

Digitalisierung im Metabolismus-Labor

N. Kohl, H. Krüger, K. Schmeer, Grünenthal GmbH

Contents

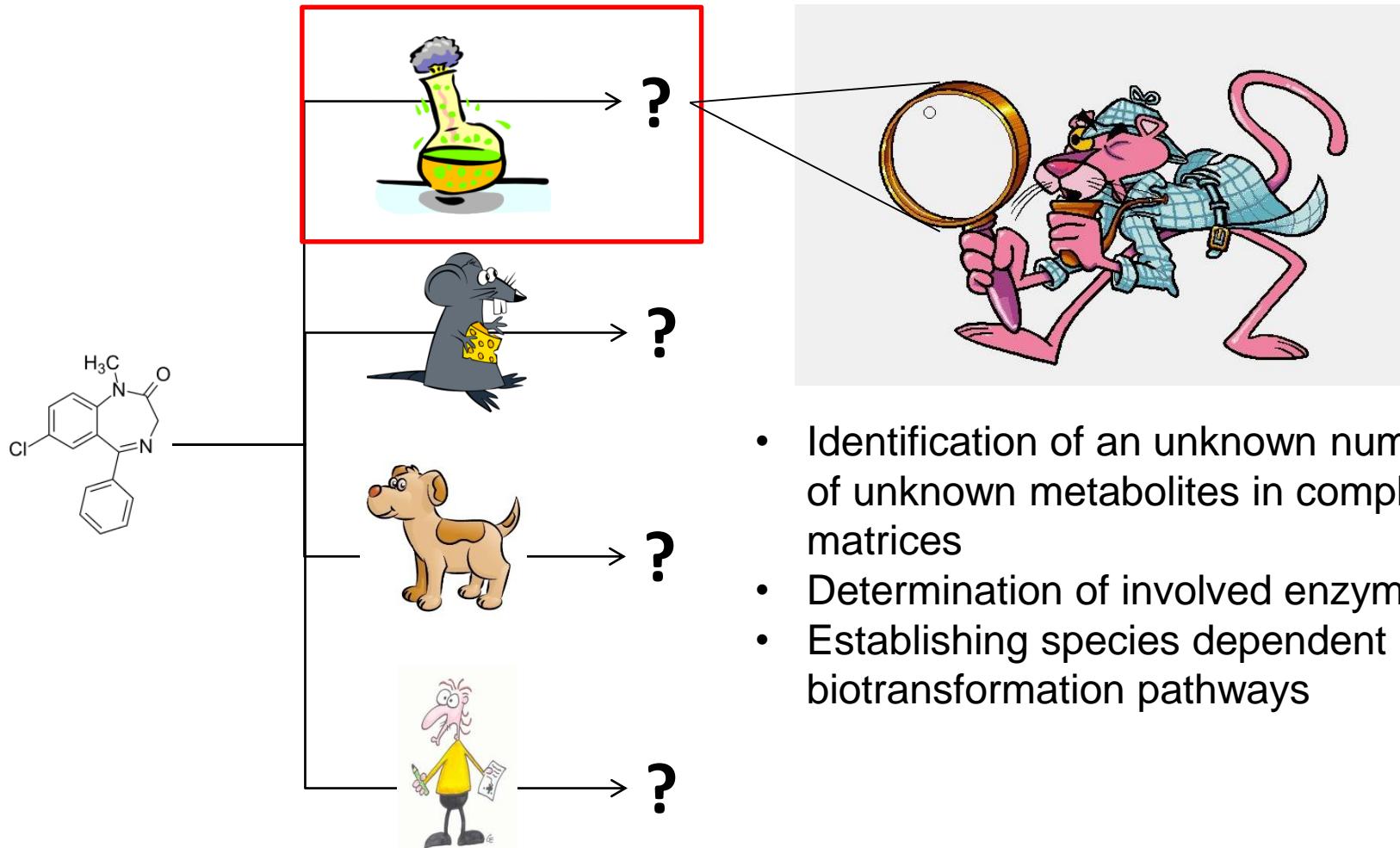
1. Metabolism, definition and tasks
2. Lab organisation
3. Linking-up; ULI
4. Conclusions

Xenobiotics

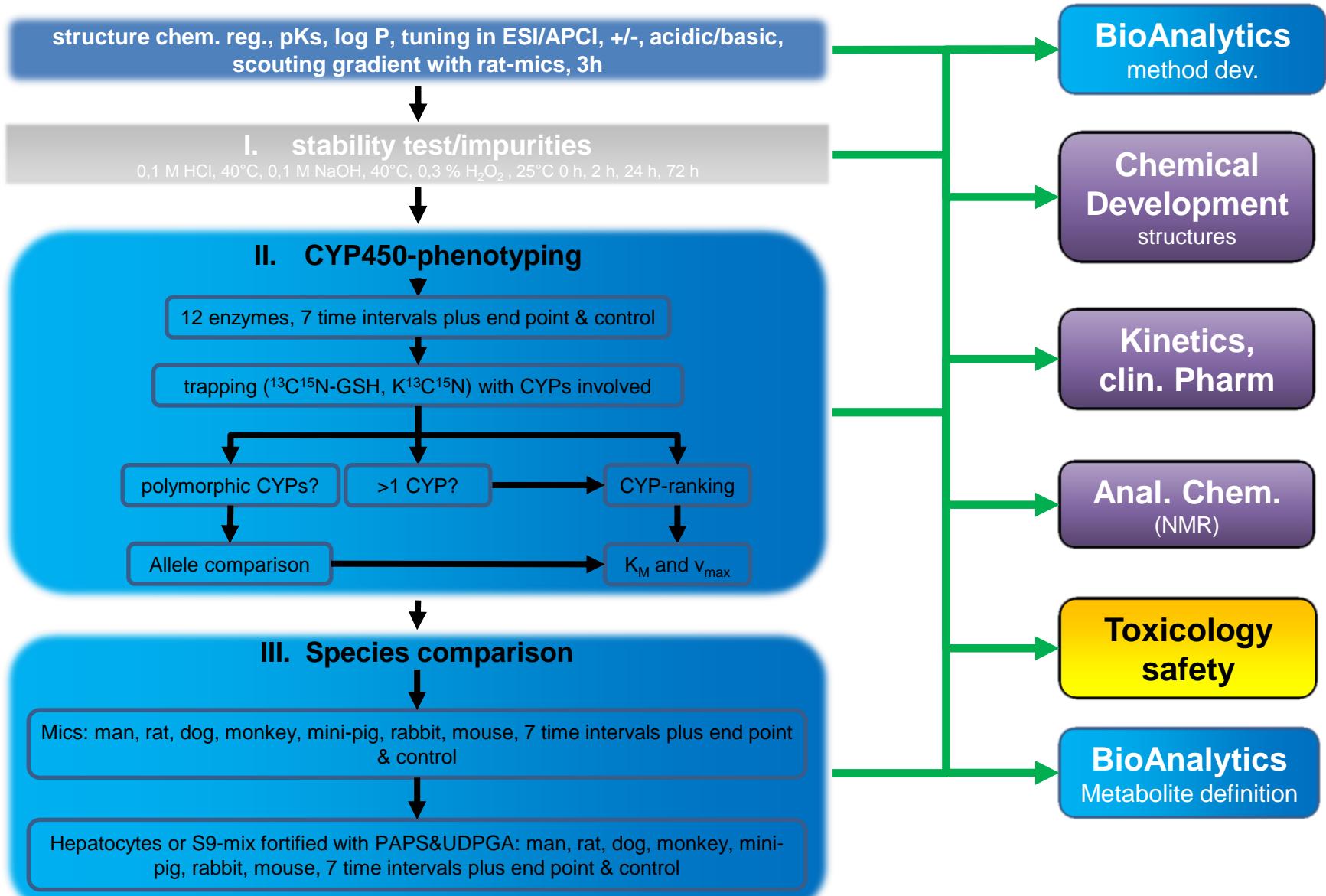


Metabolism

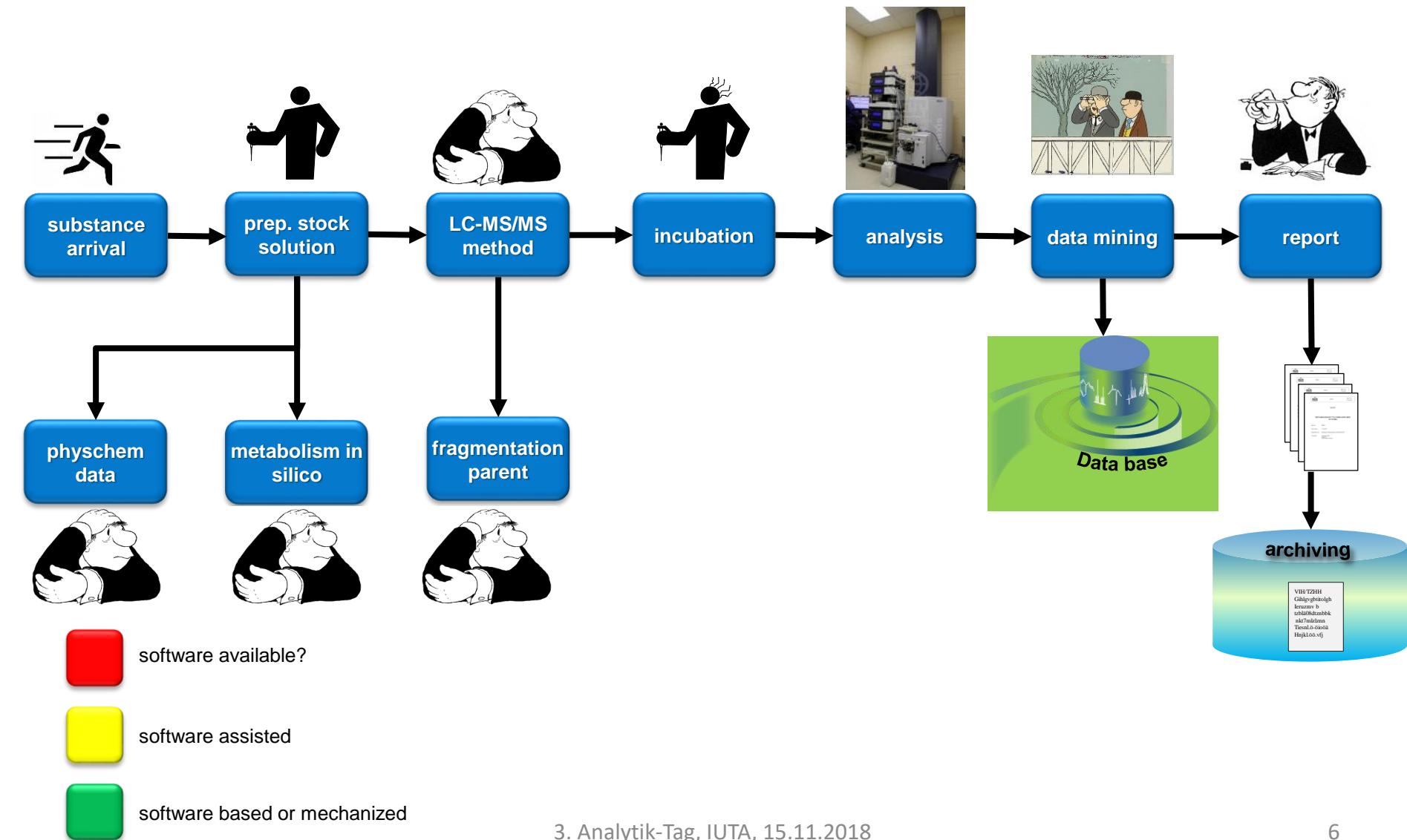
(gr: μεταβολή, "change")



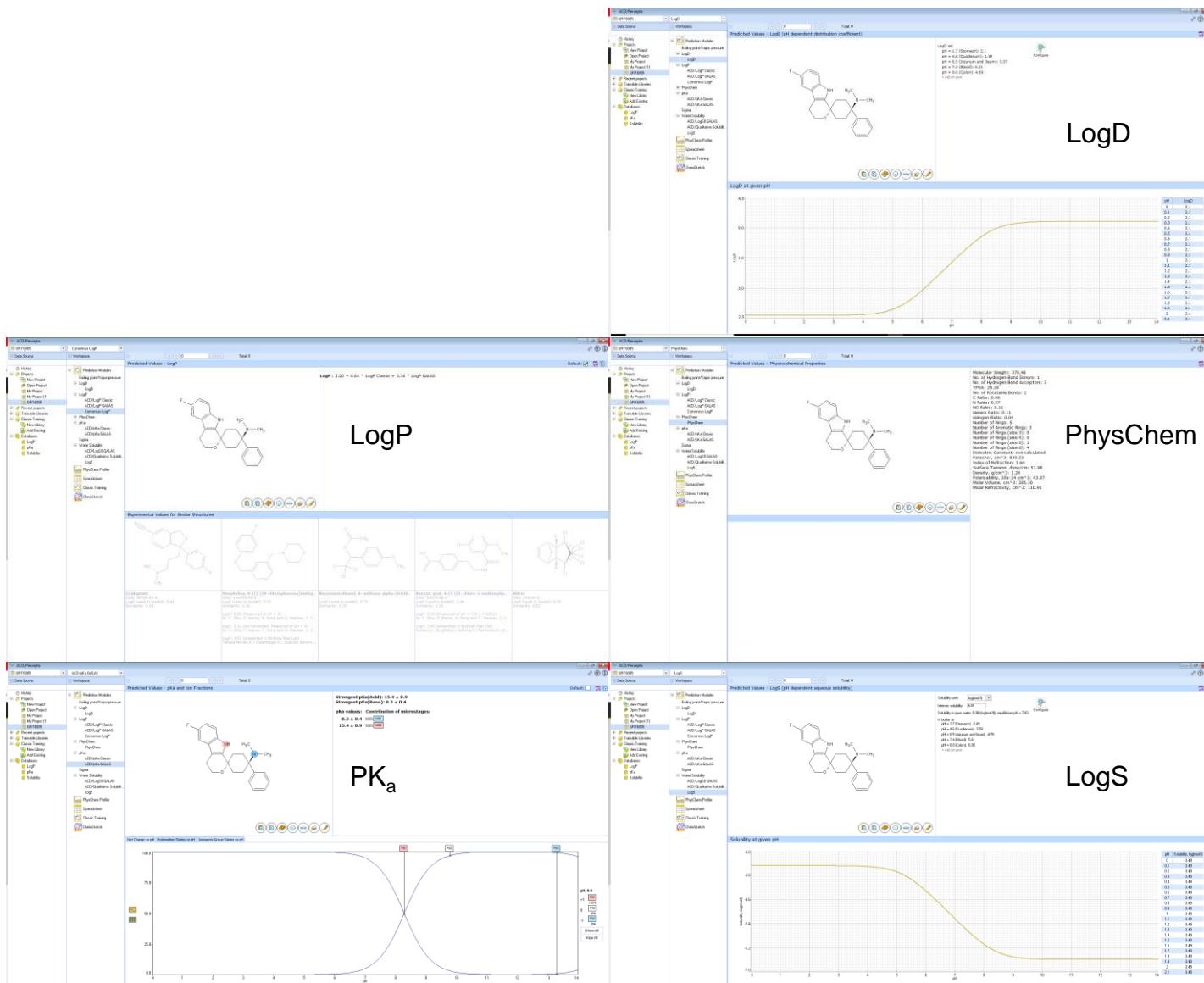
Work-flow, cross-links



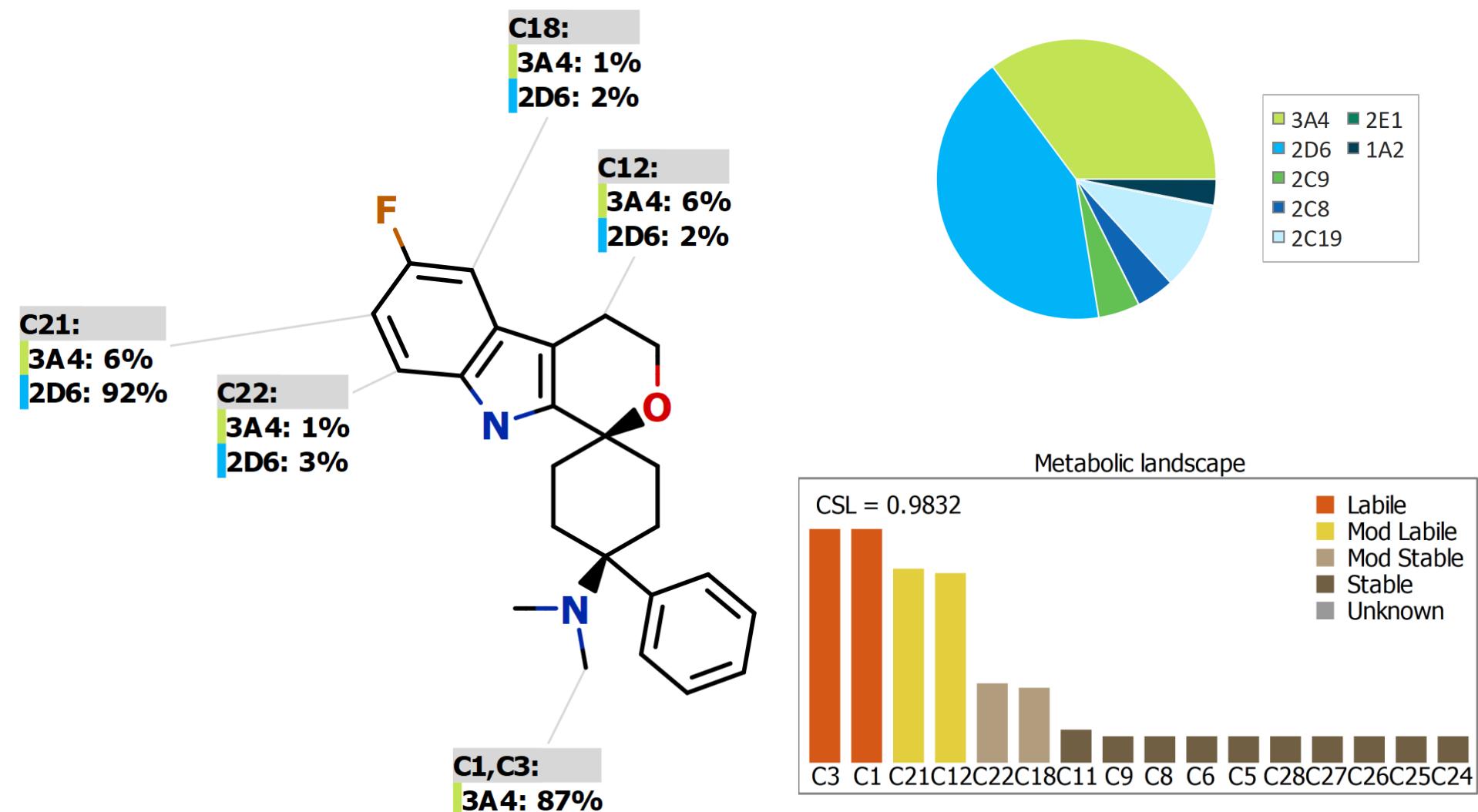
Lab organisation, work-flow



Calculation of PhysChem data



Metabolism in silico



work-flow: incubations



Incubation vial

Mix buffer, microsomes,
regenerating system

Start of reaction by
addition of substrate

Incubation at 37°C on
shaker for 60 min

Incubation at 37°C on
shaker for 120 min

Stop of reaction by
addition of ACN

96 well plate

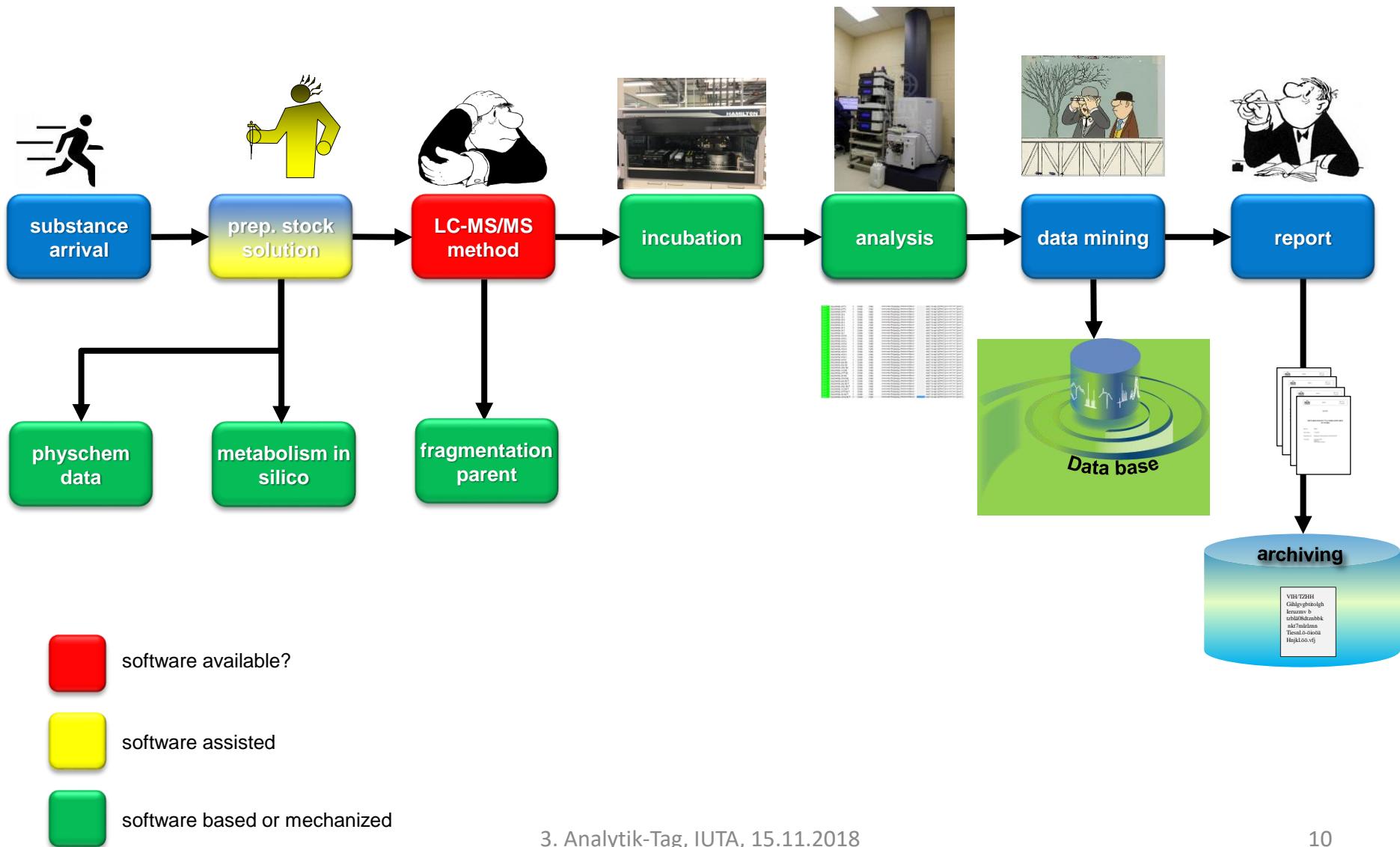
Remove six aliquots at
fixed time points

Transfer into 96 well
plates (stop with ACN)

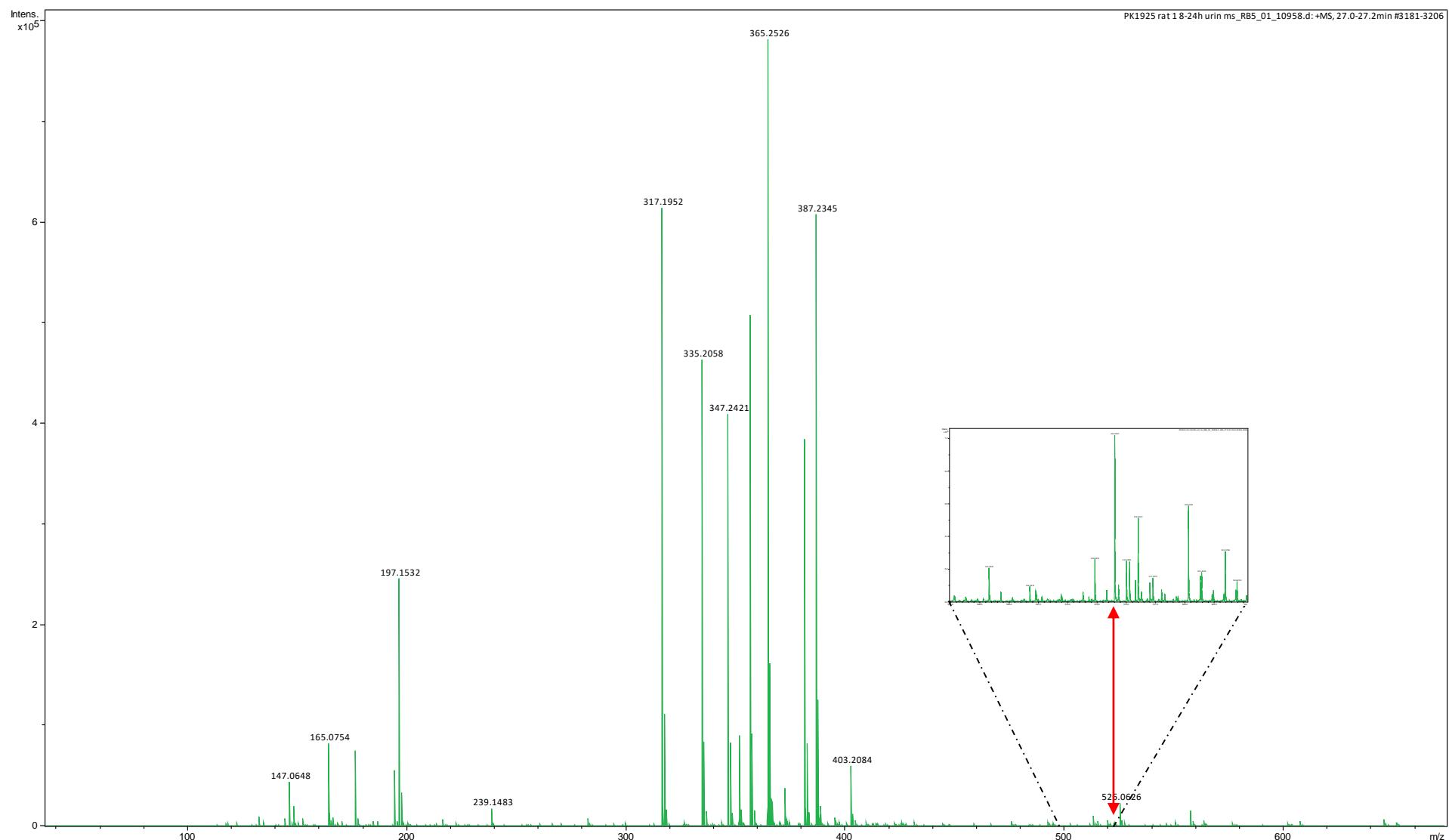
Protein precipitation
centrifugation

Evaporate to dryness
Reconstitute with eluent

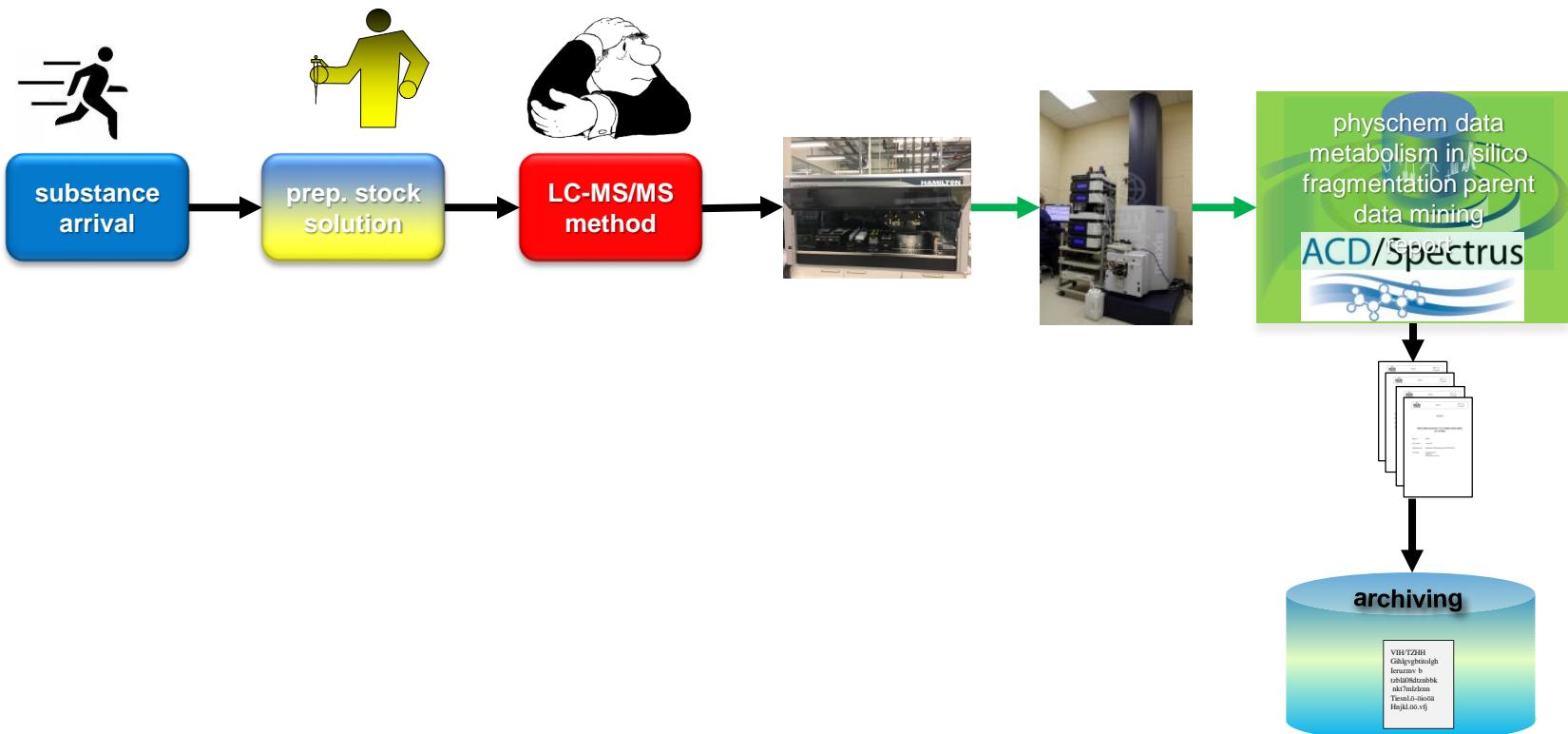
Lab organisation, work-flow



Lab organisation, data analysis

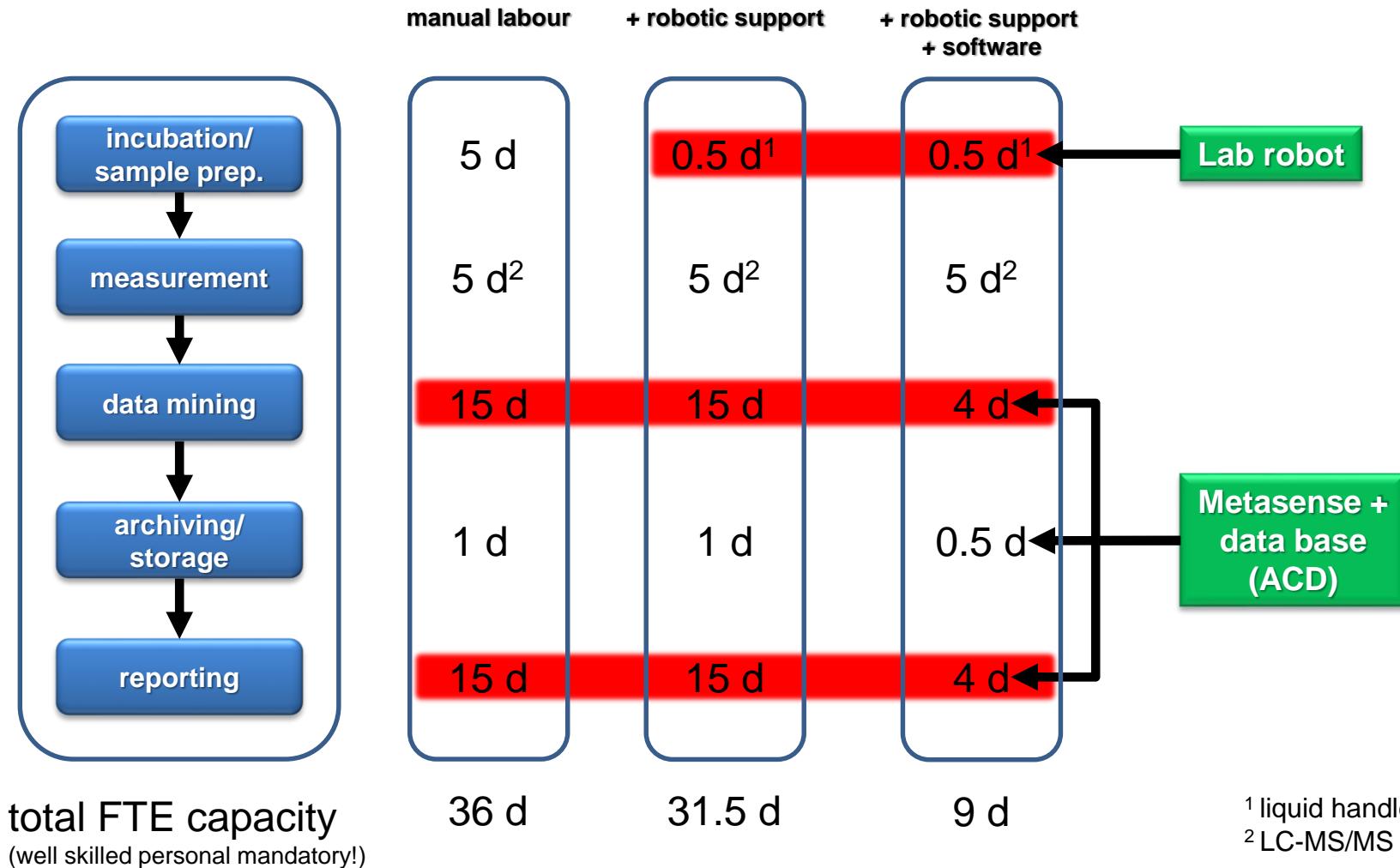


Lab organisation, work-flow

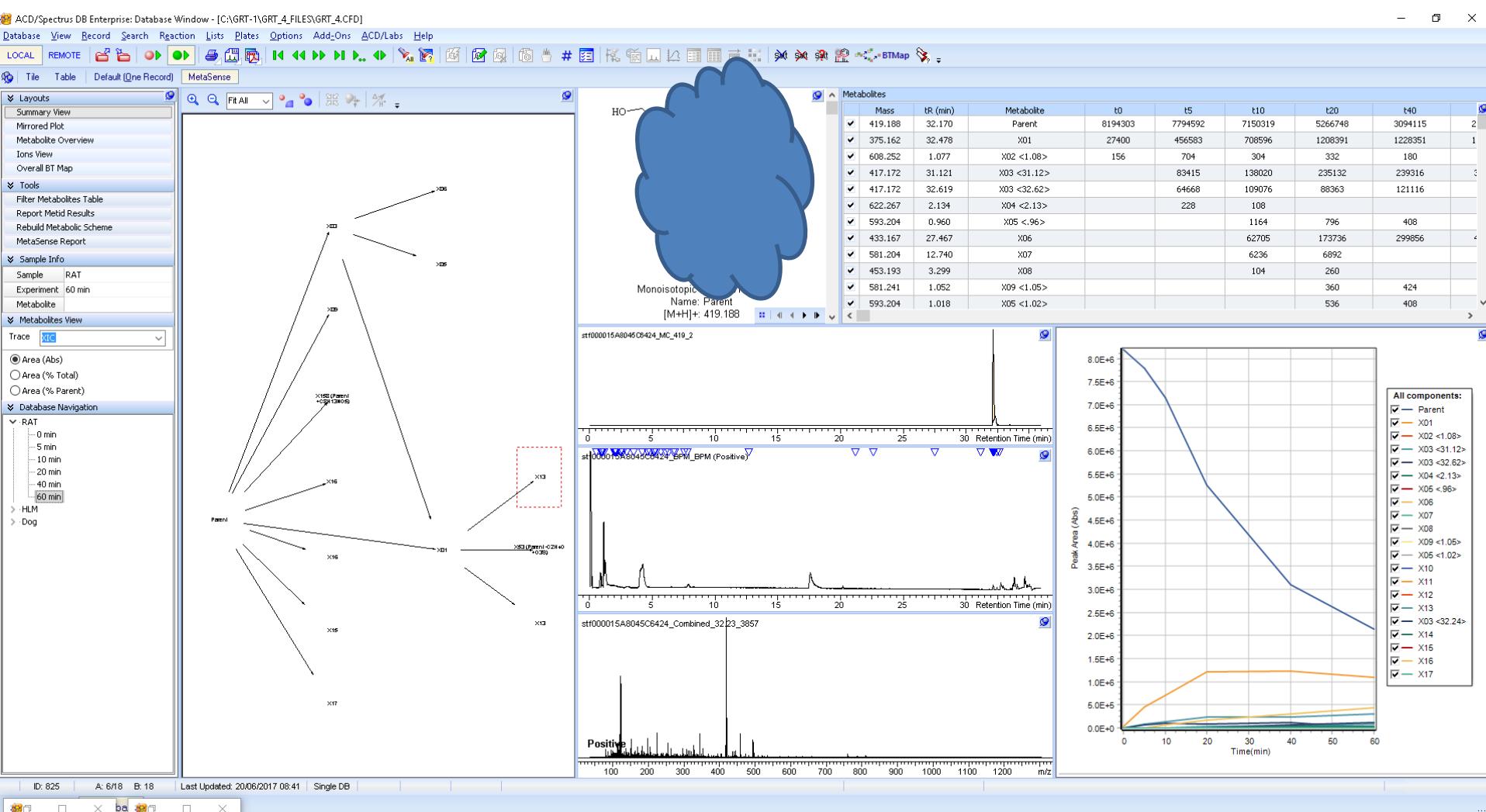


Capacities

A typical pre-clin. work package contains app. 500 samples (per NCE)



Linking-up, ULI Result table



Linking-up, ULI Result table

ACD/Spectrus DB Enterprise: Database Window - [de86585] is now connected to Spectrus on des5323:7189 <SpectrusMET>

Database View Record Search Reaction Lists Plates Options Add-Ons ACD/Labs Help

LOCAL REMOTE

Fit All

The goals in evaluating in vitro drug metabolism are: (1) to identify all of the major metabolic pathways that affect the test drug and its metabolites, including the specific enzymes responsible for elimination and the intermediates formed
Guidance for Industry Drug Metabolism/Drug Interactions Studies in the Drug Development Process: Studies In Vitro, April 1997

Technical Drug Development (LC, MS, UV, NMR)

chemical stability/lability

species comparison

- hepatic metabolism
- tox species
- plasma metabolites

Toxicology

Contributing enzymes

- polymorphisms
- DDI's
- reactive species
- extrahepatic metabolism**
- renal, intestinal

structures

- Phys-chem. data
- Nomenclature
- pK_s , logP, logD, IUPAC-names
- LC, MS, MS/MS, UV

Mass Spectrum Data:

m/z	TIC(%)
121.101	7.509
133.103	7.875
149.136	6.593
155.085	5.678
159.120	6.868
178.068	10.256
214.071	7.692
274.913	5.128
318.213	7.601
332.145	16.300
350.156	18.498

In silico metabolism

1-ChemSketch 2-Database 3-Processor

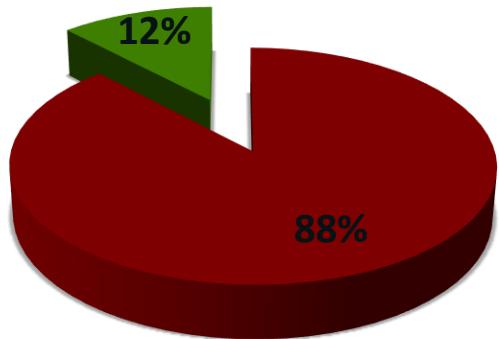
Owners: E66142

ULI (Unified Lab Information)

with courtesy from ACD-LABS

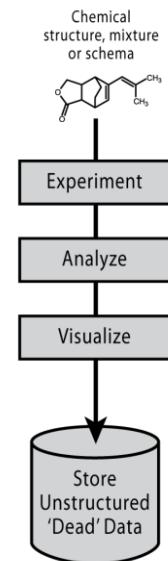
88% of R&D organizations lack adequate systems to automatically collect data for reporting, analysis, and decision-making¹

¹*Scientific Computing Research Study 2011*

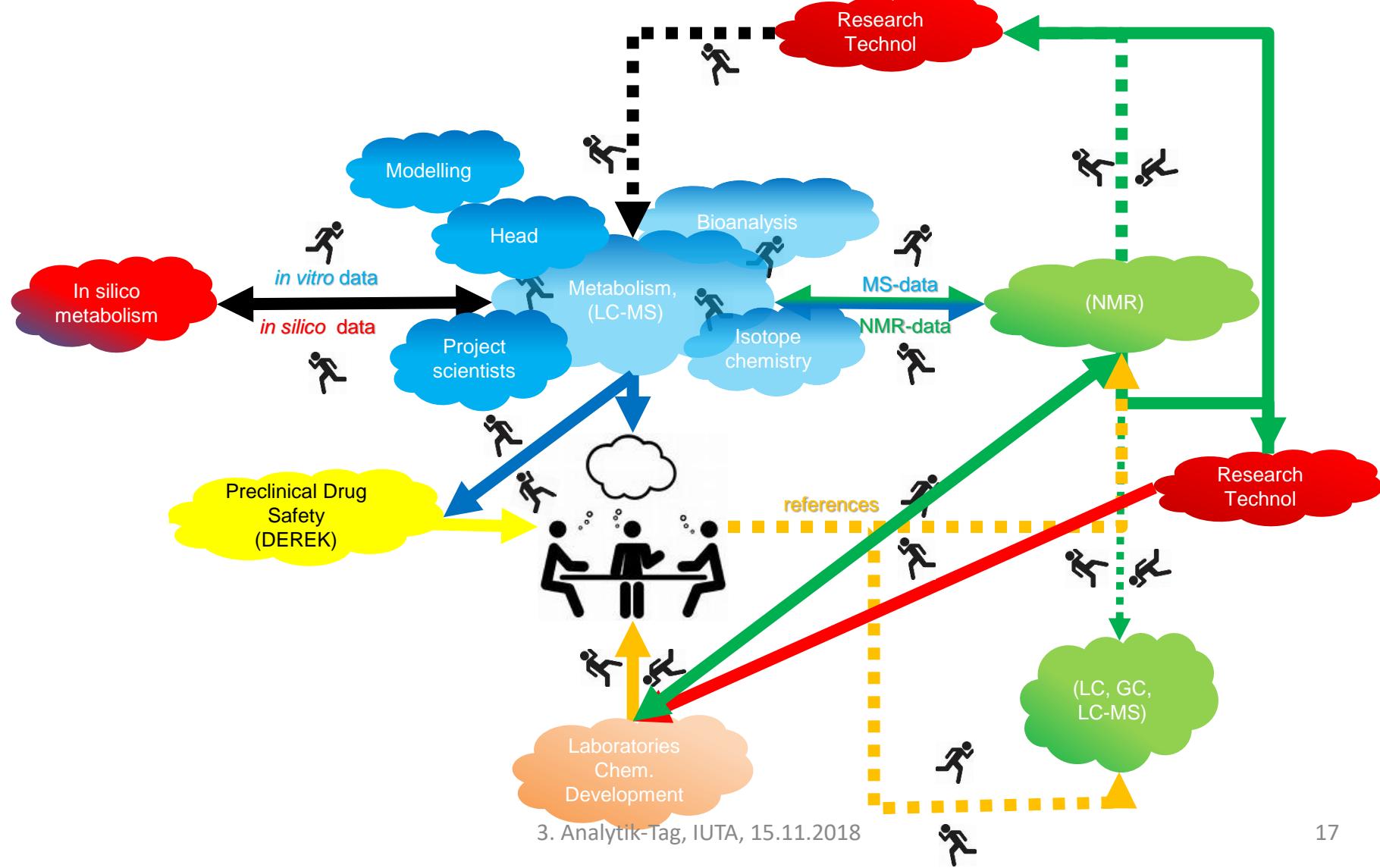


One-to-Many One-and-Done

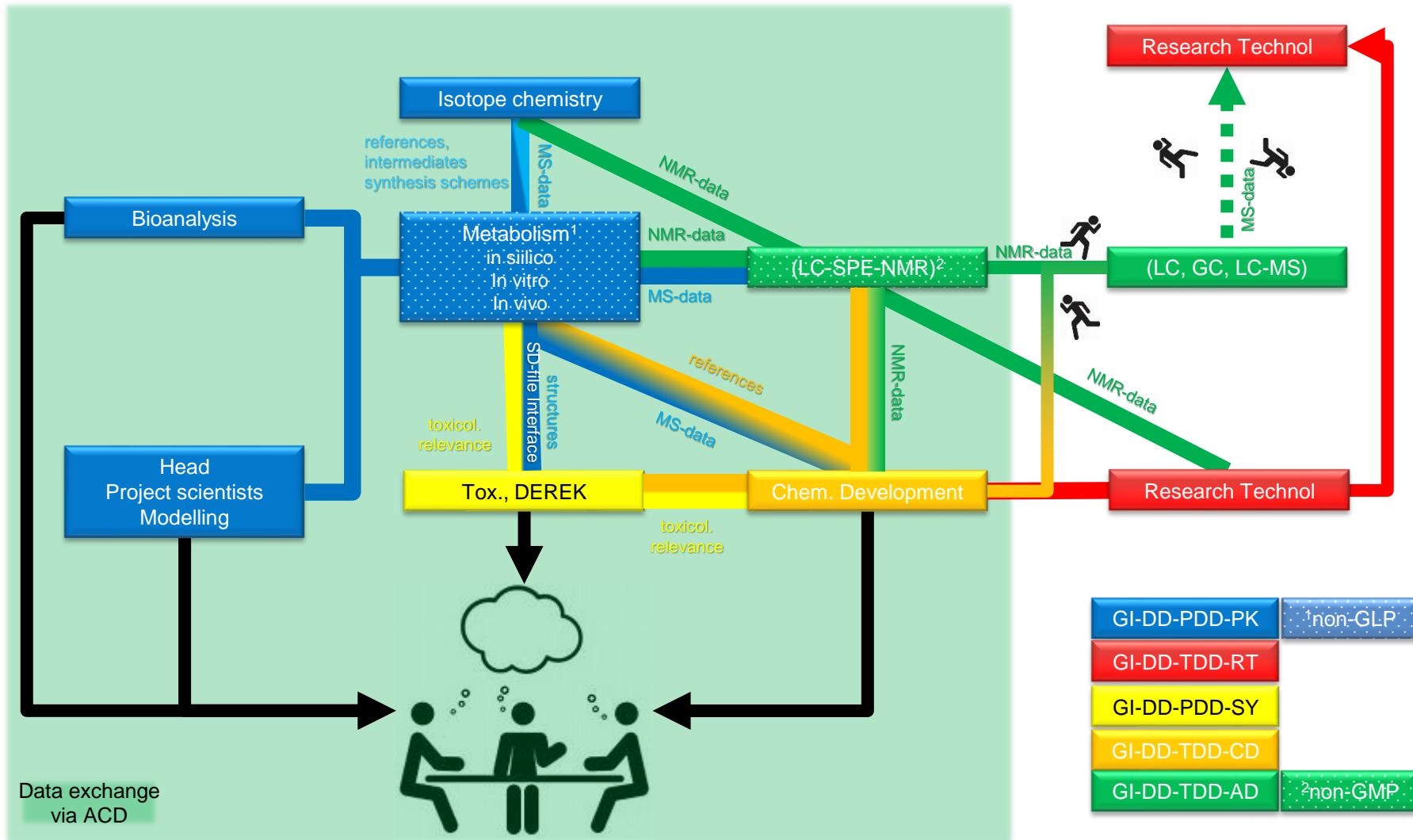
'Live' Data	Dead Data
Structured	Unstructured
Homogeneous	Heterogeneous
Unified Data	Siloed Data
Metadata for Search	Metadata for Search?
Analyze Repeatedly	Analyze Once
Accumulate Knowledge	Discrete Knowledge
Create Intelligence and Gain Insight	—



Data exchange



Data exchange



Conclusions

- Regulatory demands are constantly increasing
- Automation allows an efficiency increase at constant head count by replacing manual labour
- However: The full benefits of automation can **only** be obtained by implementing software solutions for data analysis
- A common data base allows fast and simple cross-functional data- and knowledge-transfer (ULI)

Hurdels

1. Time & money
2. Human factors: staff needs to
 - have or acquire skills in laboratory robotics, liquid handling, pipetting robots, analytical technologies, sample tracking/data base management, laboratory software
 - accept new work-flows
 - overcome fears
 - be stable

Acknowledgements

Grünenthal:

Nicole Kohl
Heike Krüger
Dr. Rolf Terlinden
Dr. Klaus Pusecker
Dr. Dieter Albert

ACD:

Dr. Barbara Brandau-Krug
Dr. Gerd Rheinwald
Dr. Hans deBie

Hamilton:

Dr. Ulrich Zander
Dr. Björn Kaiser
Frank Schmitt

Müller Industrie-Systeme:

Andreas Müller

IUTA:

Dr. Thorsten Teutenberg

Vielen Dank!