REPO-TRIAL:
A Systems Medicine Approach to Rational Drug Repurposing

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Work Package 4 Leader

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Systems Medicine: Defining Disease Phenotypes Based on Common Mechanisms

Classical medicine has an organ-centric view of disease

It does recognize systems (e.g. cardiovascular, CNS, urogenital,…), and their interactions -- but maintains a „physical“ and localized perspective

This „boxed thinking“ is enforced by healthcare, regulators, marketing… ect.

Systems medicine pivots to a mechanism-based perspective:

- Disease phenotypes are defined not by symptoms but by signaling networks
  - E.g., „XXX kinase overactivation,“ „RhoA pathway disturbance,“…
- Organs are primarily seen as effector sites where mechanistic deregulations will manifest by causing site-specifc symptoms

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Repurposing Trials in Mechanism-based Patient Cohorts

1) Update the human Diseasome: connect diseases based on shared genes and pathways; incorporate co-morbidity and drug pleiotropy data → hypothesis
2) Validate at the animal level, feed-back into (1) for cluster refinement
3) Design clinical Ph II+ mini-trials with precise, multi-scale patient stratification
4) Do FtO analysis, confirm patentability & regulatory compatibility
5) GO!

Drug repurposing with generic APIs fits this disruptive concept perfectly:

- Big Data / Thick Data strategies can be designed based on existing information
  - In systems medicine, complex biomarkers rule
- NNT can be kept extremely low on the pre-clinical and clinical level

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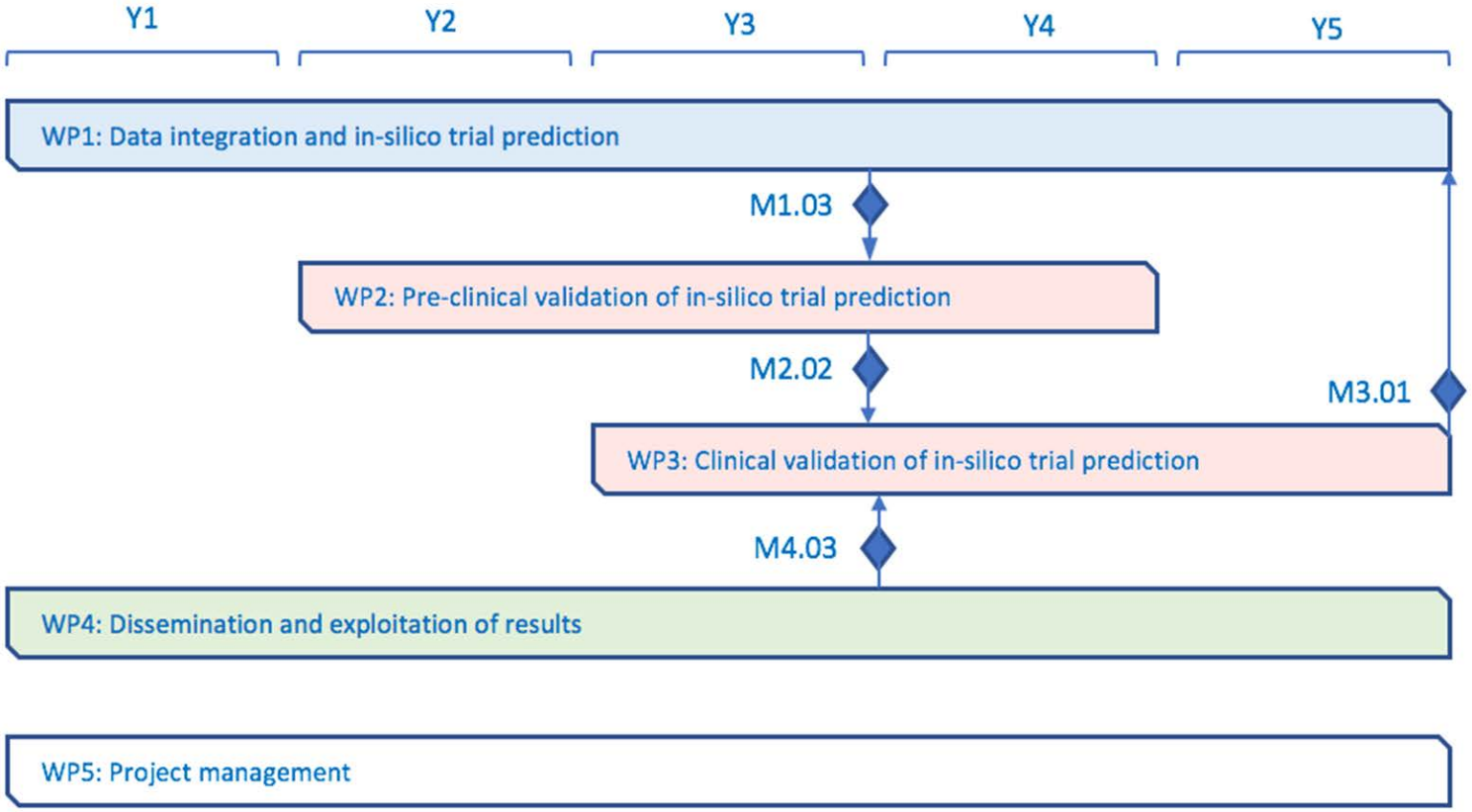
REPO-TRIAL Timeline



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REPO-TRIAL Cornerstones

„An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes"

Five-year European Union H2020 project, Feb. 2018 – Jan 2023, budget €5.6m

Coordinator: Prof. Dr. Harald Schmidt
Maastricht University, Dept. of Pharmacology and Personalized Medicine

Online presence:

Website: http://www.repo-trial.eu

Twitter: https://twitter.com/repotrialH2020 (@RepoTrialH2020)

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REPO-TRIAL Consortium Members

Maastricht University
(NL, coordinator & pharmacology)

Techn. Univ. Munich
University Newcastle
(DE, UK; bioinformatics)

University clinics
Hannover & Essen
(DE; clinical studies)

SomaLogic
Biocrates Life Sciences
(UK, AT; biomarkers)

H.M. Pharma Consultancy
(AT; FtO, patenting, exploitation)

Concentris Res. Mngmt.
(DE; administration)

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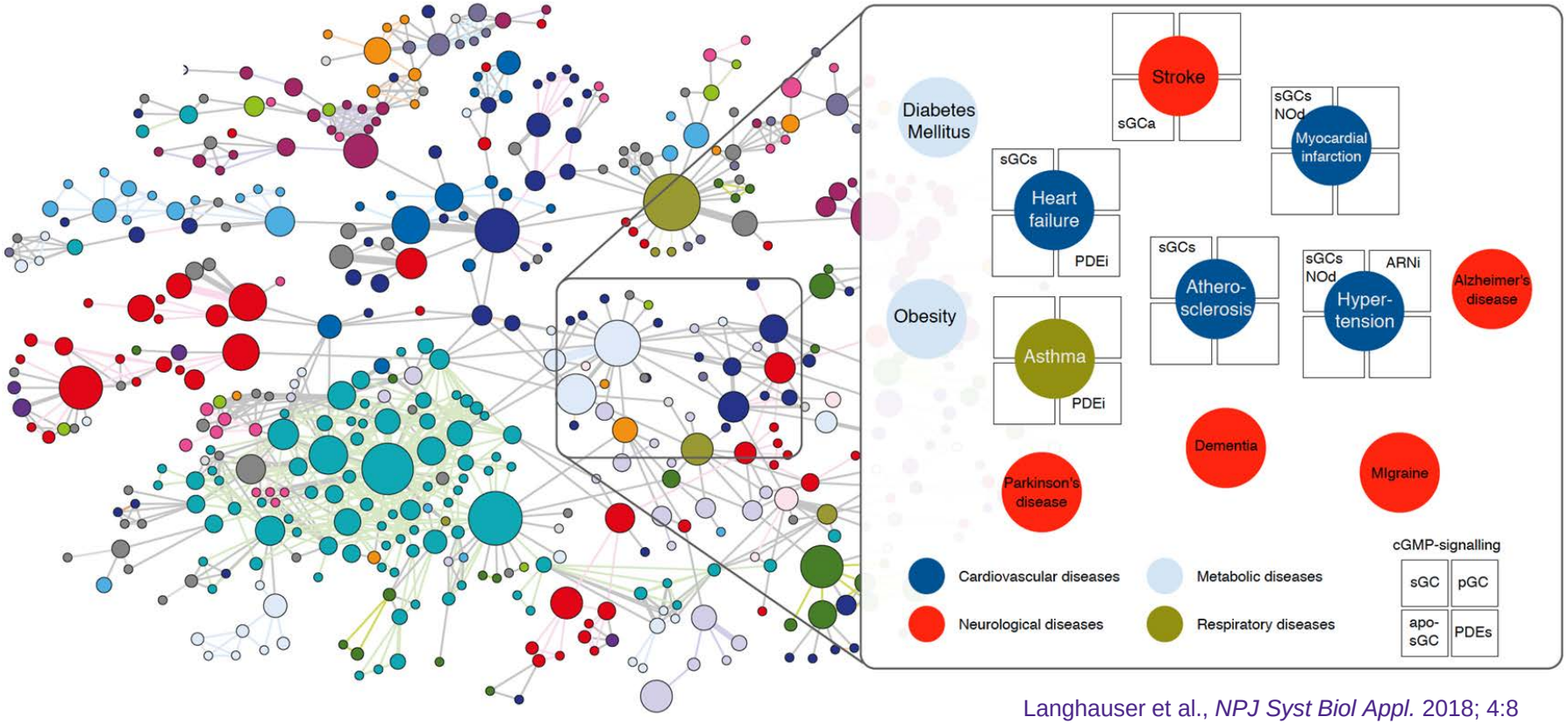
*comm*ROCG: Repurposing of sGC activators

Common mechanism cluster

Drug-centric re-clustering



Langhauser et al., *NPJ Syst Biol Appl.* 2018; 4:8
doi: 10.1038/s41540-017-0039-7

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The REPO-TRIAL Approach is Highly Disruptive

Collides with conventional outlook on clinical medicine

Will test synergistic combinations, also of several low-dose drugs

Is not immediately compatible with established drug development paths

Will face regulatory challenges

And yet, more than sufficient reason for confidence:

- Systems medicine is the Next Big Step, based on increased understanding of molecular physiology
- Clinical repurposing of drugs in combination has been done before
  - Sun et al. Drug Discovery Today 2016; Ziyan et al. 2014; FRAXA/Healx project;…
- EMA Modelling and Innovation group has been involved, and is positive

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REPO-TRIAL Expected Deliverables & Impacts

Preliminary validation of repurposed drug combinations based on *in silico*-driven systems medicine workflows

Demonstration of „ultra-dense“ preclinical and clinical trials, with dramatically reduced animal/patient numbers, short duration, and low cost

Virtual patient libraries for re-use in pre- and post-competitive drug testing

Deliver seminal data for new treatments and commercial opportunities

A new beginning, not an end in itself:

- Even as REPO-TRIAL gears up, transatlantic follow-up projects are under consideration
- Algorithms, biomarkers, and the drug pool can be significantly expanded

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REPO-TRIAL Scientific Sites and Key Persons

Consortium Member	Leader	Country
Universiteit Maastricht	Harald Schmidt	NL
Technische Univ. München	Jan Baumbach	DE
Univ. Newcastle	Anil Wipat	UK
Universitätsklinikum Essen	Christoph Kleinschütz	DE
Med. Hochschule Hannover	Johann Bauersachs	DE
Universiteit Utrecht	Timothy Radstake	NL
SomaLogic Ltd.	Anthony Bartlett	UK
Biocrates Life Sciences AG	Guido Dallmann	AT
H.M. Pharma Consultancy eU	Hermann Mucke	AT

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REPOTRIAL

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*** THANK YOU FOR YOUR ATTENTION ***

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