Building Bridges

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Rheinfelden, Germany

Introduction Perspective

A perspective on our challenges and goals - transferring new scientific evidence to impact professional practice

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Building Bridges – creating a Community of Practice and Innovation

- bring practitioners from cross-disciplinary and sector backgrounds together
- share knowledge
- identify opportunities for problem solving and solution development
- translational goal - how do we combine emerging research methods, data science, stem cell biology and engineering to further goals in health and safety practice?

Challenges

a) Biology is creating an increasing number of methods that can generate human *in vitro* evidence in the laboratory; **How do we best use and verify?**

b) An increasingly large amount of biological data is being created in academic, government and industry labs and programs; **How do we organize and make sense of the data?**

c) Computational modelling and simulation is advancing so as to enable detailed simulations of processes on different scales: molecular, cellular, tissue, organ, through to human individuals and populations; **How do we develop and apply models and knowledge to practice?**

d) Current professional practice in safety assessment or clinical decision making is often based on practices that stem from a previous era. **How do we generate, organise and manipulate data to be usable in practice?**

Goals for the group

a) developing together use cases for decision making that would define the information needed for making a better judgement;
b) identifying integrated strategies that would bring the evidence together required by the use cases;
c) implementing the strategy to generate the data and organising it in a reliable and usable way;
d) learning from the experience and improving our solutions.

Today we will discuss stem cell biology in particular, combined with emerging *in silico* and *in vitro* methods, as an area, where we could progress the above framework.

Overview of Scenario

Today, advanced cell therapies founded on human embryonic and induced pluripotent stem cells have entered clinical evaluation. These resources are also being integrated in the drug discovery process to confirm causative roles of mutated genes in various diseases and discover new therapeutic drugs to ameliorate disease pathologies.

The socioeconomic impact of ongoing and future accomplishments is critically reliant on interdisciplinary engagements between diverse stakeholders informing standards of practice, conduct and care and translating knowledge into real-world practice.

Drawing on our diverse professional expertise, the mission of Building Bridges today is to promote the understanding of this field and network amongst participants. We hope to create new interdisciplinary opportunities to advance the safety, efficacy and impact of the emerging field of personalised medicine.

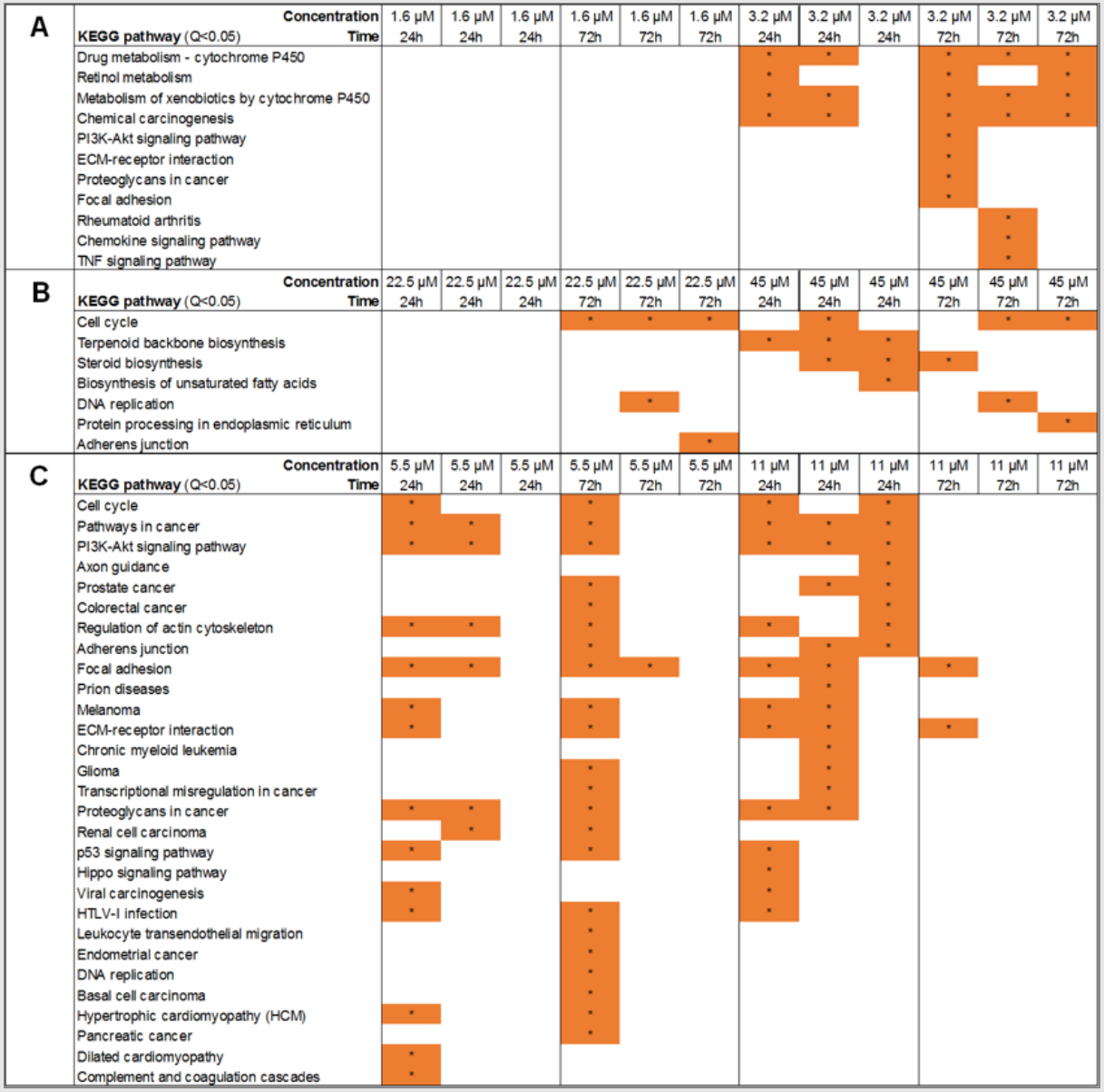
Our Thought Leadership

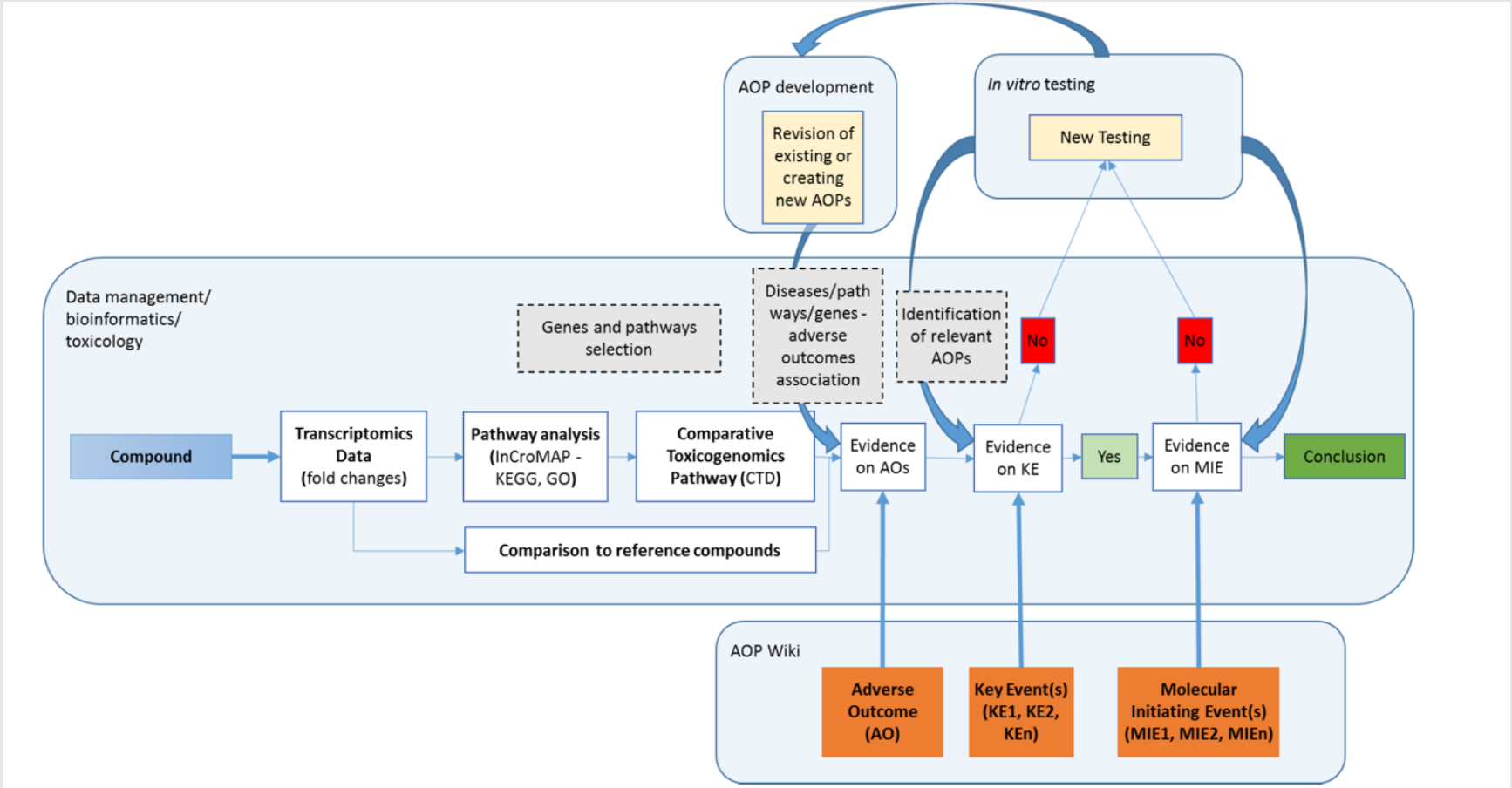
Costanza Rovida, REACH Mastery, Como
Maria Chatzou, Phd, Centre for Genomic Regulation, Barcelona
Selina Wray, PhD, UCL Institute of Neurology, London
Glyn Stacey, PhD, National Institute for Biological Standards and Control, Hertfordshire, UK
Rex FitzGerald, PhD, Swiss Centre for Applied Human Toxicology, Basel
Tomo Saric, M.D., Ph.D., Institute for Neurophysiology, Cologne
Barry Hardy, PhD, Douglas Connect, Basel

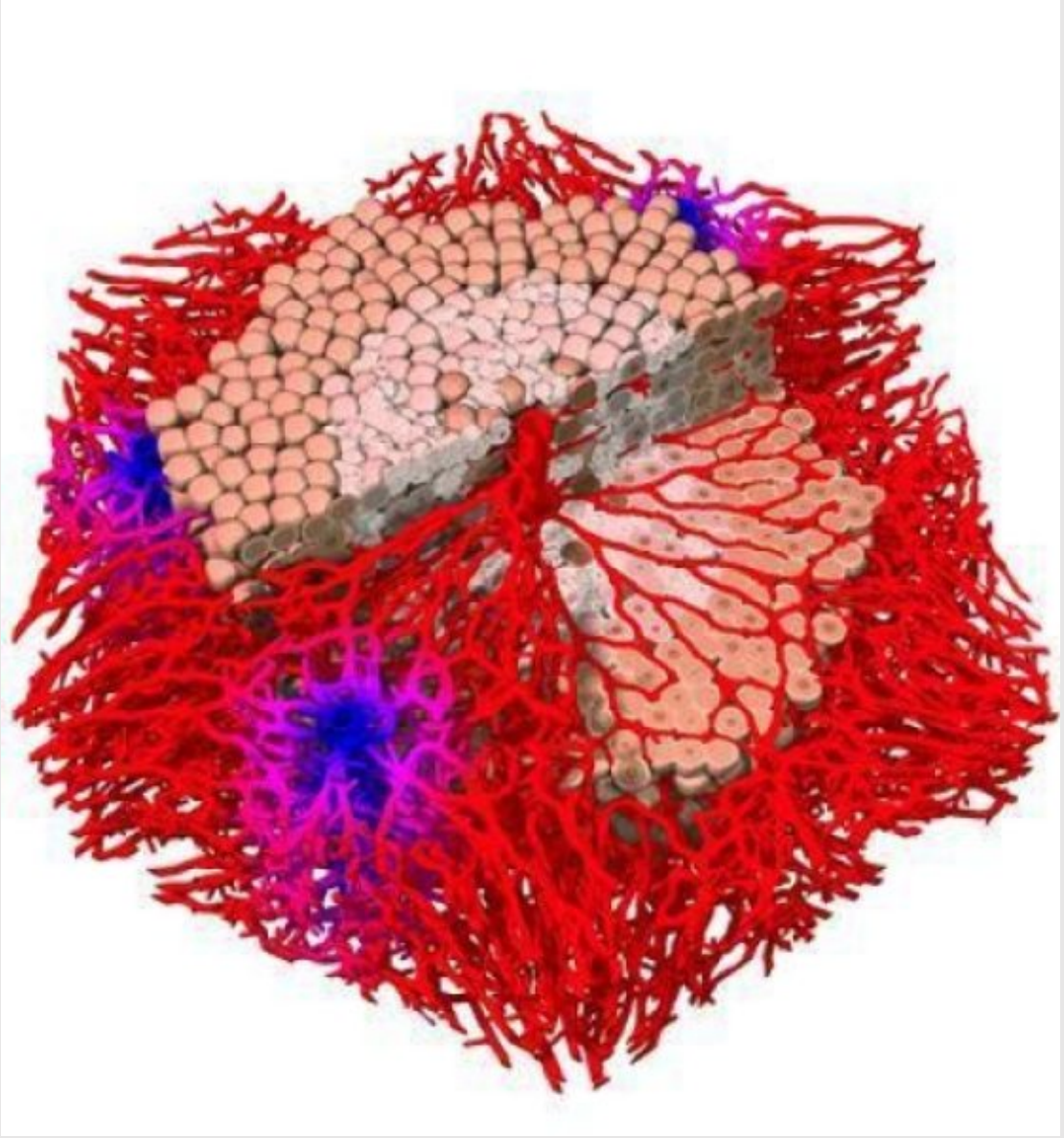
And our existing connections, networks, resources and projects

Topics

- Stem Cell Science
- Stem Cells in applications
- Use of Stem Cells to model disease
- Identifying adverse effects of substances by mode-of-action analysis
- Computational Challenges of Personalised Medicine
- Stem Cell banking - usages and ethics
- Regulatory acceptance of new methods
- Reproducibility
- Quality and References
- Practice


A
Concentration
KEGG pathway (Q<0.05)
Time
1.6 µM 24h
1.6 µM 24h
1.6 µM 24h
1.6 µM 72h
1.6 µM 72h
1.6 µM 72h
3.2 µM 24h
3.2 µM 24h
3.2 µM 24h
3.2 µM 72h
3.2 µM 72h
3.2 µM 72h
Drug metabolism - cytochrome P450
Retinol metabolism
Metabolism of xenobiotics by cytochrome P450
Chemical carcinogenesis
PI3K-Akt signaling pathway
ECM-receptor interaction
Proteoglycans in cancer
Focal adhesion
Rheumatoid arthritis
Chemokine signaling pathway
TNF signaling pathway
B
Concentration
KEGG pathway (Q<0.05)
Time
22.5 µM 24h
22.5 µM 24h
22.5 µM 24h
22.5 µM 72h
22.5 µM 72h
22.5 µM 72h
45 µM 24h
45 µM 24h
45 µM 24h
45 µM 72h
45 µM 72h
45 µM 72h
Cell cycle
Terpenoid backbone biosynthesis
Steroid biosynthesis
Biosynthesis of unsaturated fatty acids
DNA replication
Protein processing in endoplasmic reticulum
Adherens junction
C
Concentration
KEGG pathway (Q<0.05)
Time
5.5 µM 24h
5.5 µM 24h
5.5 µM 24h
5.5 µM 72h
5.5 µM 72h
5.5 µM 72h
11 µM 24h
11 µM 24h
11 µM 24h
11 µM 72h
11 µM 72h
11 µM 72h
Cell cycle
Pathways in cancer
PI3K-Akt signaling pathway
Axon guidance
Prostate cancer
Colorectal cancer
Regulation of actin cytoskeleton
Adherens junction
Focal adhesion
Prion diseases
Melanoma
ECM-receptor interaction
Chronic myeloid leukemia
Glioma
Transcriptional misregulation in cancer
Proteoglycans in cancer
Renal cell carcinoma
p53 signaling pathway
Hippo signaling pathway
Viral carcinogenesis
HTLV-I infection
Leukocyte transendothelial migration
Endometrial cancer
DNA replication
Basal cell carcinoma
Hypertrophic cardiomyopathy (HCM)
Pancreatic cancer
Dilated cardiomyopathy
Complement and coagulation cascades


AOP development
Revision of existing or creating new AOPs
In vitro testing
New Testing
Data management/ bioinformatics/ toxicology
Genes and pathways selection
Diseases/pathways/genes - adverse outcomes association
Identification of relevant AOPs
No
No
Compound
Transcriptomics Data (fold changes)
Pathway analysis (InCroMAP - KEGG, GO)
Comparative Toxicogenomics Pathway (CTD)
Comparison to reference compounds
Evidence on AOs
Evidence on KE
Yes
Evidence on MIE
Conclusion
AOP Wiki
Adverse Outcome (AO)
Key Event(s) (KE1, KE2, KEn)
Molecular Initiating Event(s) (MIE1, MIE2, MIEn)



Potential Outcomes

- What could we do together as a community?
- Define Use Cases e.g., Provide evidence so that clinician could obtain better information to choose a particular drug for a particular patient and condition? Could we determine heightened risk of off target effects?
- Define an initial demonstration project – which indication, use case?
- Define a scenario where we generate personalized scientific evidence on cohort of cell lines
- How do we generate, analyse and process data. Simplify and Visualise it?
- How do we present evidence to the clinician so they can make a better judgement?
- Could the workflow help provide human verification of *in vitro* methods?