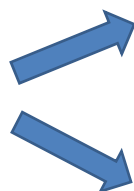


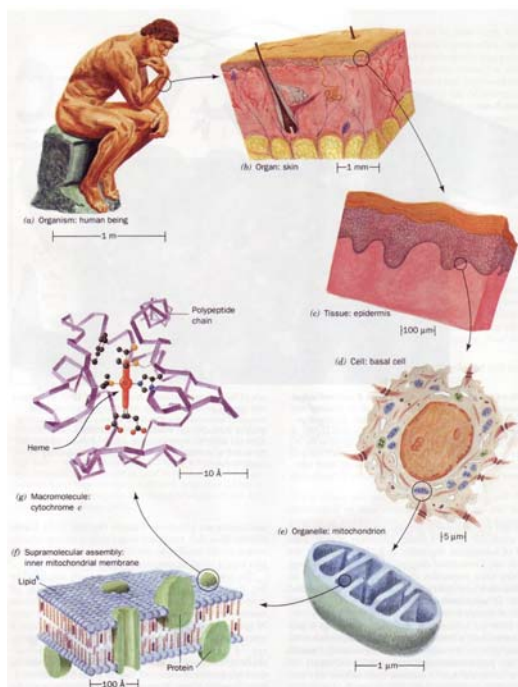
Systems Biology Approaches Supported by Microdevice Engineering

Elmar Heinzle
Biochemical Engineering
Saarland University
Saarbrücken, Germany

Classical
molecular
research

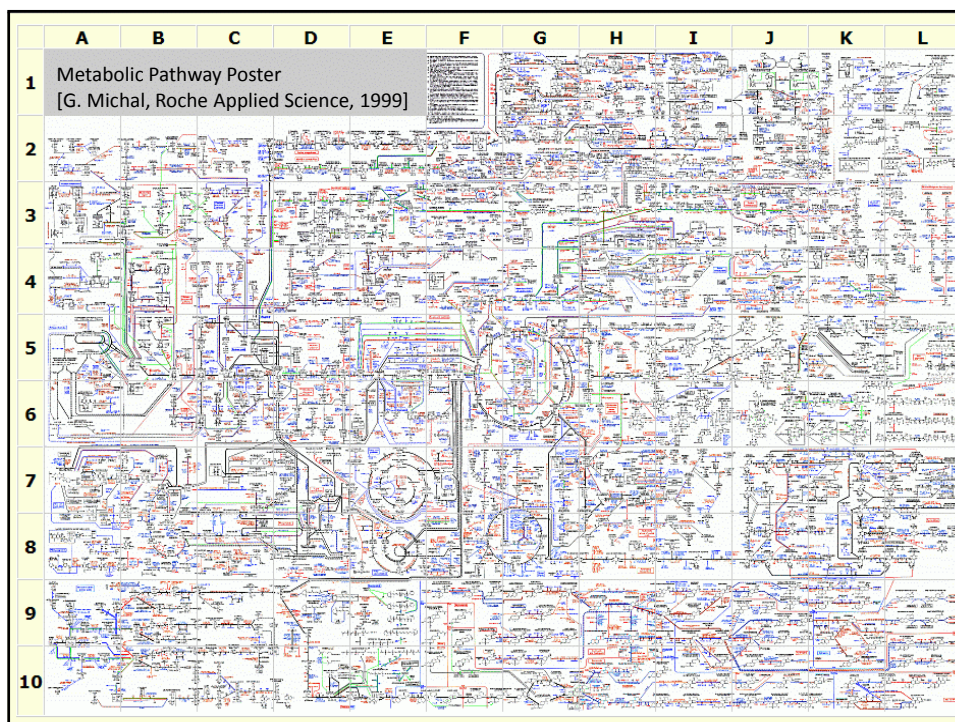


Lehninger



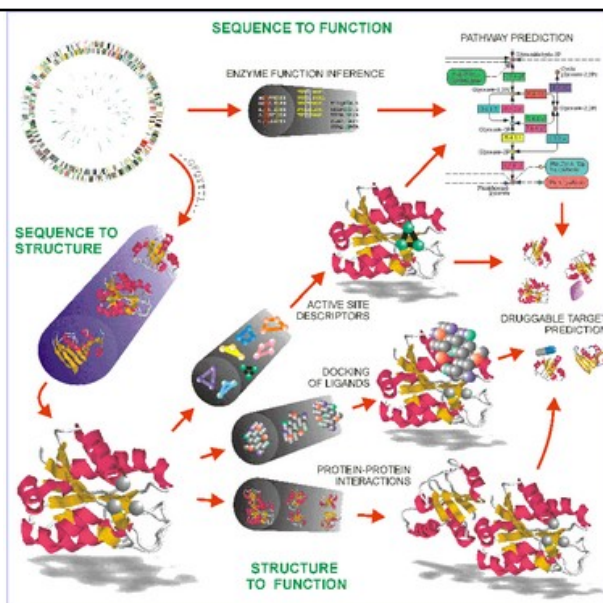
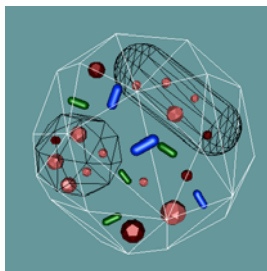
Types of Bio-Research

- Classical for elucidation of mechanism, pathway, etc.
 - Hypothesis driven, focus on details and single elements
 - → Experiment with design to show effect by elimination of all other influences
 - → Proof (signalling, biochemical mechanism,
- Systems biology
 - Focus on whole systems, networks
 - Omics methods for the analysis
 - Bioinformatic and mechanistic models for system description and prediction



Systems biology

"omics and modeling"
From structure to function to structure....

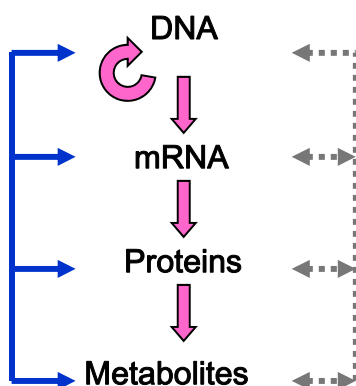


Self-organized, integrated wholes made up of interacting components. The behavior of these components and their interactions give rise to the system's observed behavior. Simulation provides a means of exploring **emergent** behavior that is not easily predictable.

Cellular Networks and their Identification

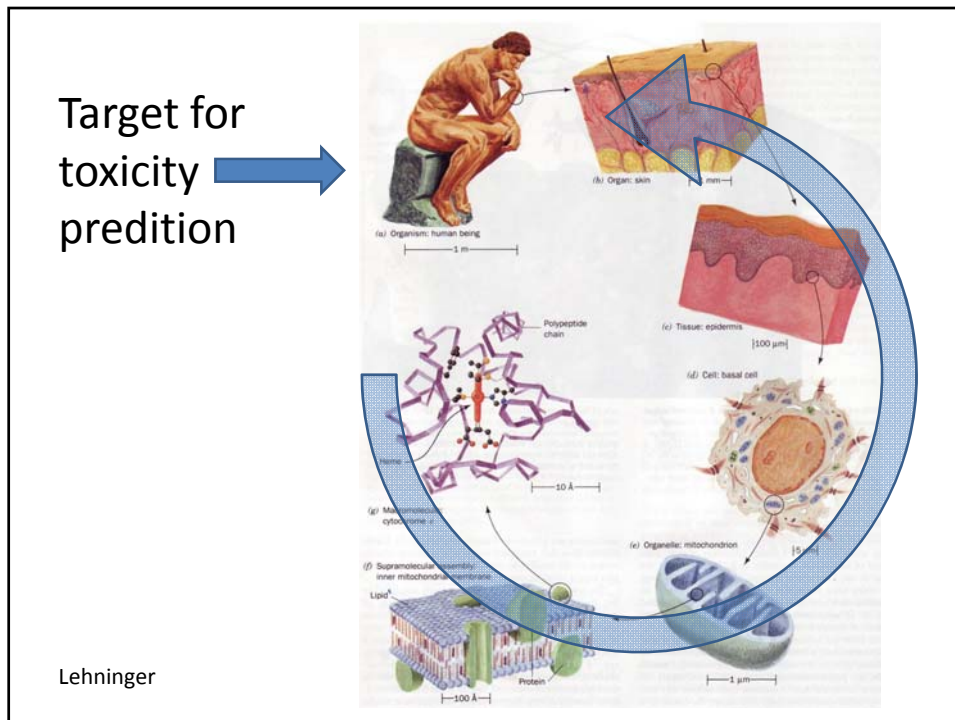
Elements & material flux

- Genome
- Transcriptome
- Proteome
- Metabolome
- Fluxome



Control

- Mutants
- Transcriptome
- Kinetics
- Dynamics of cellular systems
- Models
- Reporters



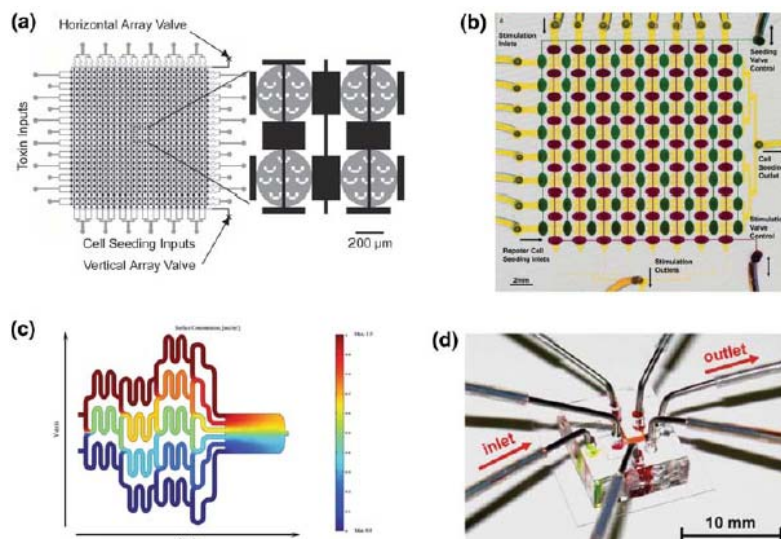
Future Toxicology Based on Systems Biology

- Focus on human systems, even considering heterogenous population
- Develop molecular or cellular systems responding as close as possible to real human
- Use human organotypic cultures (stem cell based)
- Make “omics” analysis
- Analyze and study system behavior using bioinformatic and physical models
- Make predictions based on well designed experiments and model prediction

Human Systems

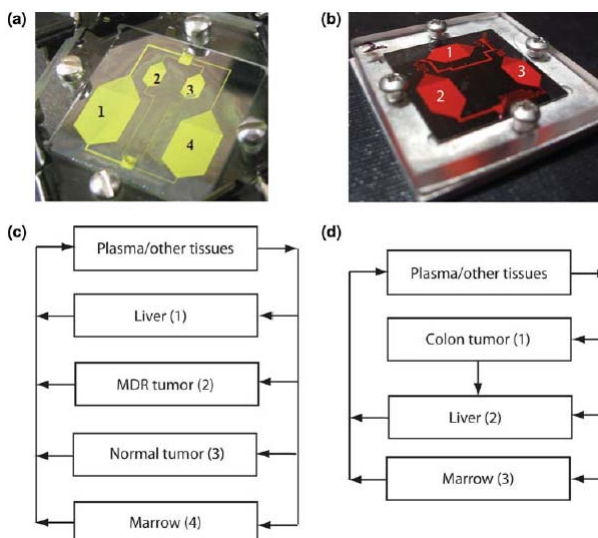
- Organs
- Organotypic cultures
- Tissue (primary)
- Tissue culture systems
- Cells – isolated primary cells (patients)
- Cells – cell lines from human stem cells
- Microdevices for large scale screening

Microfluidic devices



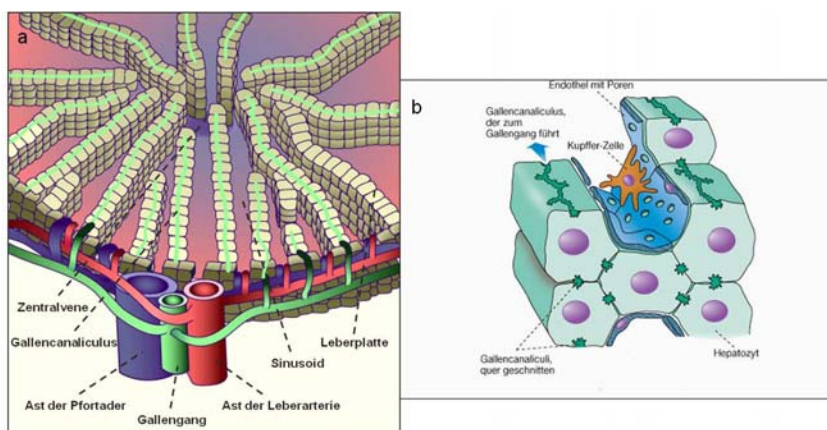
Jong Hwan Sung & Michael L. Shuler: In vitro microscale systems for systematic drug toxicity study. *Biotechnol. Prog.*, 2010

Body-on-a-Chip

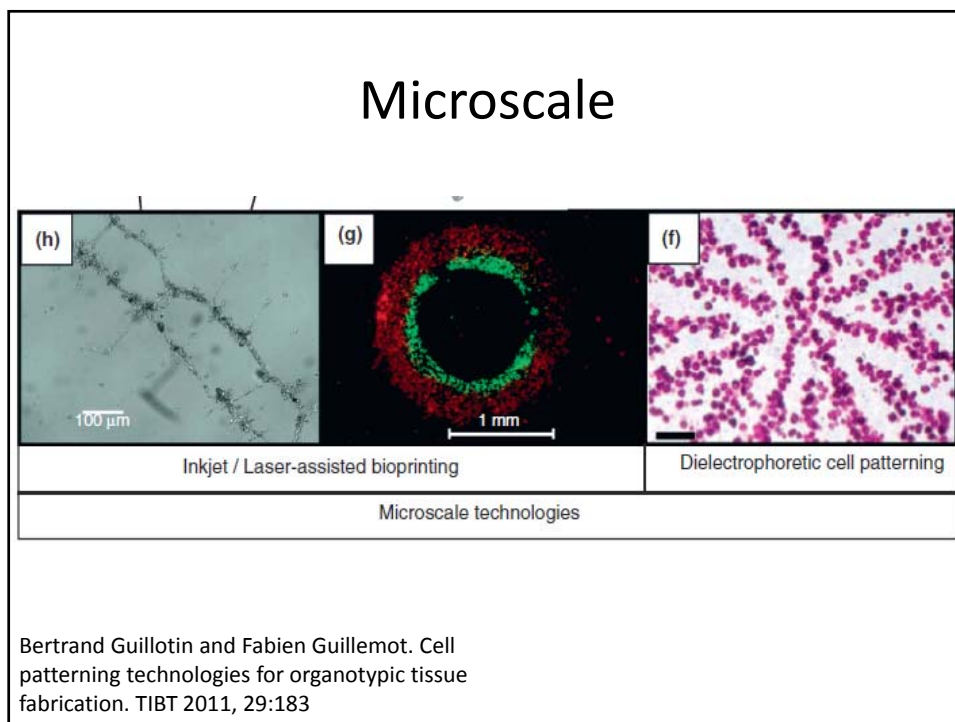
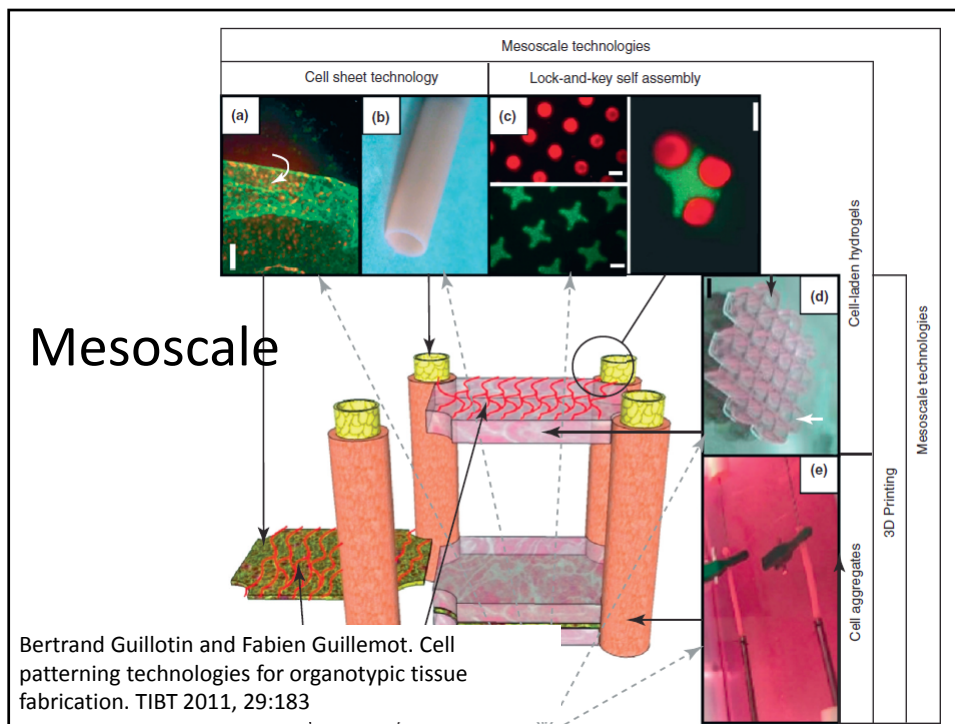


Jong Hwan Sung & Michael L. Shuler: In vitro microscale systems for systematic drug toxicity study. *Biotechnol. Prog.*, 2010

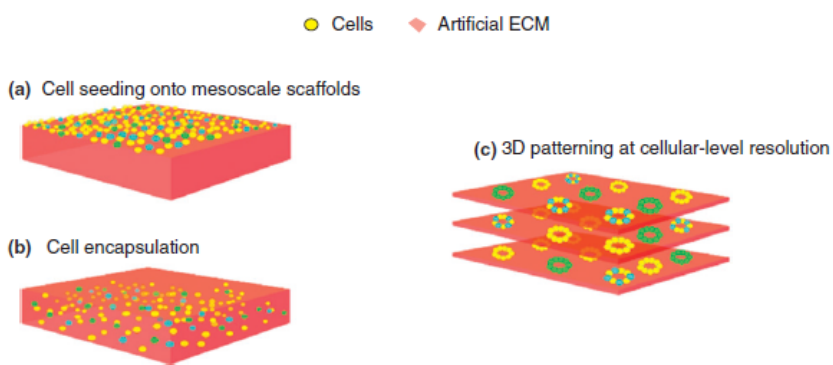
Liver Structures



www.studentconsult.de

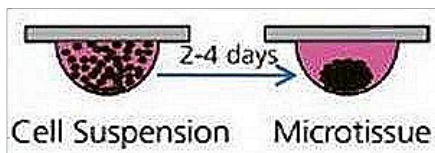
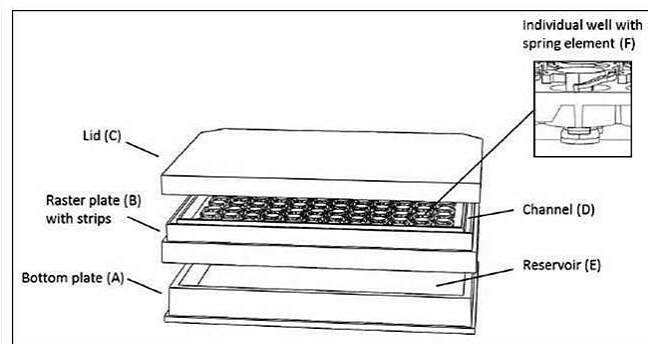


Engineered 3D Structures

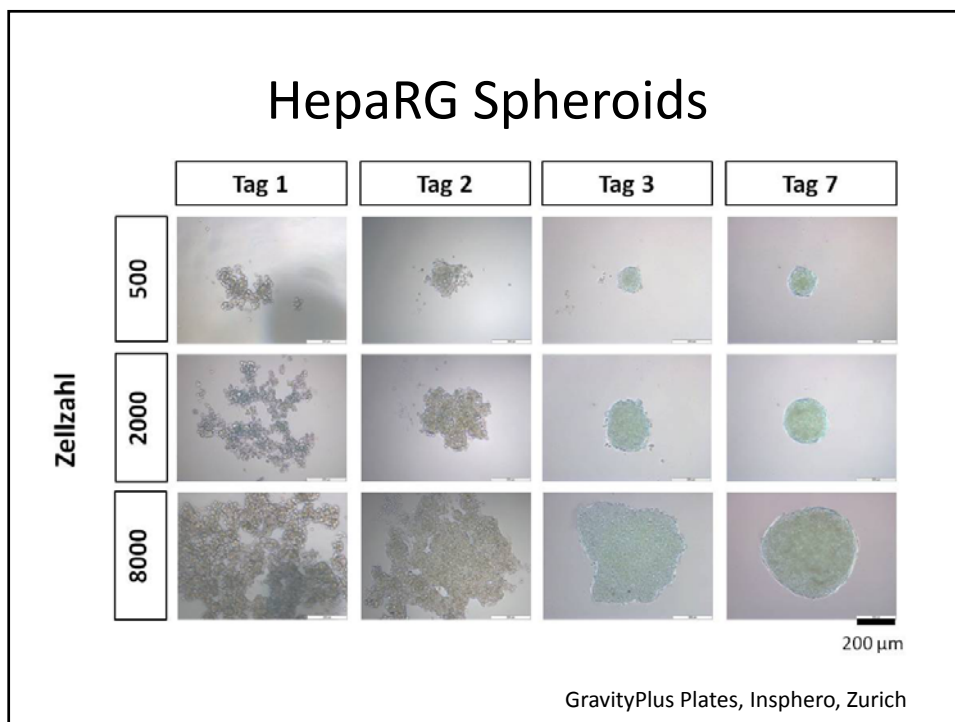
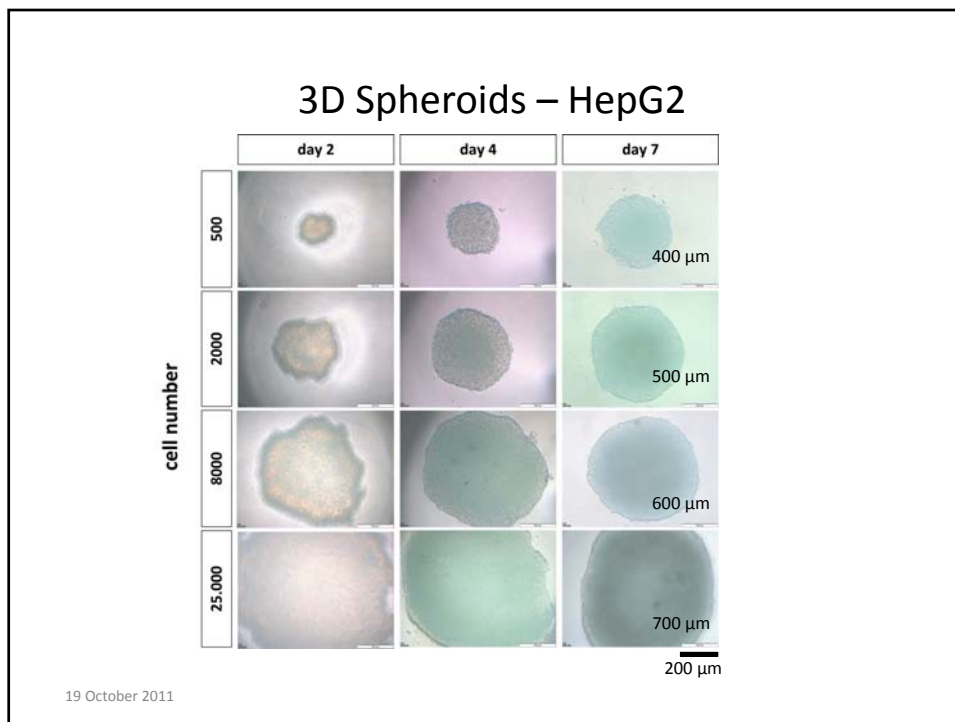


Bertrand Guillotin and Fabien Guillemot. Cell patterning technologies for organotypic tissue fabrication. TIBT 2011, 29:183

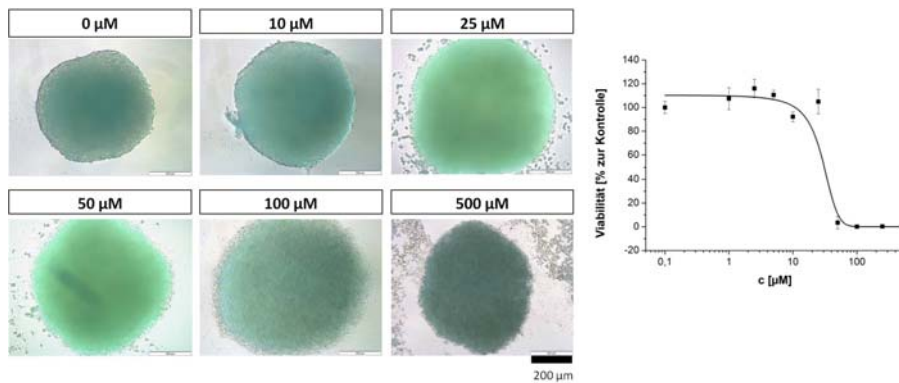
Spheroid Culture



GravityPlus Plates, Insphero, Zurich



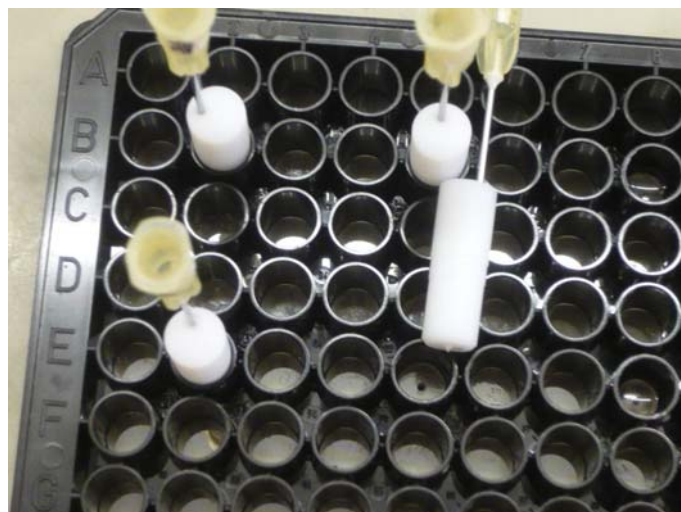
HepaRG Spheroids



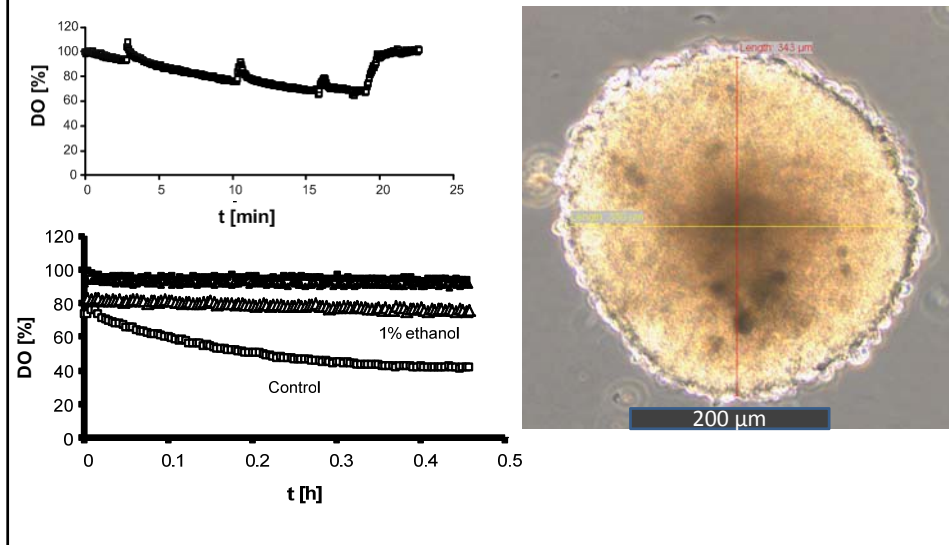
Tamoxifen, 24 h

GravityPlus Plates, Insphero, Zurich

Microrespiration Measurement



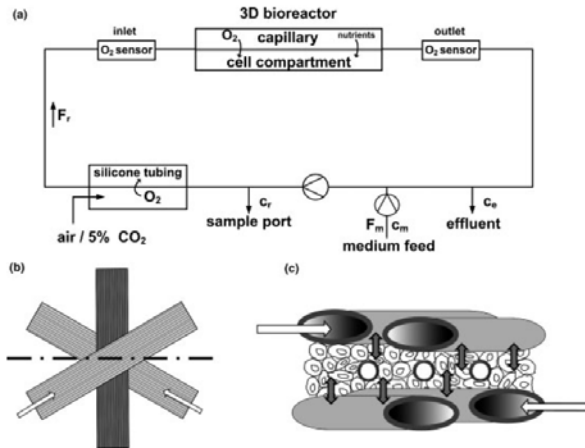
hESC derived Cardiomyocytes



Video - Heart

6 month continuous beating in the lab

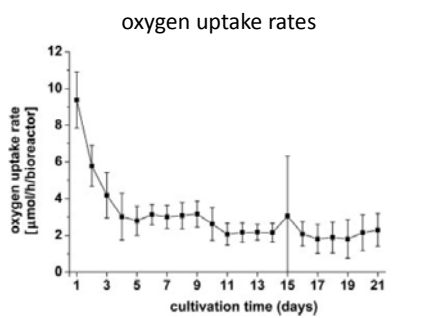
3D Hollow-Fiber Bioreactor



19 October 2011

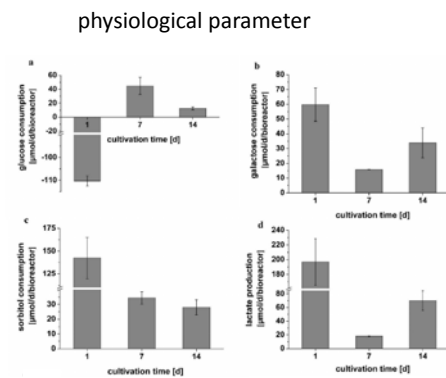
Zeilinger et al. Tissue Eng. 2011
Mueller D. et al. J Tissue Eng Regen Med (2011)

Long-Term Culture of Human Primary Hepatocytes in 3D Hollow-Fiber Reactor

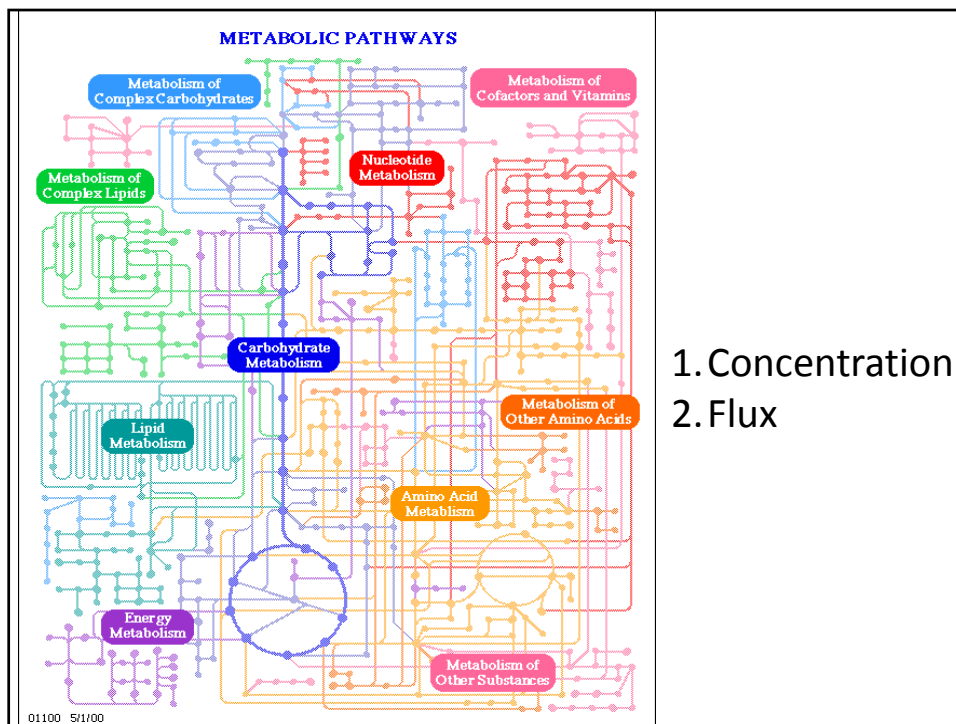


$$OUR = F_r \times (c_{O_2,in} - c_{O_2,out}) = F_r \times \Delta c_{O_2}$$

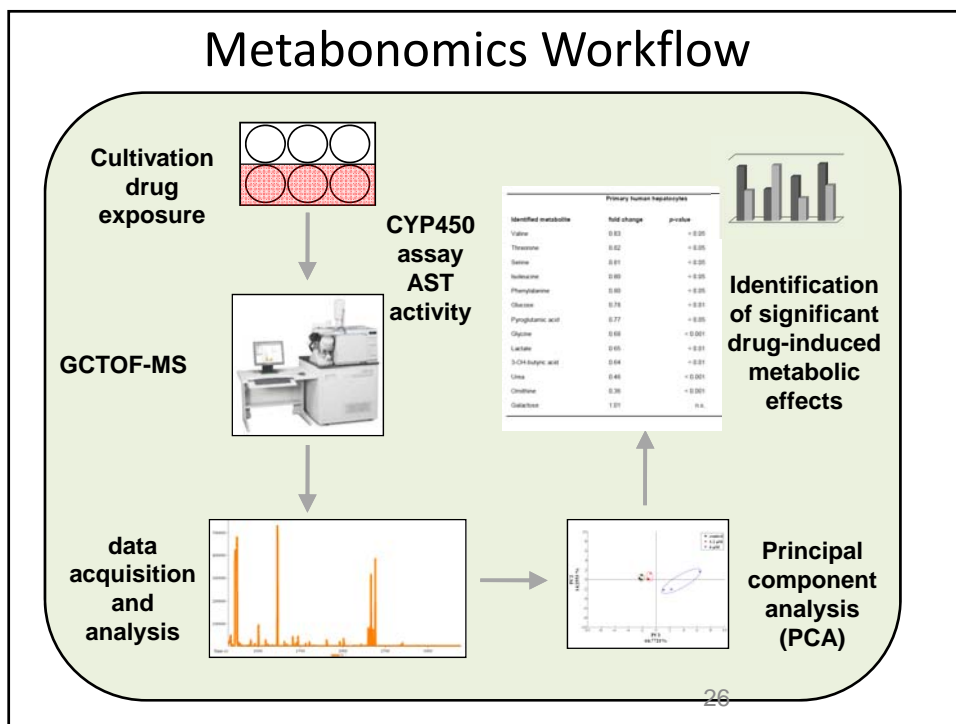
19 October 2011



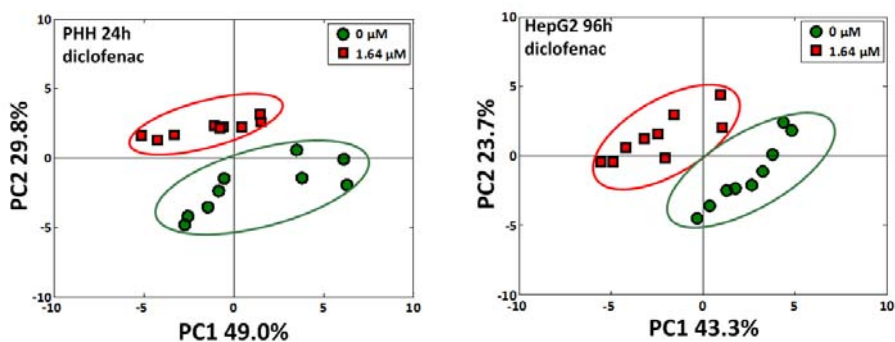
Mueller D. et al. J Tissue Eng Regen Med (2011)



1. Concentration
2. Flux

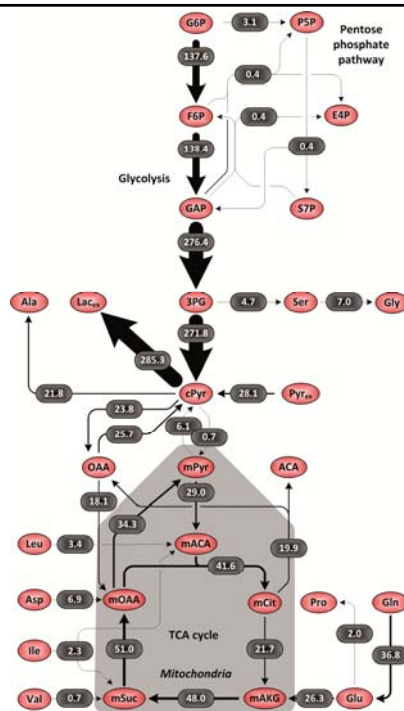


Subtoxic Drug Effects on Metabolome



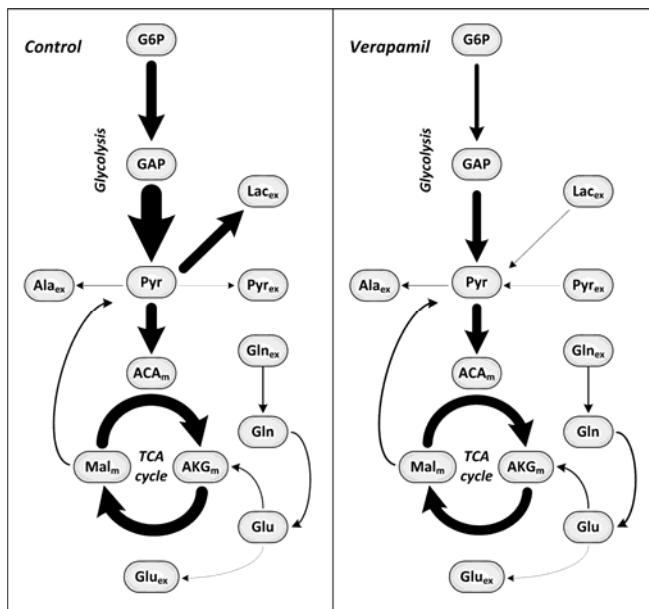
Human Cell Line AGE1.HN

- From human brain tissue sample
- immortalized with plasmid with adenoviral E1 A and B genes of human adenovirus type 5 & human pGK and endogenous E1B promoters
- ProBioGen, Berlin



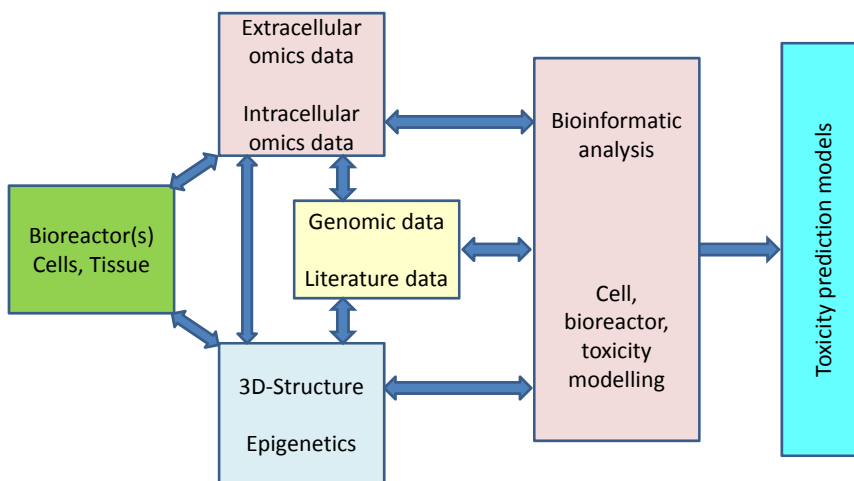
Metabolic Flux Analysis

- HL1 cells
- 4 μ M Verapamil (channel blocker)
- 13 C-steady state flux analysis



Strigun et al., J. Biotechnol, 2011

Toxicity Modeling and Prediction



Part.	Participant organisation name	Acronym	Country
1	SAARLAND UNIVERSITY Biochemical Engineering Institute, Prof. Elmar Heinzle, USAAR-EH Genetics Institute, Prof. Jörn Walter USAAR-JW	USAAR	DE
2	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE Department of analytical sciences, Hubert Curien Pluridisciplinary Institute, University of Strasbourg, Laboratory of BioOrganic Mass Spectrometry, Prof. Alain van Dorselaer, Strasbourg	CNRS	FR
3	STICHTING HET NEDERLANDS KANKER INSTITUUT Department of Cell Biology, Prof. Peter J. Peters, Amsterdam	NKI	NL
4	KAROLINSKA INSTITUTET Section of Pharmacogenetics, Prof. Magnus Ingelman-Sundberg, Stockholm	KI	SE
5	INSILICO BIOTECHNOLOGY AG Dr. Klaus Maier, Stuttgart	INSIL	DE
6	INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE Multicellular Systems Group, Dr. Dirk Drasdo, Le Chesnay (Paris)	INRIA	FR
7	DEUTSCHES FORSCHUNGSZENTRUM FUER KUENSTLICHE INTELLIGENZ Agents and Simulated Reality, Prof. Philipp Slusallek, Saarbrücken	DFKI	DE
8	LEIBNIZ FORSCHUNGSGESELLSCHAFT FUR ARBEITSPHYSIOLOGIE UND ARBEITSSCHUTZ E.V. Prof. Jan Hengstler, Dortmund	IFAD	DE
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10	WEIZMANN INSTITUTE OF SCIENCE Dr. Amos Tanay, Rehovot	WIS	IL
11	CAMBRIDGE CELL NETWORKS LTD Dr. Gordana Apic, Cambridge	CCN	GB
12	EUROPEAN PROJECT OFFICE Claudia Giehl, Saarbrücken	EURICE	DE



NOTOX Members



Summary

- New organotypic cultures will greatly support toxicity testing
- Miniaturization limited by analytical capabilities
- Metabolic network studies show subtoxic effects
- Combination with systems modelling will increase predictivity in the future, also for system long-term toxicity

Acknowledgements

- Fozia Noor
- Daniel Müller
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- Michel Fritz
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- EU
- Colipa
- Pharmacelsus
- Cellartis
- Probiogen



Invitroheart

NOTOX

Hepatox
Syslogics





Thank you !

Questions ?