### OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

## TGX

Toxicogenomics-based prediction and mechanism identification

# SysGroup

A systems biology approach for grouping compounds

### Danyel Jennen

OpenRiskNet: Open e-Infrastructure to Support Data Sharing, Knowledge Integration and *in silico* Analysis and Modelling in Risk Assessment

Project Number 731075



## o<sub>o</sub>

# Toxicogenomics based prediction and mechanism identification [TGX]

CS leader: Danyel Jennen (UM), Involved: UM, VU, CRG

**AIM:** To provide a transcriptomics-based hazard prediction model for identification of specific molecular initiating events (MIE)

The foreseen transcriptomics-based hazard prediction model will be applied based on:

- **(A) top-down** Creation of prediction models based on differentially regulated genes
- **(B) bottom-up** Using knowledge of stress response pathways to integrate data sets for their activation or inhibition (bottom-up approach).

The MIEs can include, but are not limited to:

(1) Genotoxicity (p53 activation), (2) Oxidative stress (Nrf2 activation), (3) Endoplasmic Reticulum Stress (unfolded protein response), (4) Dioxin-like activity (AhR receptor activation), (5) HIF1 alpha activation and (6) Nuclear receptor activation (e.g. for endocrine disruption).

#### Risk Assessment Framework

Tier 0.3-0.4 (data collection), 1.6 (MOA)

#### **Databases**

- diXa / BioStudies (UM)
- TG-GATEs
- EU-ToxRisk (nascent)
- HeCaToS (nascent)
- ArrayExpress / GEO

#### Tools / APIs

- top-down: Data normalisation tools, prediction tools such as Caret;
- bottom-up: ToxPi

### **Service integration**

• Service integration will be needed for the omics databases; knowledge bases and data mining; processing and analysis.

#### **Activities**

- First top-down case study based on Magkoufoupolou et al 2012 paper
- Second top-down case study on meta-analysis for genotoxicity prediction in human, rat and mouse in vitro cell models

https://openrisknet.org/e-infrastructure/development/case-studies/case-study-tgx/



### Top-down approach → Case study 1

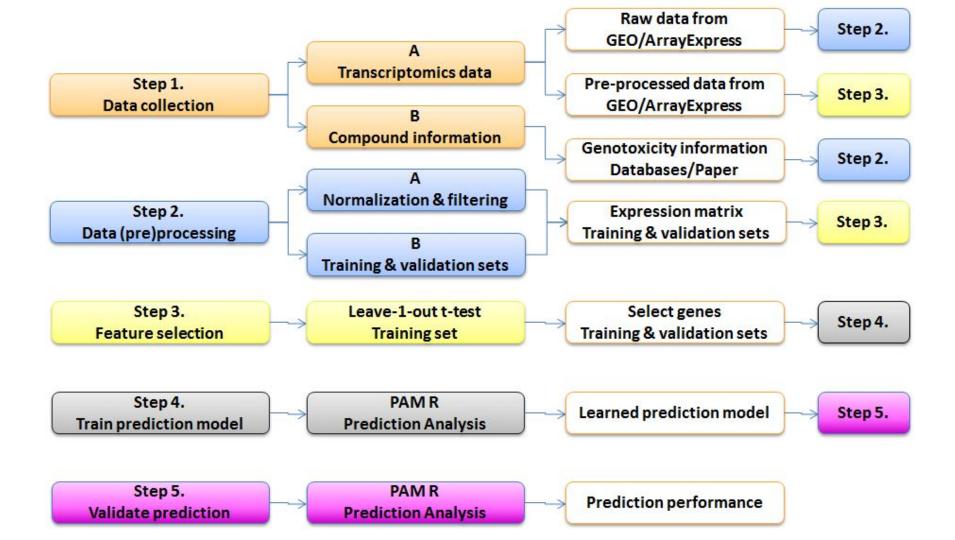
Create workflow based on Magkoufopoulou et al. 2012

Carcinogenesis vol.33 no.7 pp.1421–1429, 2012 doi:10.1093/carcin/bgs182 Advance Access Publication May 23, 2012

A transcriptomics-based in vitro assay for predicting chemical genotoxicity in vivo

C.Magkoufopoulou<sup>1,2</sup>, S.M.H.Claessen<sup>1</sup>, M.Tsamou<sup>1</sup>, D.G. J.Jennen<sup>1,2</sup>, J.C.S.Kleinjans<sup>1,2</sup>, J.H.M.van Delft<sup>1,2,\*</sup>

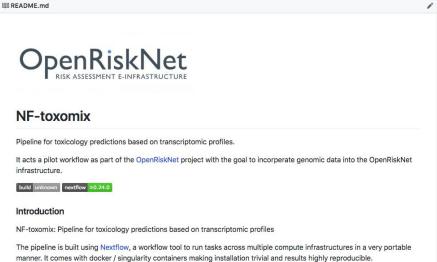




### Current status

Workflow has been established in Snakemake and is available via Gitlab Workflow was converted into NextFlow pipeline;

Converted into a generic workflow applicable to other datasets.





### Generic workflow

- Data collection from GEO/ArrayExpress → API available
- Retrieve (geno)toxicity information
  - from databases
    - possible, but depends of required data
    - expert knowledge needed
  - from paper
    - difficult as presentation of information may vary

Fraunhofer

SCAL

- online pdf → difficult, because of format; suppl. data as Word, Excel, txt files → possible
- All other steps comprise of R-scripts → easy to adapt

→ data collection relies on available metadata, used format & ontologies

### Collaboration with implementation challenge winners



Find the chemical hazard and toxicology literature you need with our information portal

Our Federated Search engine searches the content from 500+ websites and quickly delivers relevant literature.





Investigate the pathways triggered by exposure to toxic substances (coming soon)



# PDF: Table detection and -segmentation **Fraunhofer**



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response is supported by a decrease in presynaptic calcium between L4PCs and L23PCs (see Table 3, Figure 2, Eggermann) and Feldmeyer, 2009. Focal application of ACh onto the somaof LSPCs evokes a biphasic response in which a transient membrane hyperpolarization precedes a slower and longerlasting depolarization. Pharmacological evidence suggests that this effect is mediated by M1 receptors. Compared with the pressure application of ACh, activation of cholinergic synapses with brief bursts provides relatively weak activation. (Golfodge et al., 2007). of mACNRs that often fulls to affect the somatic membrane potential at rest (Hedrick and Waters, 2015). One possible: interpretation of these results might be that emaptically released primarily mAChika.

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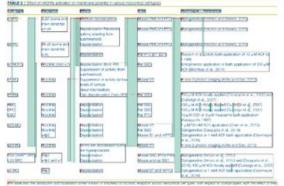
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### Top-down approach → Case study 2

Meta-analysis for genotoxicity prediction in human, rat and mouse *in vitro* cell models

In this case study transcriptomics data obtained from multiple data sources will be used to build a prediction model for *in vivo* genotoxicity.

A similar approach will be applied as in case study 1.

Preliminary results on the rat data have been presented at the ICCA-LRI workshop 2018, Ottawa, Canada Preliminary results on the human data have been presented at EUROTOX 2018, Brussels, Belgium



### Current status

The generic workflow will be applicable in this case study as well.

- Additional databases have been used, e.g. the diXa Data Warehouse
   → included in EBI's BioStudies → an API is available
- In vitro liver transcriptomics data from multiple human, rat & mouse cell models is available via Gitlab
- (Geno)toxicity data on all compounds has been collected
  - → valuable source for ToxicoDB

Other services from the implementation challenge can be incorporated.

→ ToxPlanet databases potentially can provide genotoxicity information





### A systems biology approach for grouping compounds [SysGroup]

CS leader: Danyel Jennen (UM), Involved: UM, Fraunhofer, CRG

**AIM:** To provide the services for **improved grouping** of compounds by integrating chemoinformatics and omics data.

Will use the approach of the diXa / DECO2 (Cefic-LRI AIMT4) projects to reproduce and extend the results obtained on the identification of hepatotoxicant groups based similarity in mechanisms of action on (omics-based) <u>and chemical structure</u> using services from OpenRiskNet.

### **Objectives**

This case study will implement an integrated analysis approach using chemoinformatics and omics data for improved grouping of compounds with similar toxicity and/or mode of action

#### **Risk Assessment Framework**

Tier 0.2-0.4 (data collection, read across)

#### **Databases**

- diXa /BioStudies (UM)
- PubChem
- ChEMBL

#### Tools / APIs

- PubChem
- ChEMBL or PIDGIN
- (pre)processing tools for gene expression data (e.g. microarray data) → e.g. arrayanalysis.org (UM)
- iClusterPlus

#### **Required steps**

- Chemical similarity calculated by 2D or 3D Tanimoto coefficient (PubChem)
- Protein target prediction (ChEMBL/PIDGIN)
- Interface to diXa for obtaining gene expression data
- Integration of the multiple data sources and grouping by iClusterPlus

#### **Service integration**

Integration with other case studies is needed. SysGroup acquires information from the DataCure case study and can feed into AOPLink and ModelRX.



# Flowchart SysGroup

