MOS unique approach in drug development

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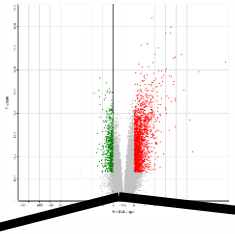
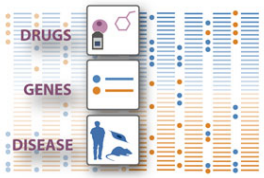
CoI: co-founder and co-owner of Mosaiques Diagnostics, Mosaiques Therapeutics, and DiaPat

Tissue omics Analysis



Differentially abundant proteins in case vs. control group

Mapping to known chemical compounds/ therapeutic agents



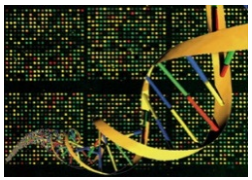
CMAP

Characterisation of COMPOUNDS

- Annotation of compounds
- Functional Annotation of targeted/ affected proteins
- Literature mining, Patent Search

Shortlisted Compounds

Identification of drug targets



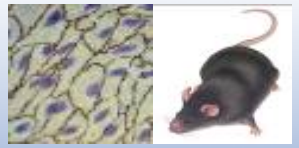
Systems biology analysis

Characterisation of PROTEINS

- Analysis of subcellular localisation
- Functional annotation of proteins
- Literature Mining

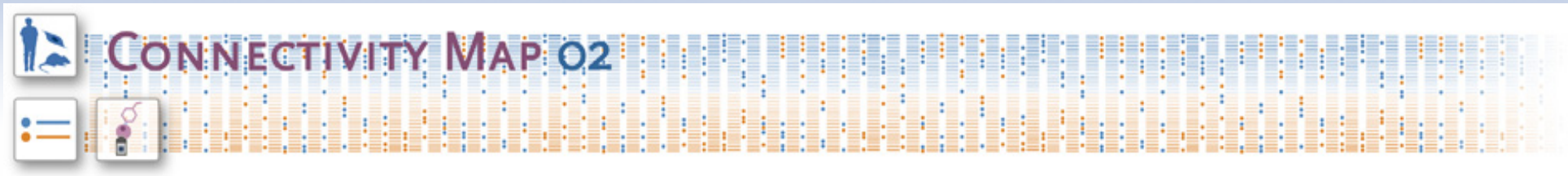
Shortlisted Proteins

Lead discovery



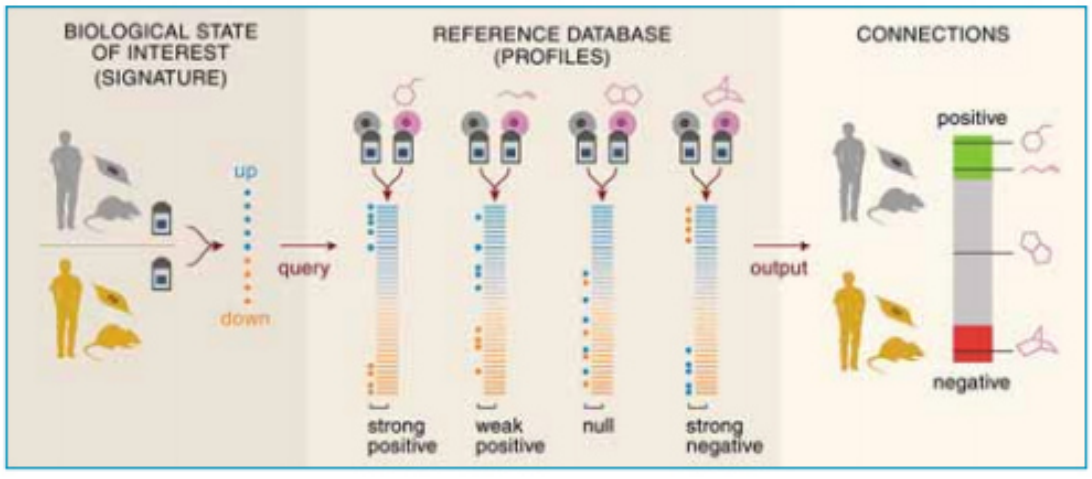
In vitro and *in vivo* experiments

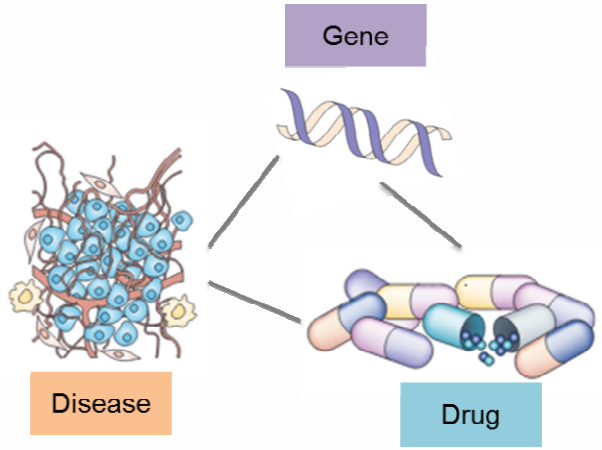
omics for prediction of potential therapeutic compounds



The Connectivity Map =
(1) transcriptional expression data from cultured cells treated with bioactive molecules
(2) pattern-matching algorithms

Discovery of functional connections between drugs, genes and diseases through the common gene-expression changes





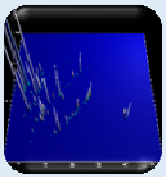
Lamb et al., Science 2006

http://portals.broadinstitute.org/cmap/

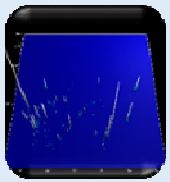
CE-MS to predict drug candidates

(1) Disease requiring new therpies

Patient derived urinary proteomics data

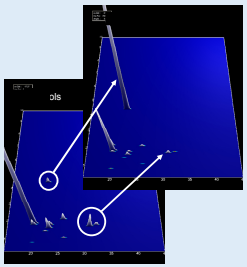


Control group

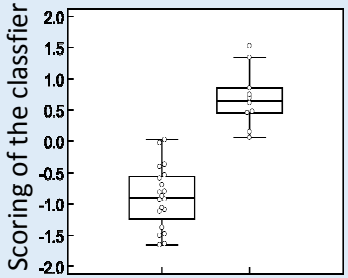


Patient group

Define molecular signature of disease



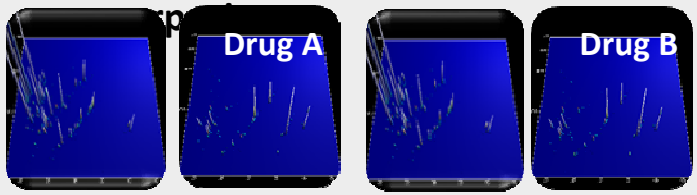
Development of the disease specific classifier



Application of disease specific classifier

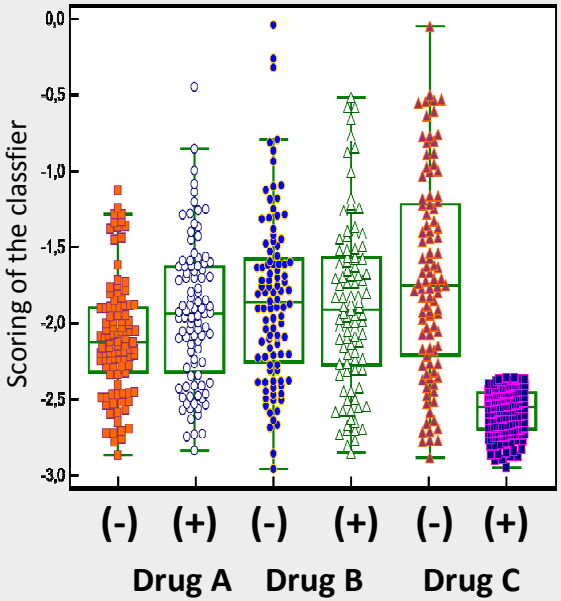
(2) Urinary proteomics-based

Patient derived urinary proteomics data on drug impact



(-) Before treatment | (+) After treatment | (-) Before treatment | (+) After treatment

Selection of drug reversing disease signature = decreasing classifier score



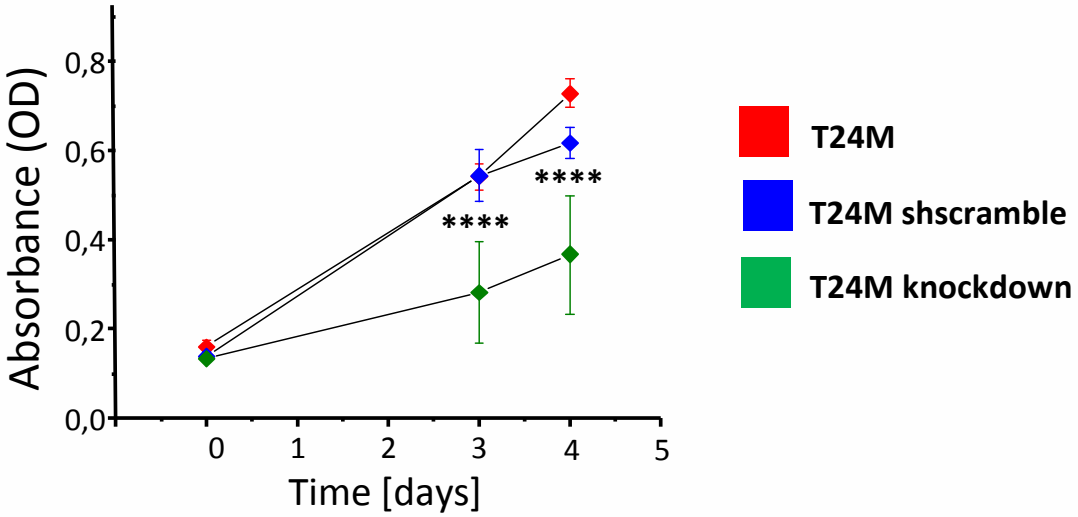
"Drug C" – candidate for drug repurposing

(3) Evaluation of the drug impact in RCT

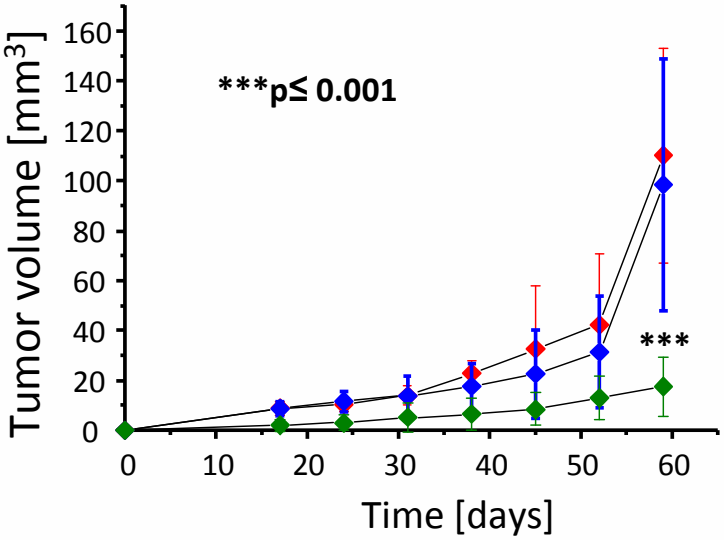
Functional Assays and Animal models

EIF3D knockdown resulted in decreased proliferation and migration rate in T24M cells and decreased tumor formation in xenograft mice models.

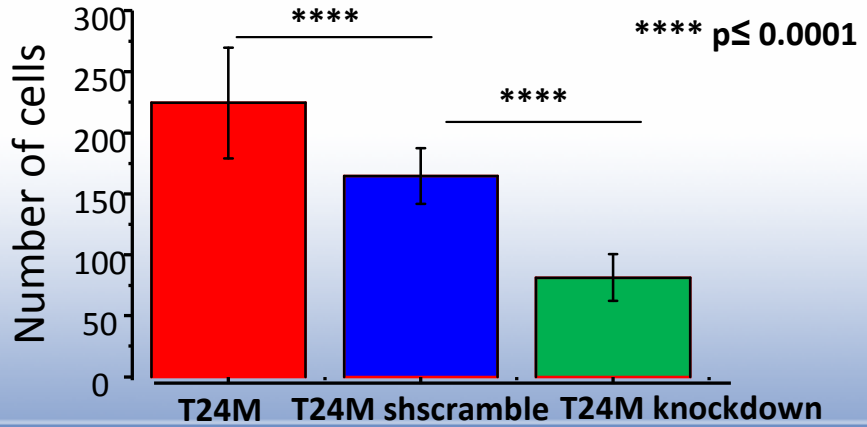
Proliferation Assay



Mice models- Tumor Formation



Migration Assay

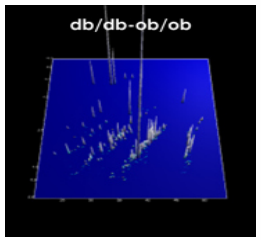


Bioinformatic investigation of the data resulted in the prediction of 29 potential agents that may reverse the disease-associated phenotype.

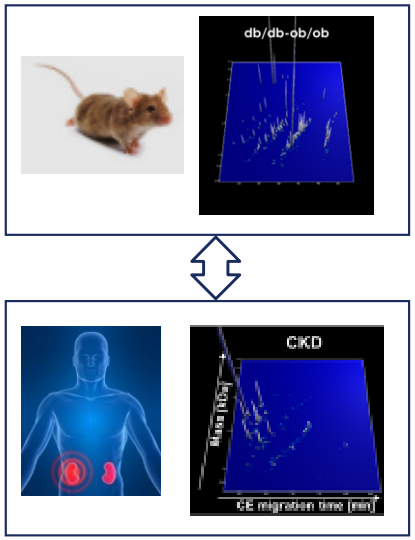
»Humanized« model concept

Disease models

Mouse urinary proteome

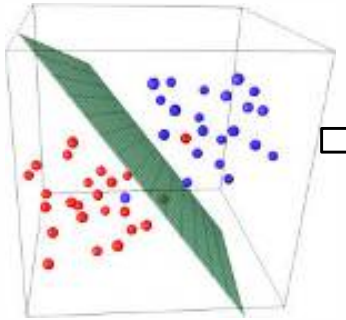


Ortholog peptides

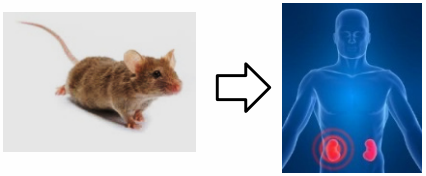


Panel of validated disease markers in humans

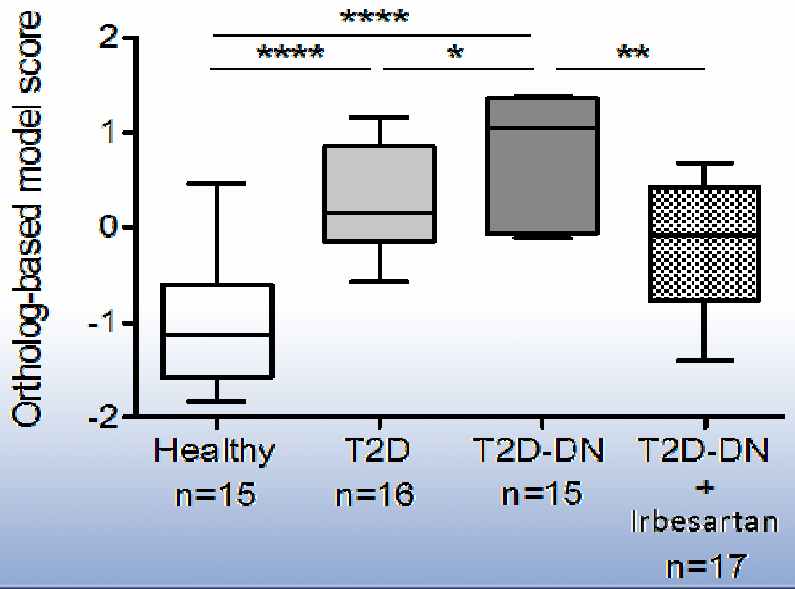
«Humanized» model = «Humanized» readout



Improved translatability



Test drugs



Klein et al., Kidney Int. 2016

Benefit of Patient Stratification

Scenario 1
without proteome analysis

- Probability to reach the endpoint*: **7%**
- Power calculations for demonstration of 30 **% benefit the drug** (decrease in reaching disease endpoint)
- Required number of patients to be enrolled: **n= 1992**

Scenario 2
with proteome analysis

- **Pre-selected Patients**, Probability to reach the endpoint*: **20 %**
- Power calculations for demonstration of 30 **% benefit the drug**
- Required number of patients to be enrolled: **n= 616**

substantial reduction of costs!

***transition from CKD stage 2 to 3 (suggested in EMA draft guideline 2014)**


Thank you
CLUB DES
SOMMELIERS
2009
MONBAZILLAC