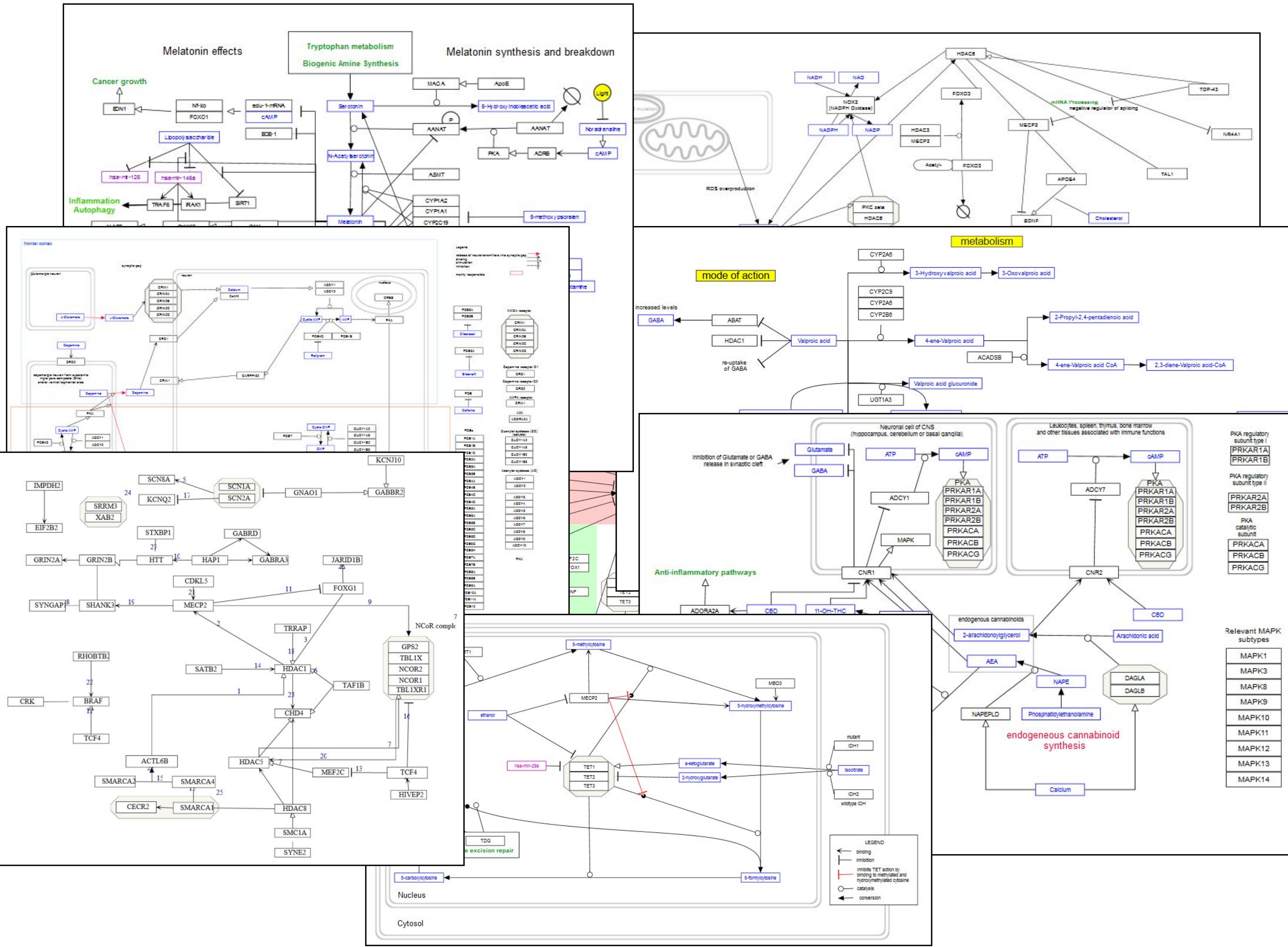
Ehrhart *et al. Orphanet Journal of Rare Diseases* (2016) 11:158
DOI 10.1186/s13023-016-0545-5

Orphanet Journal of Rare Diseases

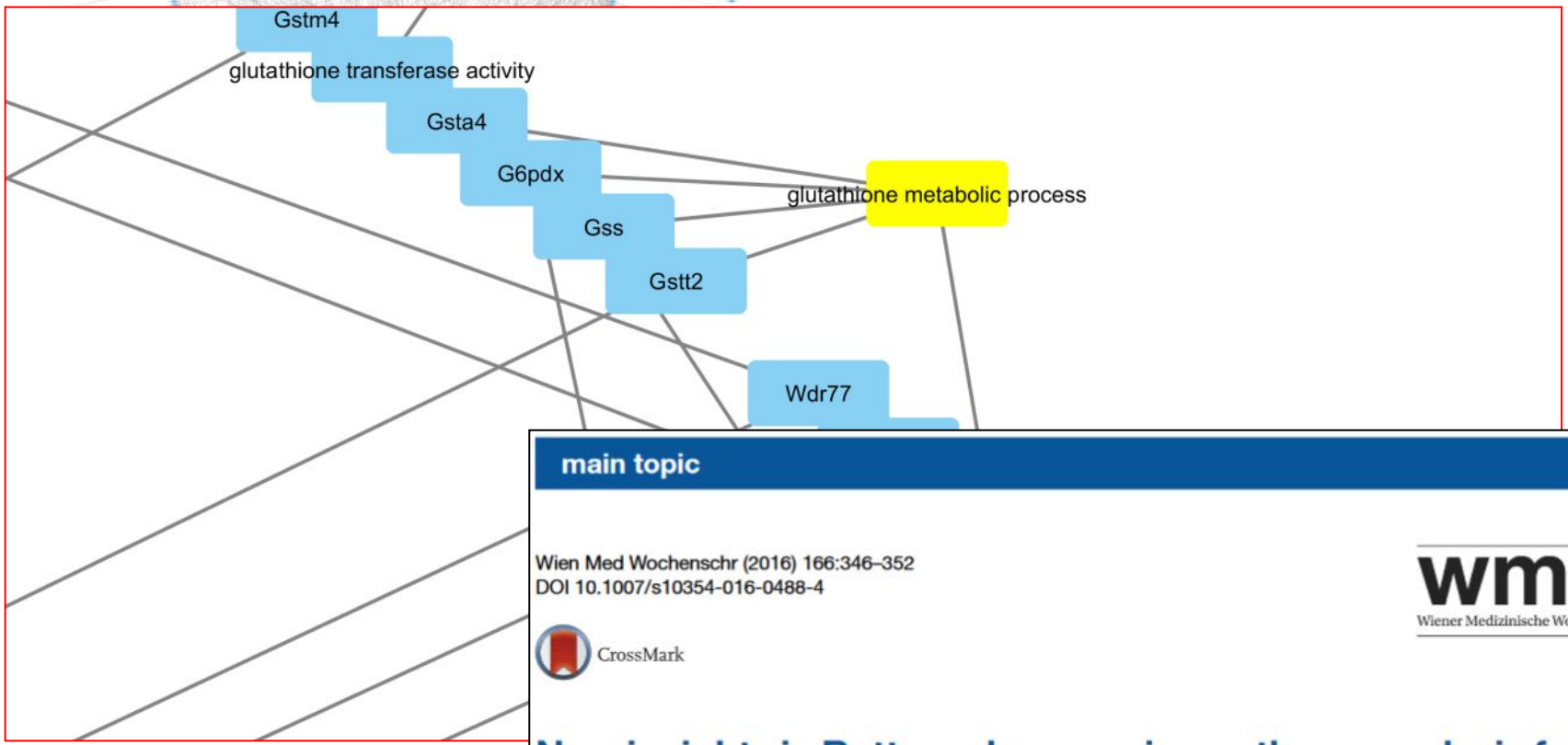
REVIEW Open Access

Rett syndrome – biological pathways leading from MECP2 to disorder phenotypes

Friederike Ehrhart[1,2*], Susan L. M. Coort[2], Elisa Cirillo[2], Eric Smeets[1], Chris T. Evelo[1,2] and Leopold M. G. Curfs[1]



Melatonin effects
Tryptophan metabolism
Biogenic Amine Synthesis
Melatonin synthesis and breakdown
Cancer growth
EDN1
Nf-kb
FOXO1
edu-1-mRNA
cAMP
EDE-1
Lipopolysaccharide
hsa-mir-126
hsa-mir-146a
Inflammation
Autophagy
TRAF6
IRAK1
SIRT1
Serotonin
N-Acetylserotonin
Melatonin
MAOA
ApoE
5-Hydroxyindoleacetic acid
AANAT
Light
Noradrenaline
PKA
ADRB
cAMP
ASMT
CYP1A2
CYP1A1
CYP2C19
5-methoxypsoralen
HDAC6
NADH
NAD
NOX2
(NADPH Oxidase)
NADPH
NADP
FOXO3
HDAC3
MECP2
Acetyl-
miRNA Processing
negative regulator of splicing
TDP-43
NR4A1
APOE4
TAL1
ROS overproduction
PKC zeta
BDNF
Cholesterol
metabolism
mode of action
CYP2A6
3-Hydroxyvalproic acid
3-Oxovalproic acid
CYP2C9
CYP2B6
increased levels
GABA
ABAT
HDAC1
Valproic acid
4-ene-Valproic acid
2-Propyl-2,4-pentadienoic acid
re-uptake
of GABA
ACADSB
4-ene-Valproic acid CoA
2,3-diene-Valproic acid-CoA
Valproic acid glucuronide
UGT1A3
Neuronal cell of CNS
(hippocampus, cerebellum or basal ganglia)
Leukocytes, spleen, thymus, bone marrow
and other tissues associated with immune functions
PKA regulatory
subunit type I
PRKAR1A
PRKAR1B
PKA regulatory
subunit type II
PRKAR2A
PRKAR2B
PKA
catalytic
subunit
PRKACA
PRKACB
PRKACG
Inhibition of Glutamate or GABA
release in synaptic cleft
Glutamate
ATP
ADCY1
MAPK
ADCY7
CNR1
CNR2
Anti-inflammatory pathways
ADORA2A
CBD
11-OH-THC
endogenous cannabinoids
2-arachidonoylglycerol
Arachidonic acid
AEA
NAPE
DAGLA
DAGLB
NAPEPLD
Phosphatidylethanolamine
endogeneous cannabinoid
synthesis
Calcium
Relevant MAPK
subtypes
MAPK1
MAPK3
MAPK8
MAPK9
MAPK10
MAPK11
MAPK12
MAPK13
MAPK14
KCNJ10
IMPDH2
SCN8A
SCN1A
SCN2A
KCNQ2
GNAO1
GABBR2
SRRM3
XAB2
EIF2B2
STXBP1
GABRD
GRIN2A
GRIN2B
HTT
HAP1
GABRA3
JARID1B
CDKL5
FOXG1
SYNGAP1
SHANK3
MECP2
NCoR complex
TRRAP
GPS2
TBL1X
NCOR2
NCOR1
TBL1XR1
RHOBTB2
SATB2
HDAC1
TAF1B
CRK
BRAF
CHD4
TCF4
ACTL6B
HDAC5
MEF2C
SMARCA2
SMARCA4
HIVEP2
CECR2
SMARCA1
HDAC8
SMC1A
SYNE2
5-methylcytosine
MBD3
ethanol
5-hydroxymethylcytosine
mutant
IDH1
hsa-mir-29a
TET1
TET2
TET3
a-ketoglutarate
2-hydroxyglutarate
isocitrate
IDH2
wildtype IDH
TDG
base excision repair
LEGEND
binding
inhibition
inhibits TET action by binding to methylated and hydroxymethylated cytosine
catalysis
conversion
5-carboxylcytosine
5-formylcytosine
Nucleus
Cytosol



main topic

Wien Med Wochenschr (2016) 166:346–352
DOI 10.1007/s10354-016-0488-4

wmw
Wiener Medizinische Wochenschrift

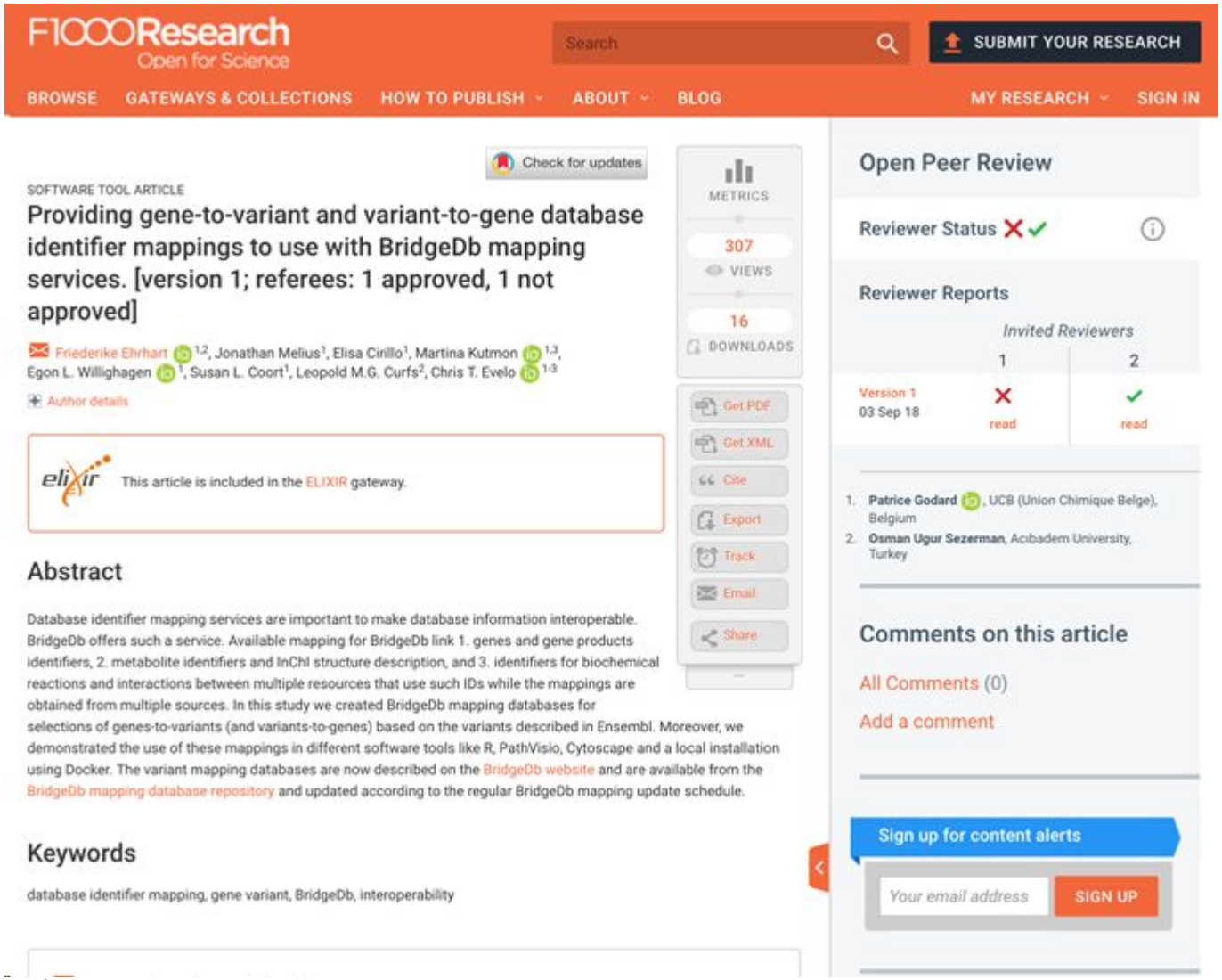
CrossMark

New insights in Rett syndrome using pathway analysis for transcriptomics data

Friederike Ehrhart · Susan L. M. Coort · Elisa Cirillo · Eric Smeets · Chris T. Evelo · Leopold Curfs

13.1.2: Mapping to genes.

BridgeDb



Available for SNPs (will need maintenance and large file support)

Not yet (operationally) available for:

- InDels (Insertions and Deletions)
- CNVs (Copy Number Variations)

Standardized variant descriptions evaluated at FAIR BYOD in Maastricht
(Where is it? Does it cover CNVs?)

Problems:

1) Cluster various variants occurring in close proximity
2) See when InDels CNVs and various SNPs occur in same region (e.g. protein domain).

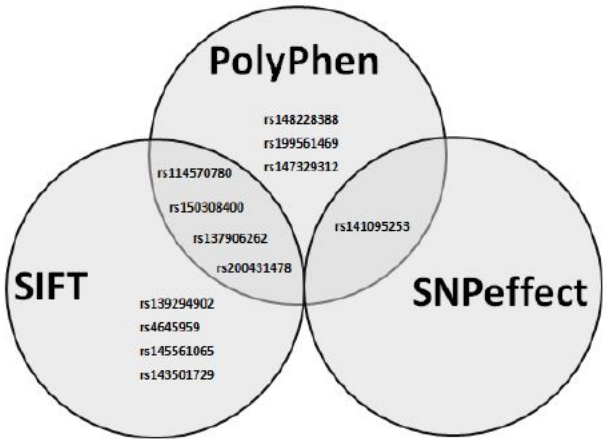
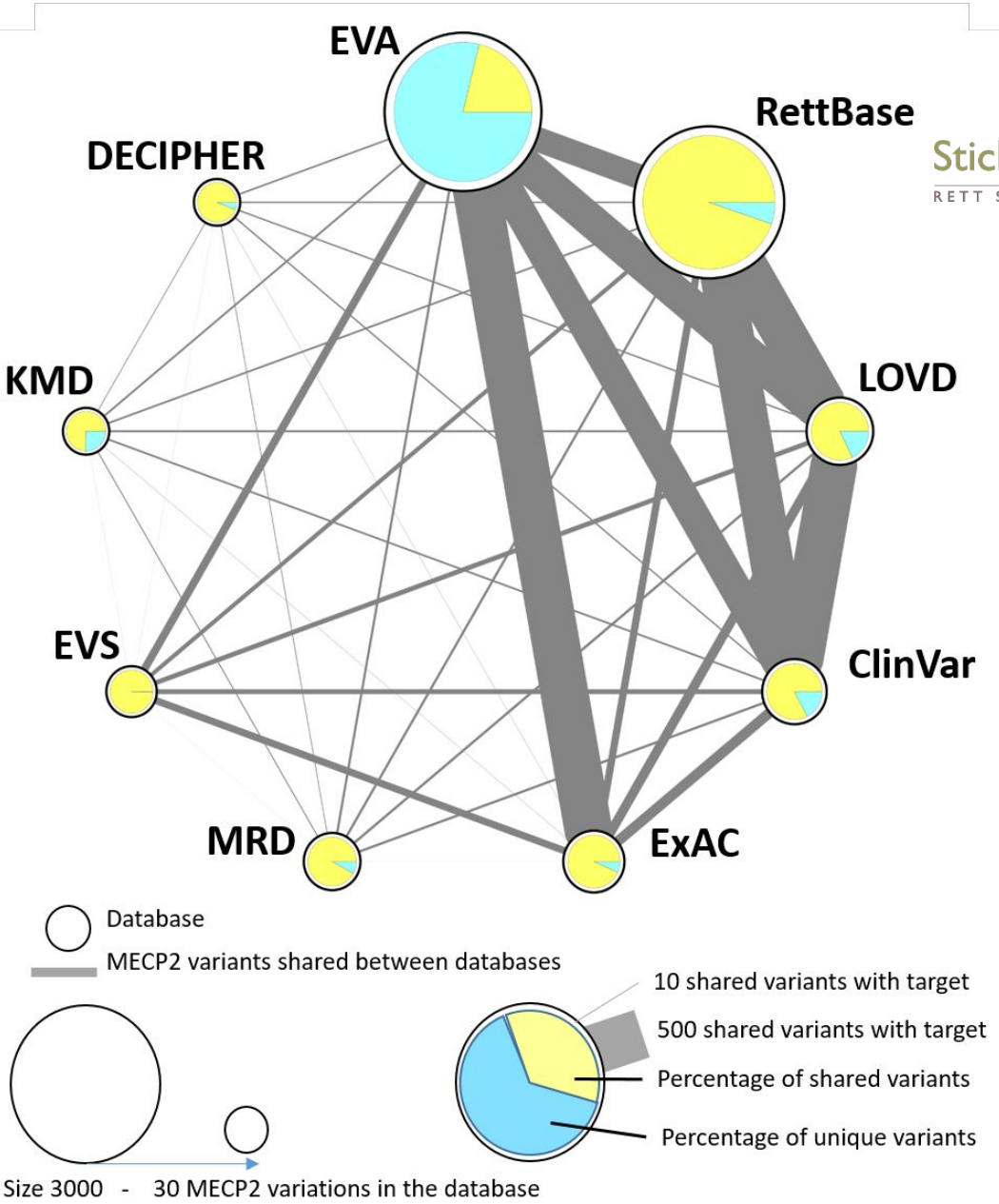
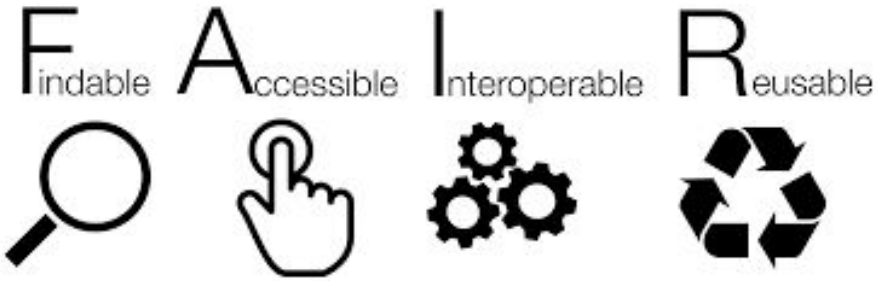


Fig. 4. nsSNPs of human c-Myc1 protein predicted by SIFT, PolyPhen and SNPeffect algorithms to have some biological importance.

The landscape of MECP2 variants in the different databases



Paper in preparation
863 variants of RTT… 2019



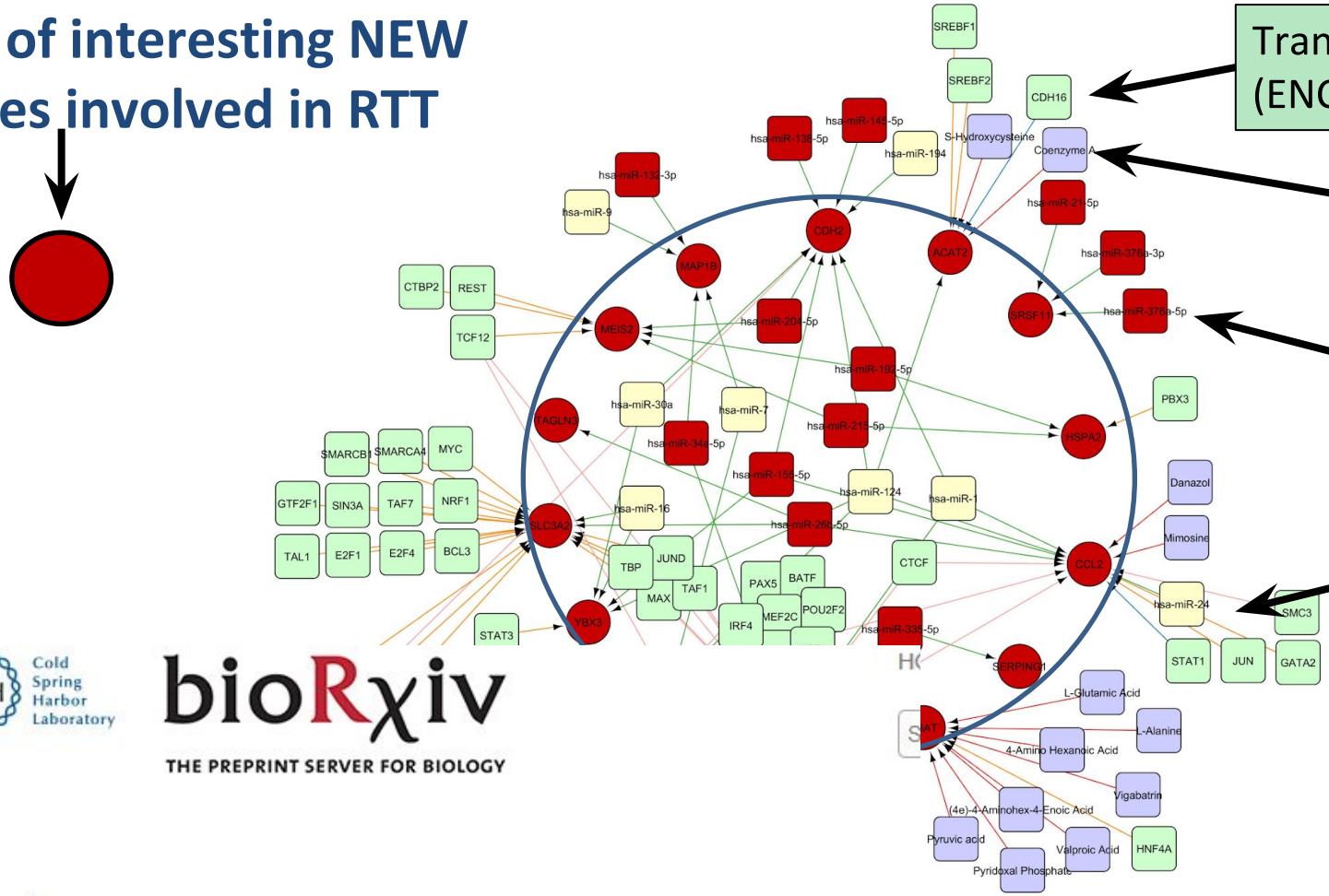
HORIZON 2020

FAIRplus

WP12

A federated Open PHACTS??

List of interesting NEW genes involved in RTT



Transcription factors (ENCODE)

Drugs

microRNA mature sequence

microRNA base sequence

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

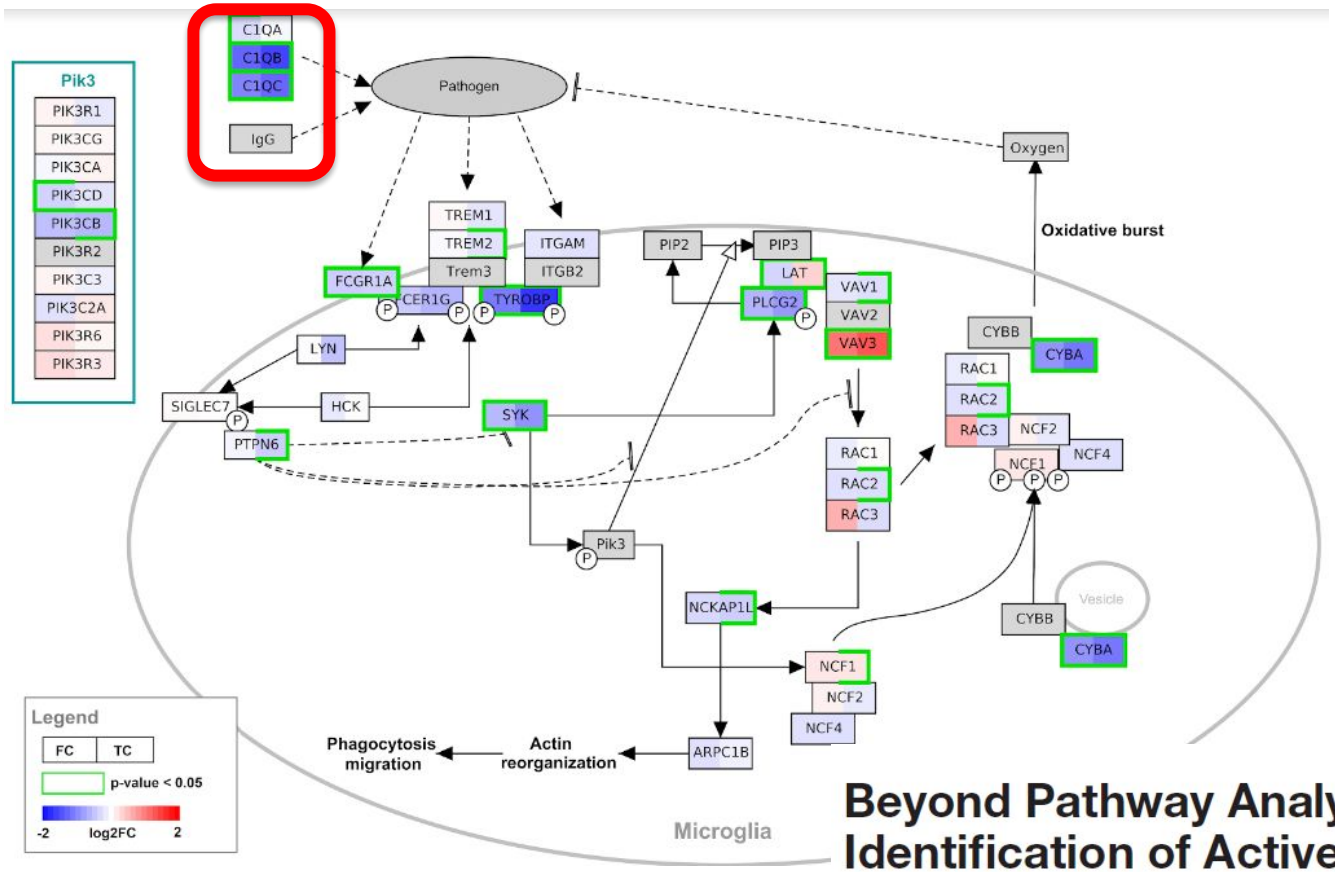
New Results

Integrated analysis of human transcriptome data for Rett syndrome finds a network of involved genes

Friederike Ehrhart, Susan L Coort, Lars Eijssen, Elisa Cirillo, Eric Smeets, Nasim Bahram Sangani, Chris Evelo, Leopold M.G. Curfs

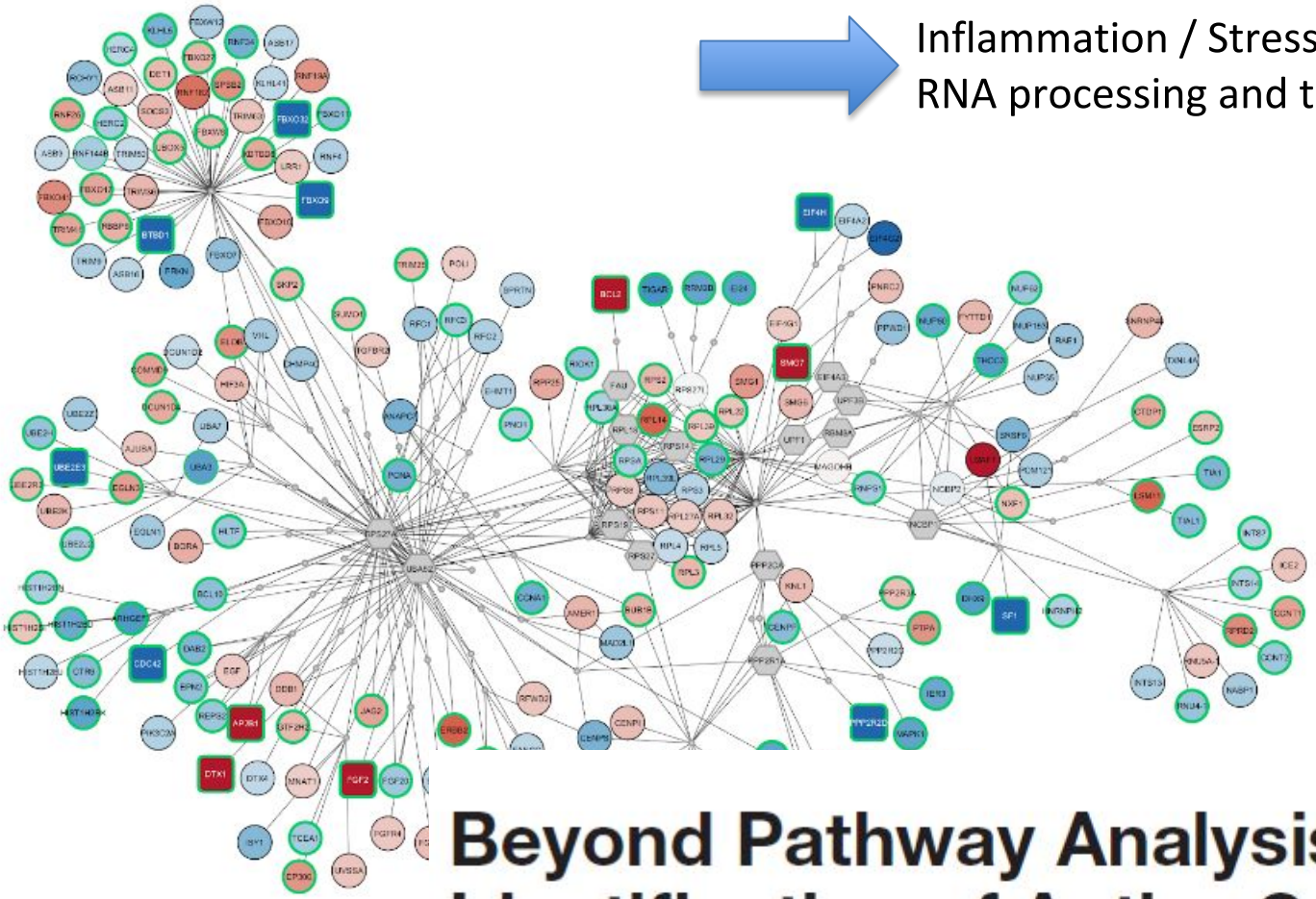
doi: https://doi.org/10.1101/274258

Beyond pathway analysis – using of integrated network of ALL pathways



Beyond Pathway Analysis: Identification of Active Subnetworks in Rett Syndrome

Ryan A. Miller[1†], Friederike Ehrhart[1,2†], Lars M. T. Eijssen[1,3], Denise N. Slenter[1], Leopold M. G. Curfs[2], Chris T. Evelo[1,2,4], Egon L. Willighagen[1] and Martina Kutmon[1,4]*



Inflammation / Stress
RNA processing and translation processes

Beyond Pathway Analysis: Identification of Active Subnetworks in Rett Syndrome

Ryan A. Miller[1†], Friederike Ehrhart[1,2†], Lars M. T. Eijssen[1,3], Denise N. Slenter[1], Leopold M. G. Curfs[2], Chris T. Evelo[1,2,4], Egon L. Willighagen[1] and Martina Kutmon[1,4]*

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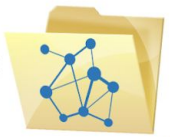
Search Examples
Search for networks, users, and groups
Perform Search Term Expansion (Genes and Proteins only)

Featured Content



DisGeNET
DisGeNET is a discovery platform containing one of the largest publicly available collections of genes and variants associated to human diseases.

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Use the **Search Panel** above to explore the public networks available in NDEx. Our **Featured Networks** are a great place to start, examples of high-quality content from different projects and laboratories. If you use **Search Term Expansion**, common aliases for human gene and protein identifiers will be added to the search. >> Learn More...

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NDEx supports access to data according to **FAIR** principles. Individual users and organizations can make networks public, findable and accessible in NDEx. Each public network has its unique, stable URL and can always be downloaded either manually or programmatically, via our **REST API**.

Tweets by @NDExProject

The NDEx Project
@NDExProject

HumanNet v2 integrated networks now available in @NDExProject .
Find them here: goo.gl/SWeUQB

For more info, please visit the HumaNet v2 website at:
inetbio.org/humannet/#networkbiology #nciitcr #compbio @cytoscape @CancerCellMap

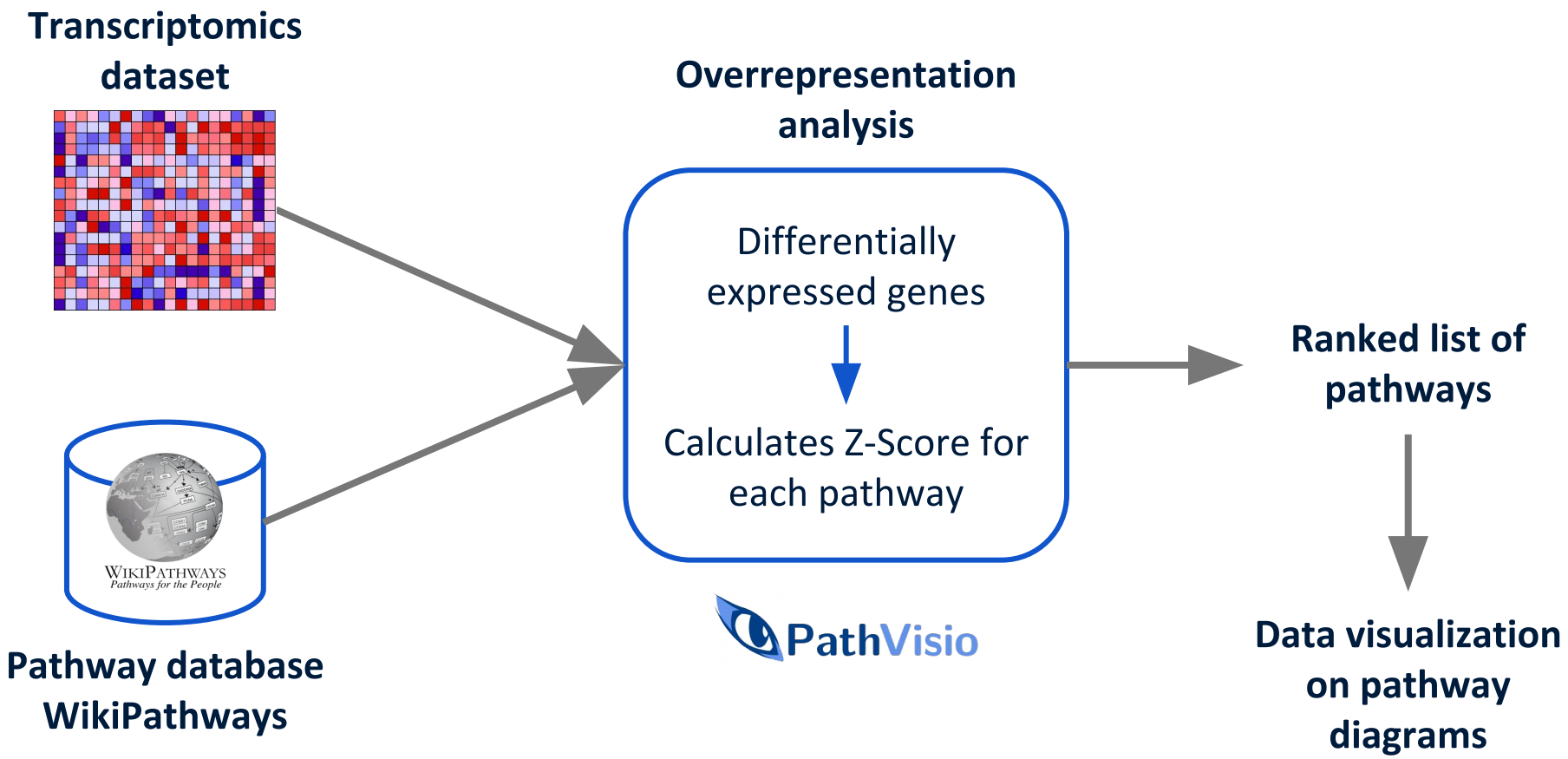
Feb 20, 2019

The NDEx Project
@NDExProject

Up-to-date data from @DrugBankDB v5.1.2 and @DisGeNET v6 now available in NDEx! Access here: goo.gl/WNBjra#networkbiology #nciitcr #compbio @cytoscape @CancerCellMap

PLOS UC San Diego School of Medicine Cytoscape Scientific Data Pfizer janssen

Pathway analysis-method

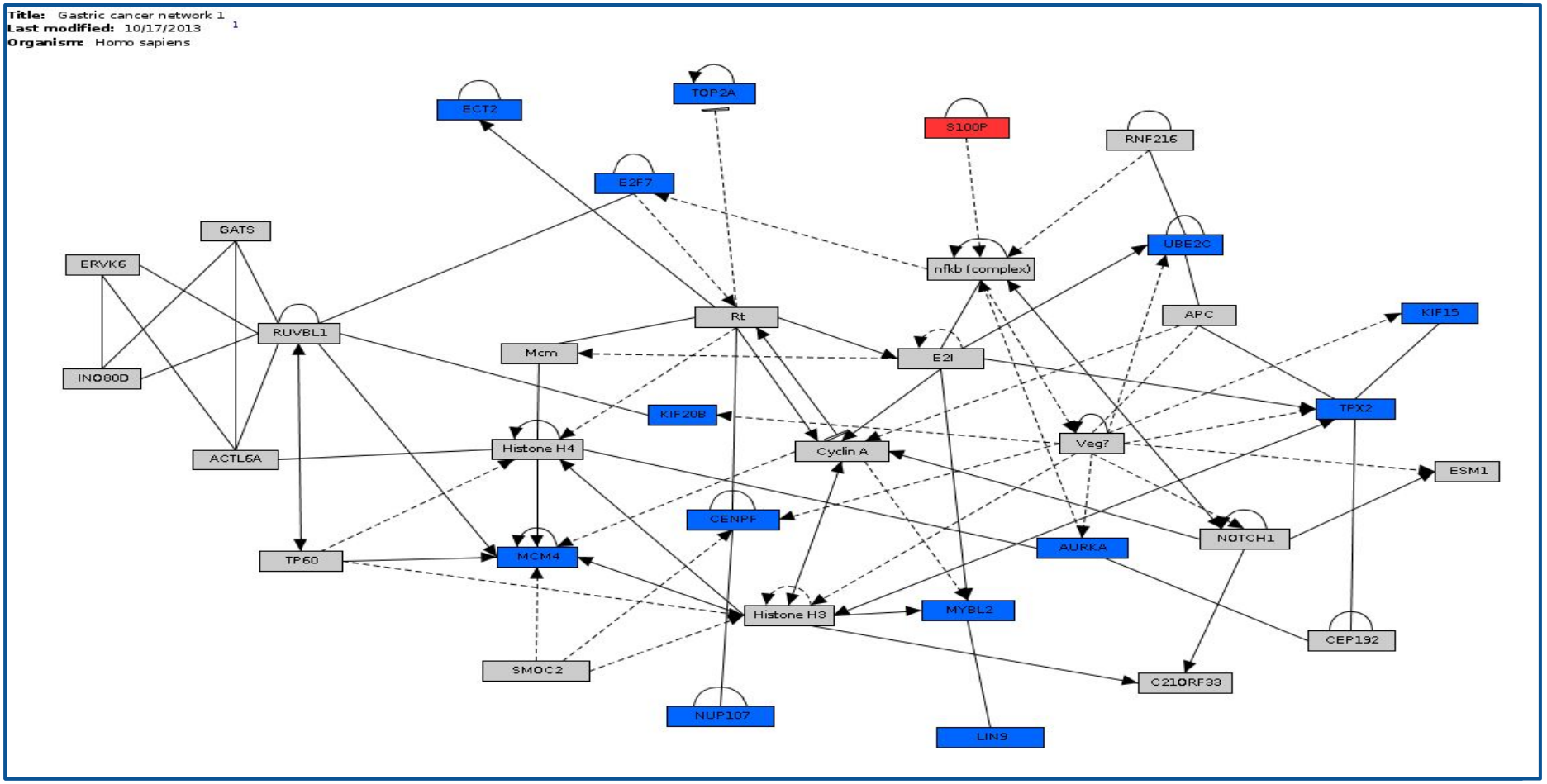


Significantly altered pathways after $1.25(OH)_2D_3$ treatment in prostate cancer cells

- 8 general cell cycle related pathways
- 7 cancer related pathways

Pathway	Z-Score	Category	Pathway	Z-Score	Category
DNA Replication	11.91	general	Retinoblastoma (RB) in Cancer	12.63	cancer
Cell Cycle	11.04	general	Gastric cancer network 1	10.44	cancer
Histone Modifications	10.44	general	Gastric cancer network 2	5.13	cancer
G1 to S cell cycle control	9.12	general	Integrated Pancreatic Cancer Pathway	4.08	cancer
DNA damage response	5.40	general	Integrated Cancer pathway	3.85	cancer
ATM Signaling pathway	4.87	general	Integrated Breast Cancer Pathway	3.41	cancer
Fluoropyrimidine Activity	4.16	general	Signaling Pathways in Glioblastoma	2.02	cancer
AhR signaling pathway	2.47	general			

Pathway analysis -results

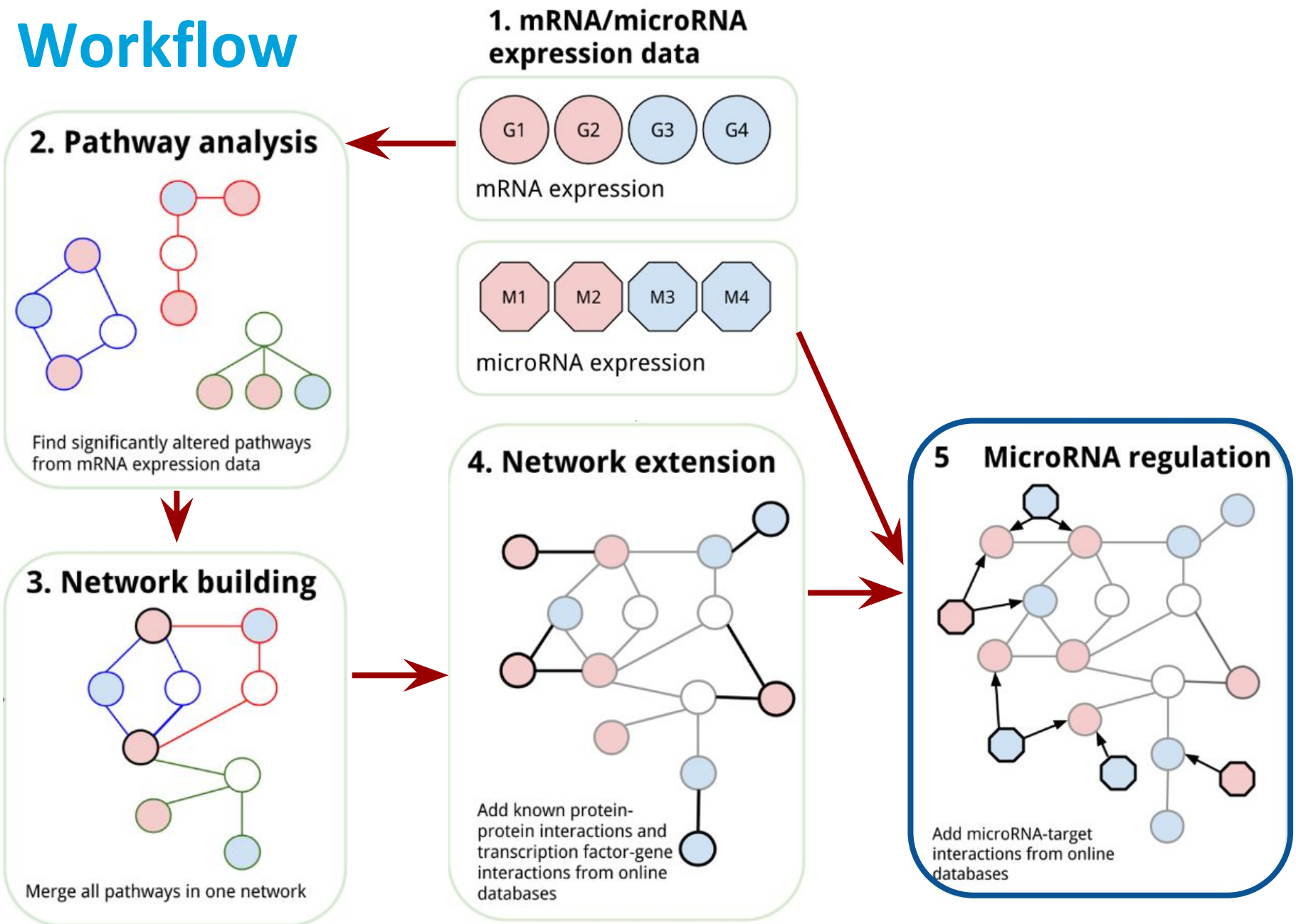


Gastric Cancer Network 1

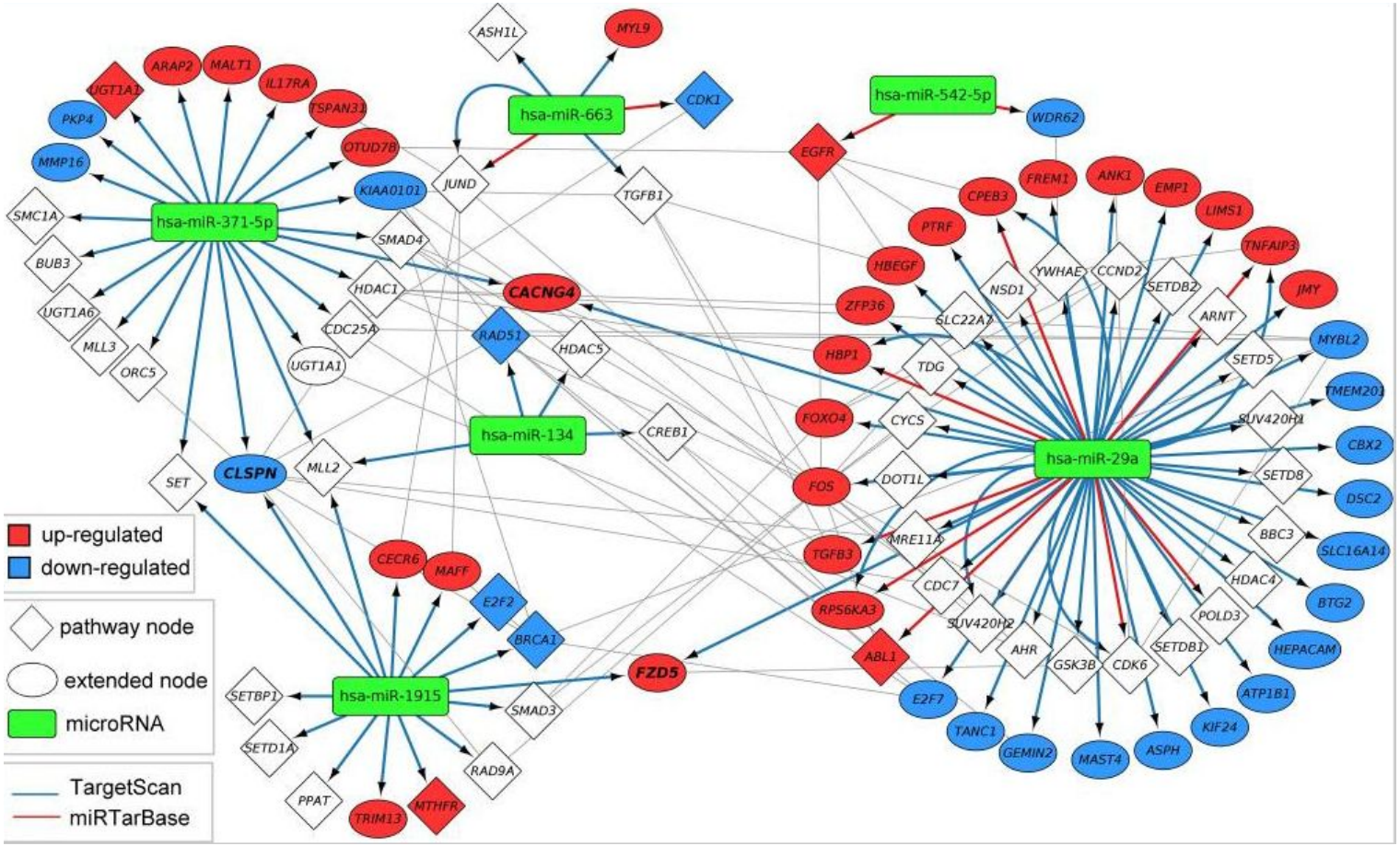
up

down

Workflow


1. mRNA/microRNA expression data
G1
G2
G3
G4
mRNA expression
M1
M2
M3
M4
microRNA expression
2. Pathway analysis
Find significantly altered pathways from mRNA expression data
3. Network building
Merge all pathways in one network
4. Network extension
Add known protein-protein interactions and transcription factor-gene interactions from online databases
5 MicroRNA regulation
Add microRNA-target interactions from online databases

Vitamin D-microRNA network



31 targets up-regulated (3 in pathways)

23 targets down-regulated (4 in pathways)

Targeted by multiple microRNAs:

CLSPN - cell cycle

FZD5 - receptor for Wnt proteins

CACNG4 - calcium channel

CyTargetLinker

a Cytoscape app for simple network extension

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- CyTargetLinker automation feature release
- A microRNA Signature Associated with Early Recurrence in Breast Cancer.
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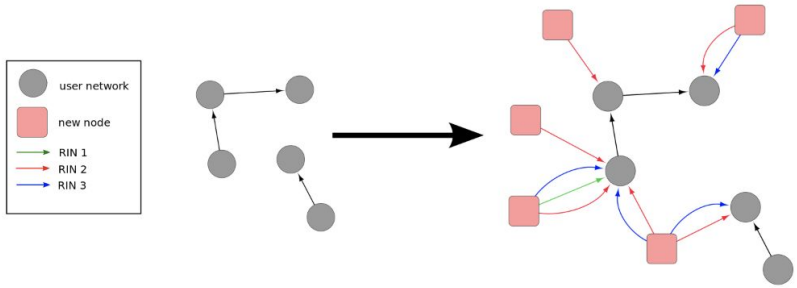
Extend your biological networks in Cytoscape with our CyTargetLinker app



Tutorials

How to use CyTargetLinker.

Learn how to use CyTargetLinker by going through one of our tutorials.

ChEMBL

Downloads

Get CyTargetLinker.

Download CyTargetLinker and the relevant regulatory interaction networks (RINs).

13.1.8:Toxicology

CyTargetLinker

a Cytoscape app for simple network extension

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A microRNA Signature Associated with Early Recurrence in Breast Cancer.

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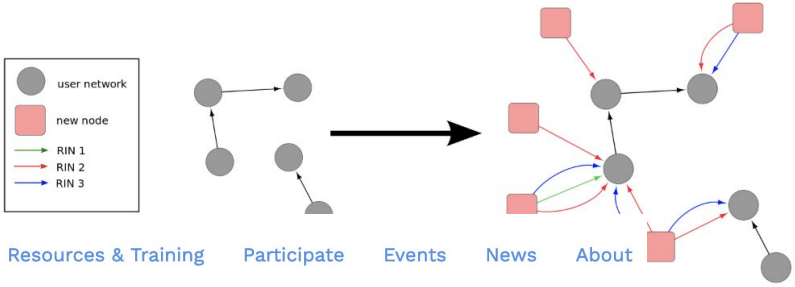
WELCOME

Extend your biological networks in Cytoscape with our CyTargetLinker app



OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

e-Infrastructure Resources & Training Participate Events News About

Open e-Infrastructure to Support Data Sharing, Knowledge Integration and in silico Analysis and Modelling in Predictive Toxicology and Risk Assessment

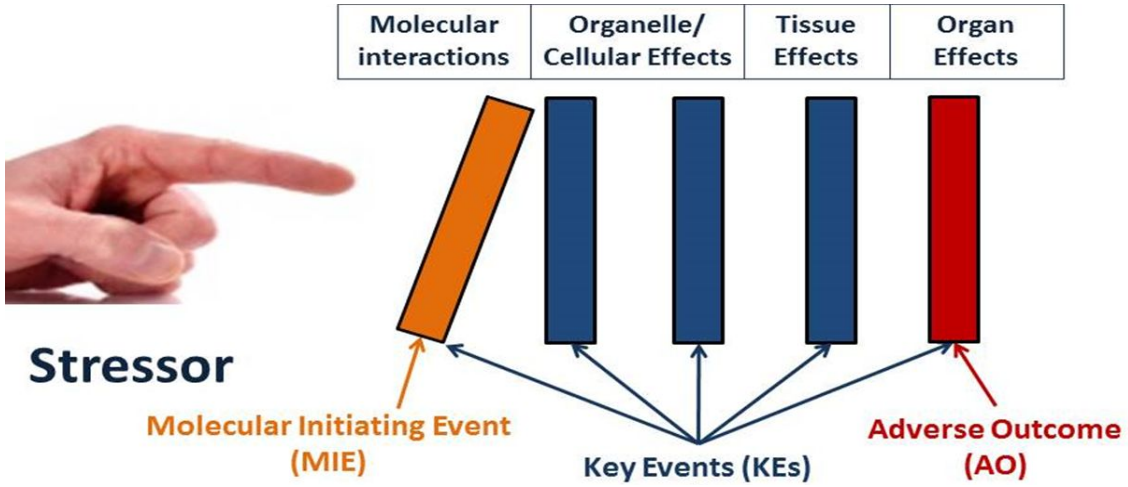
OpenRiskNet is a 3 year project with the main objective to develop an open e-Infrastructure providing resources and services to a variety of communities requiring risk assessment, including chemicals, cosmetic ingredients, therapeutic agents and nanomaterials. OpenRiskNet is working with a network of partners, organized within an Associated Partners Programme.

ur tutorials.

ChEMBL

eraction networks (RINs).

Adverse Outcome Pathways (AOPs)

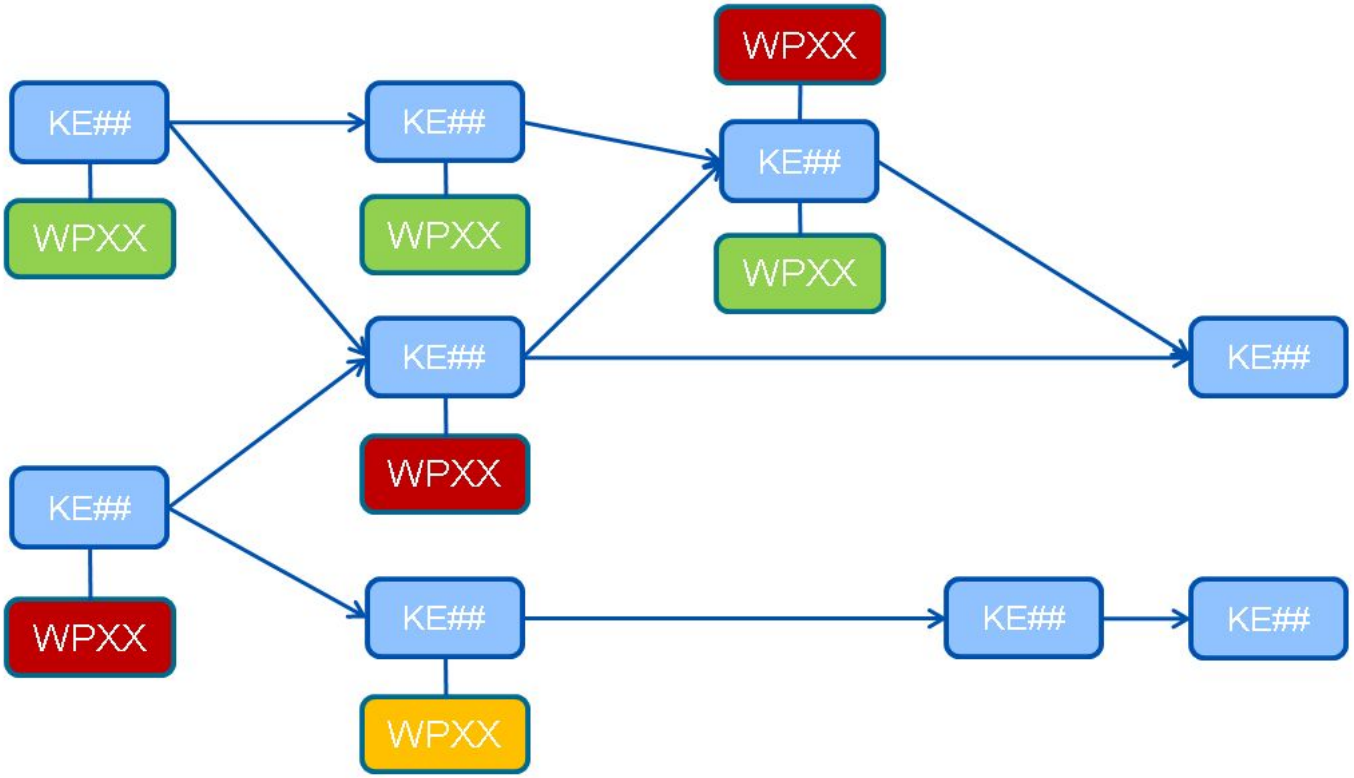


Framework with mechanistic knowledge of toxicological processes to support decision making

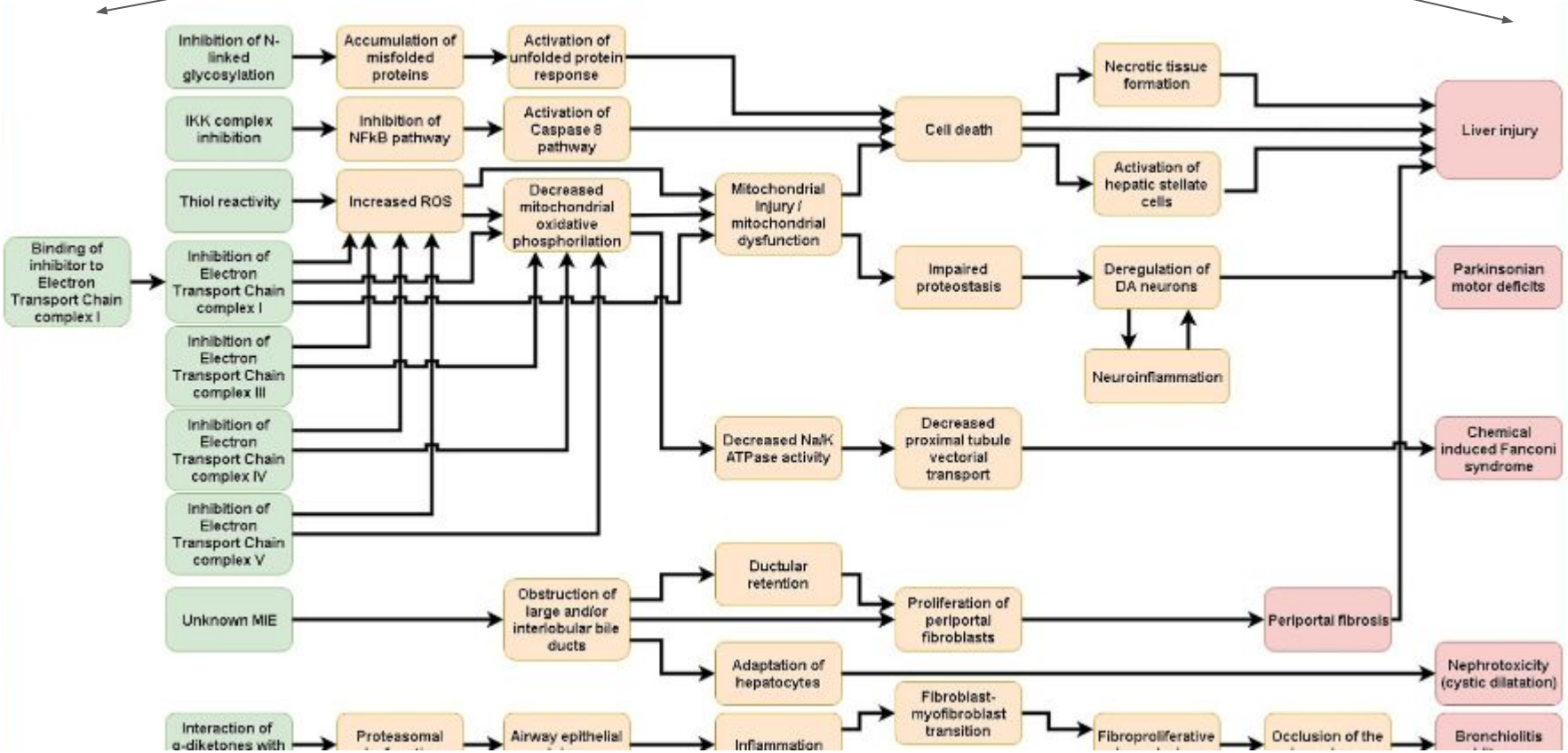
Toxicology data

Knowledge-based regulatory risk assessment

Goal: link molecular pathways to AOPs



Links to rare genetic diseases?



Reproducible Science: The Common Workflow Language

Niels Drost Follow
Mar 13, 2017 · 4 min read

Screenshot of the eWaterCycle forecast workflow, as produced by Cylc

Happy

RARE DISEASE DAY®

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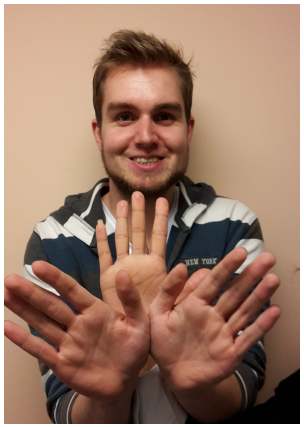

Thank you for your attention!

Contact:
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friederike.ehrhart@maastrichtuniversity.nl

WP 13 Enabling multidisciplinary, holistic approaches for rare diseases diagnostics and therapeutics

Task lead: Chris Evelo

- System biology approaches for RD
  - Biological pathways for RD
  - Understanding of disease mechanisms and diagnosis
- Variants to function mapping
  - SNP-to-protein function, disease-to-protein function
- Environmental lifestyle and toxicology
- Drugs
- Proof of principle studies
  - E.g. on Rett syndrome

Maastricht University

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