National Institute of Biomedical Imaging and Bioengineering

Fourth AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools and Models for The Pre-clinical Drug Discovery Process
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One European Perspective: Changing the Paradigm for Safety Testing of Pharmaceuticals in Europe.

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Disclaimer

The Views expressed in this presentation are of my own responsibility and may not reflect those of my affiliation Institutions

Drug Development from A – Z

Discovery & Screening

In silico — QSAR ; Prediction & Simulation

In vitro — Mutagenicity(Ames) ; hERG assay

In vitro — Cellular assays

In vivo animals

In human **Exploratory Trials (ICH M3R2)**

Lead Candidate Selection

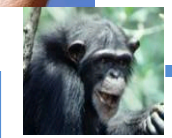
Preclinical Development (Safety, PoC)

Safety Testing Program

No Stand Alone

Single Dose Studies

Repeated Dose Studies



6 months

2-4 Weeks

1 month

3 months

9 (6, 12) months

Additional studies:
immunotox;
juvenile animals, neurotox

Genotoxicity

- *in vitro*
- *in vivo*

Carcinogenicity

1 life-span
+
1 additional model

Reproduction Toxicology

- fertility
- embryofetal toxicity
- peri-post natal toxicity

The Paradigm is Getting Old
How old??

1955 (US)

2014

1957

Historical Background of the Nonclinical Paradigm

1955- USA

Pharmacodynamics (BP, HR, Respiration)

- Acute toxicity (dose response, minimum 3 species)
- sub-acute toxicity (1 or more species; 6-12 weeks)
- Chronic toxicity
- Carcinogenicity (1960s)
- External effects (skin irritation, sensitization)
- Special studies:
  - Reproduction
  - Hematology
  - Absorption / Distribution / Excretion..

1983- Europe (Notice to Applicants)

- Pharmacokinetics
- Single dose Toxicity (2 species)
- Repeated Dose Toxicity (2 species)
  - Sub-acute
  - chronic
- Reproduction Toxicity
- Genotoxicity
- Carcinogenicity
- Other studies

Historical background on Safety Testing EUROPE – ICH

1975 — 1991 — 2014

CPMP

The Rules Governing Medicinal Products In the EC, vol.III, 1983

ICH

-Harmonisation
-New Topics
- Revisions

-Core Study Packages Unchanged

-Testing Strategies Reformulated / Updated

- Following Science / Technology Innovation

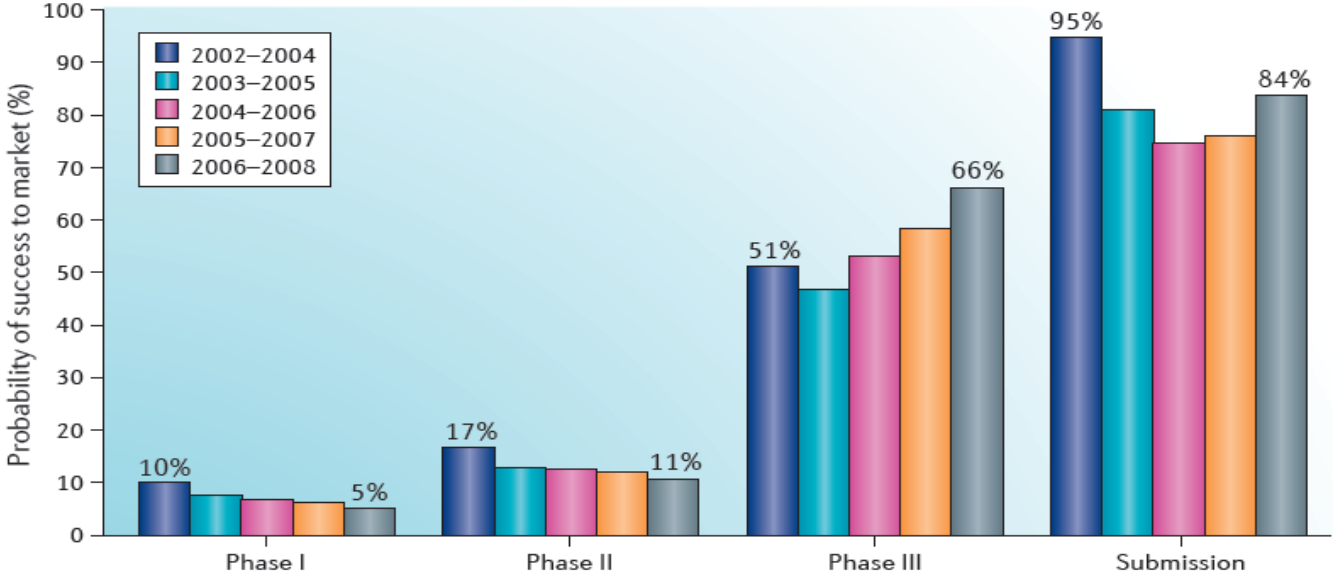
Paradigm Enriched but Format Unchanged

What About Development Success?

Attrition History

1.

2.



1- Kola and Landis (2004).. *Nature Reviews Drug Discovery*; 3: 711–715

2- J Arrowsmith(2012) , Nature Reviews Drug Discovery, 11: 17-18.

But High Attrition Rates Persist! WHY?

- Insufficient screening ?
- Wrong lead candidate selection?
- Insufficient animal predictivity? (PoC, safety)
- Inadequate Clinical Paradigms?
- All those reasons together?

Drug Innovations and Paradigm Adaptations (nonclinical)

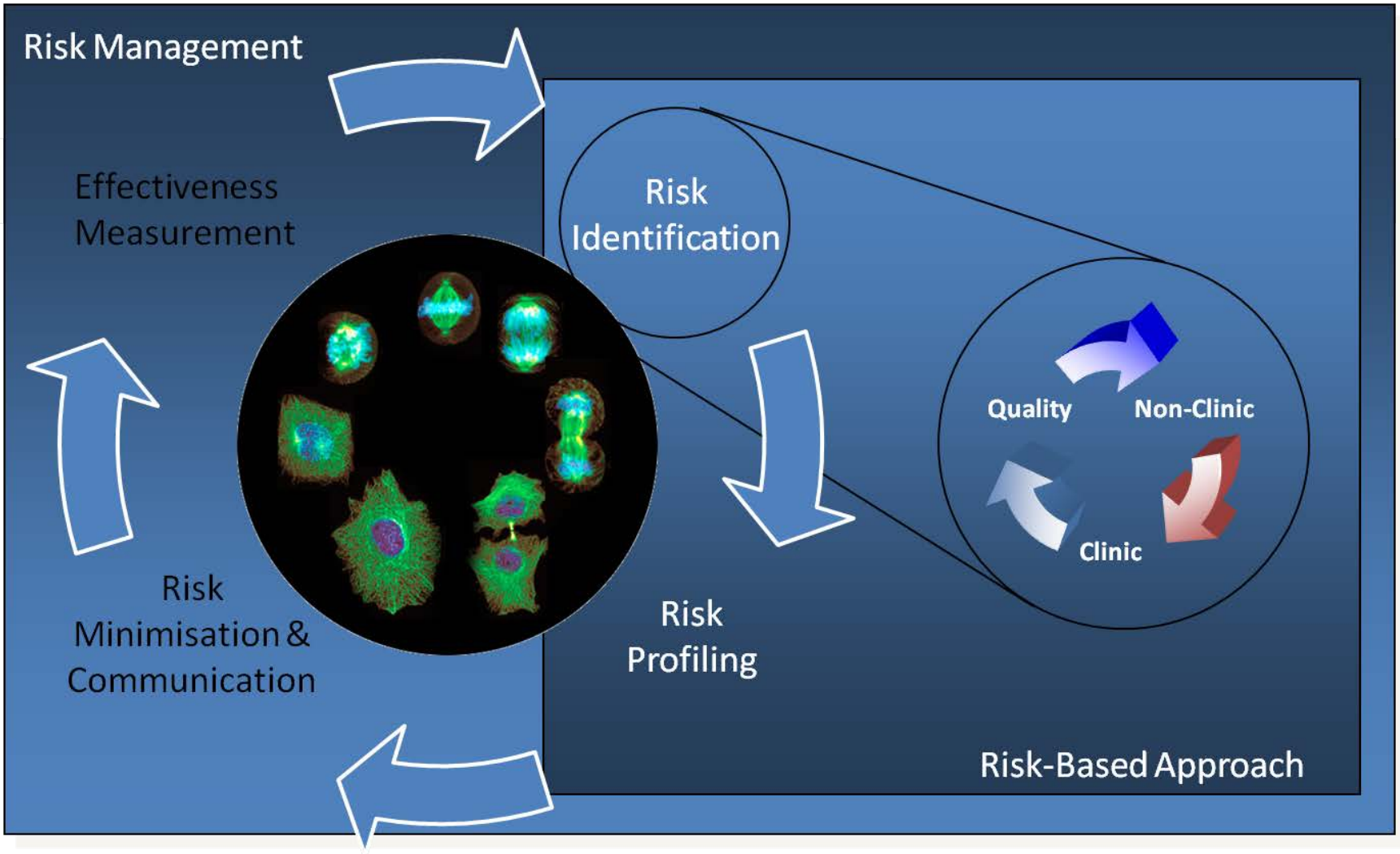
- **Biopharmaceuticals:**
  1 species; 6 Month studies; no carcinogenicity(WOE)
  vitro only acceptable (if nonrelevant species)

- **Biosimilar mAbs:** mostly comparability in vitro

- **Nanopharmaceuticas:** size-based concerns?

- **Advanced Therapies (CTMP; GTMP)**
  risk anticipation; case-based design

Risk Assessment for Advanced Therapies



NC Paradigm Improvement: what is needed?

- **Efficacy: Reinforce knowledge on:**
  - Disease
  - Target involvement on disease
  - Target biology
  - Target distribution
  - Target mediated cascades
  - Cascades Cross talk

- **Safety:**
  - Models for improved human predictivity

IMPACT ON CLINICAL PARADIGM?

Re-Thinking Drug Development in Europe: The Innovative Medicines Initiative:

Joining Forces in the Healthcare Sector

IMI Nonclinical Safety Projects

- **Intensive Joint Research Initiatives towards:**
  - In silico: databases Structure-Toxicity relationship
  - In vitro toxicity prediction: liver, kidney, vascular
  - Cancer biomarkers
  - Human cell culturing systems (iPS)
    - Healthy
    - patients

Development of reliable toxicity predictive systems

- ✓ 6th release of the Vitic Nexus eTOX database

831 substances (584 confidential) linked to 1,703 study designs
(Bayer, Boehringer, Esteve, GlaxoSmithKline, Lundbeck, Novartis, Pfizer, Roche, Sanofi, Servier, and UCB)

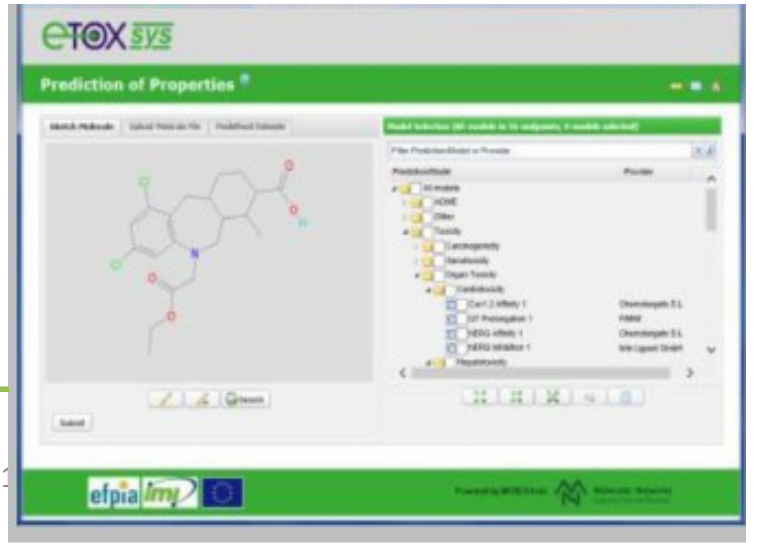
- ✓ 3rd release of the ChOX database

411 toxicology-linked targets; 162,287 distinct compounds and 701,181 activities

- ✓ Version 1 of the integration system, eTOXsys, was released to all partners

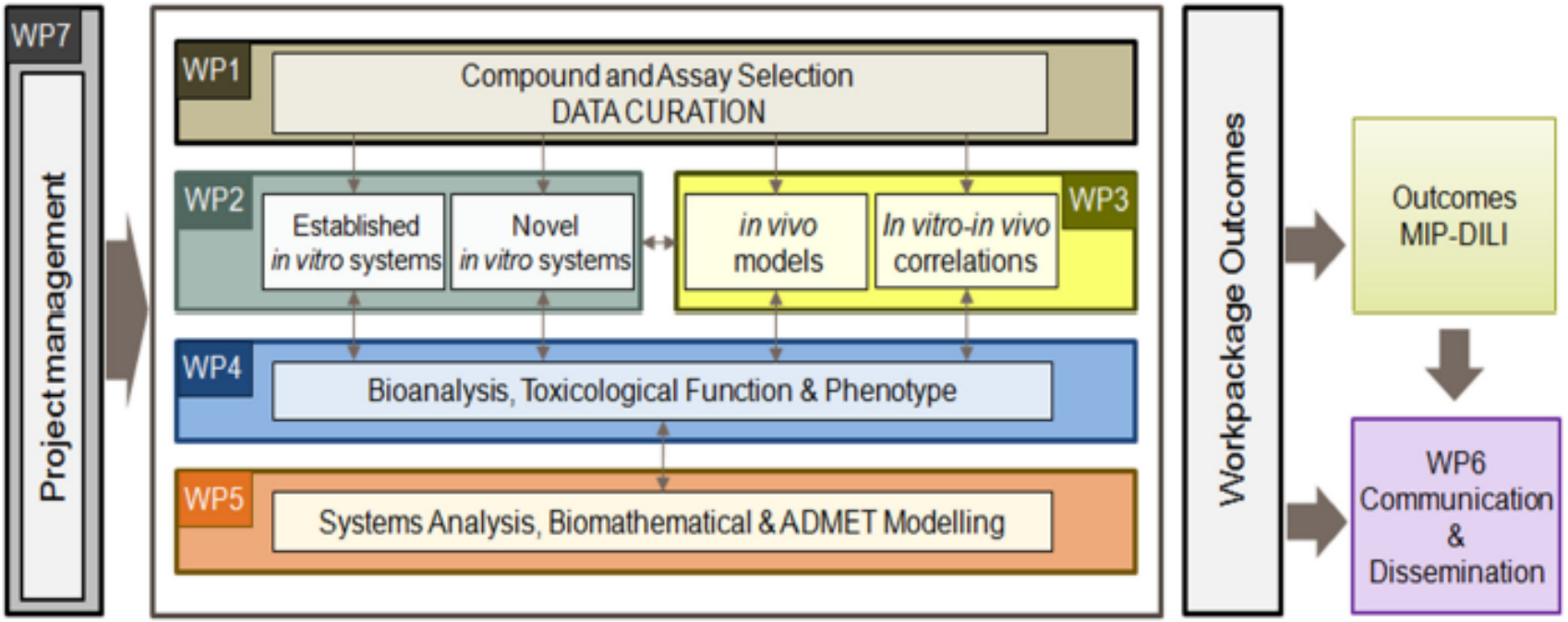
7 out of 10 companies have already a running system.

- ✓ 90 predictive models developed

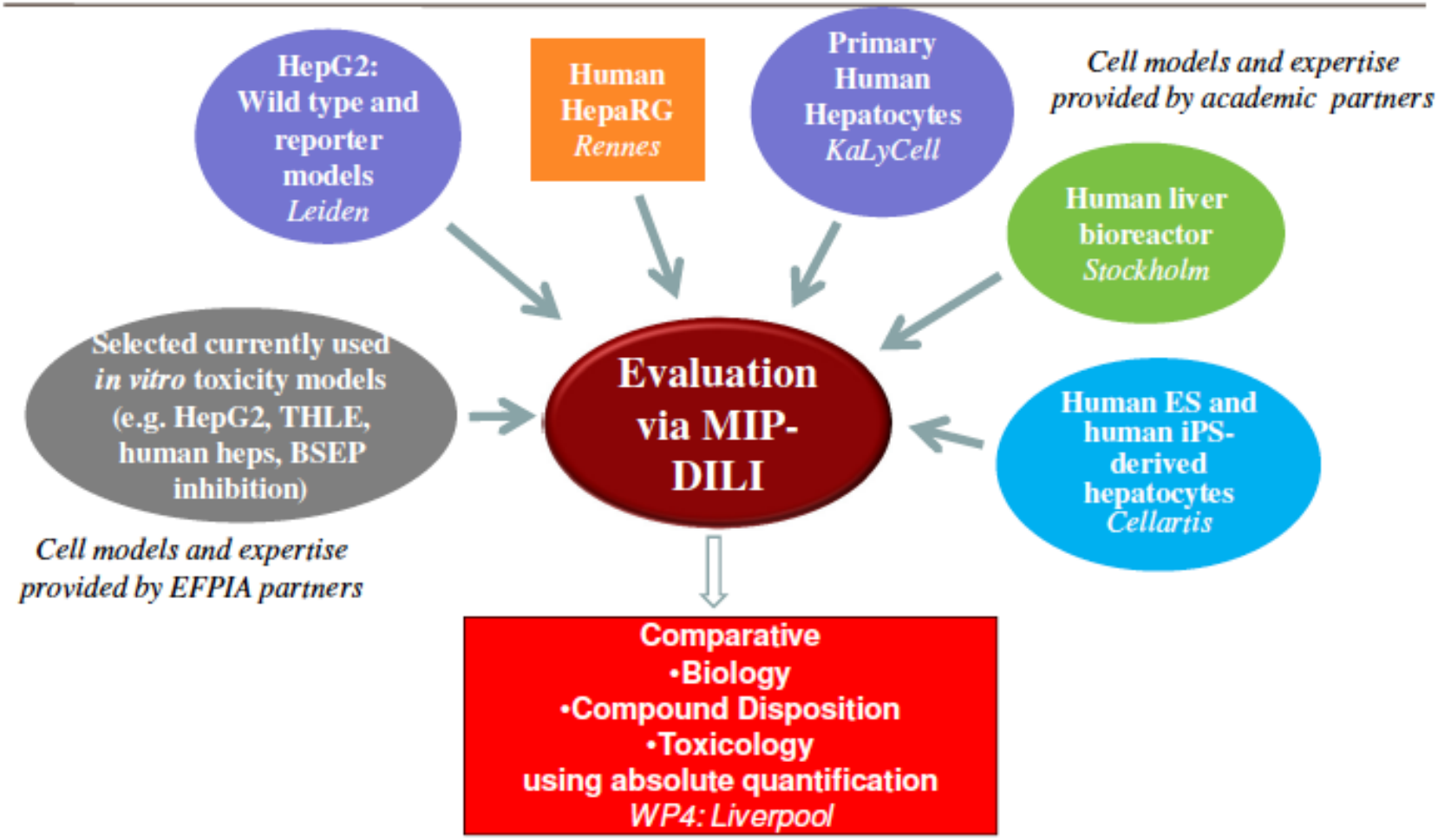


MIP-DILI Mechanism based improved prediction of drug-induced liver injury

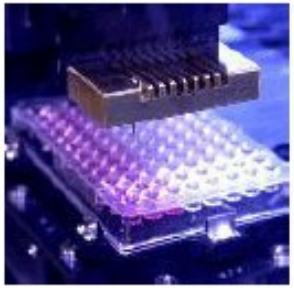
Summary Work Plan



In vitro models in MIP-DILI



Safer and Faster
Evidence Based Translation



Evaluated 153 potential biomarker candidates for drug-induced injury of the kidney, liver, and vascular system

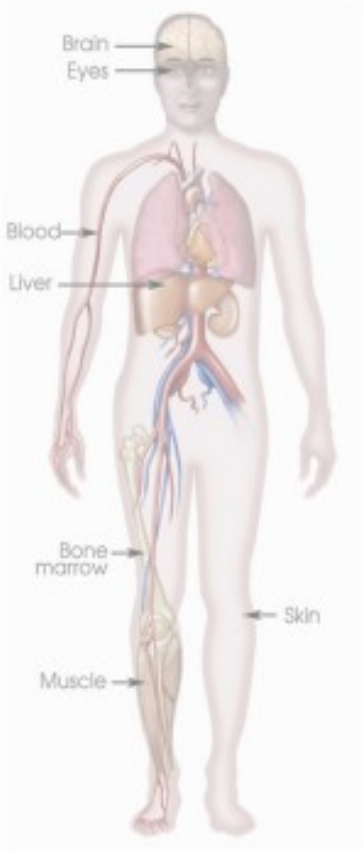
17 exploratory clinical studies started or completed

> 6500 retrospective samples collected

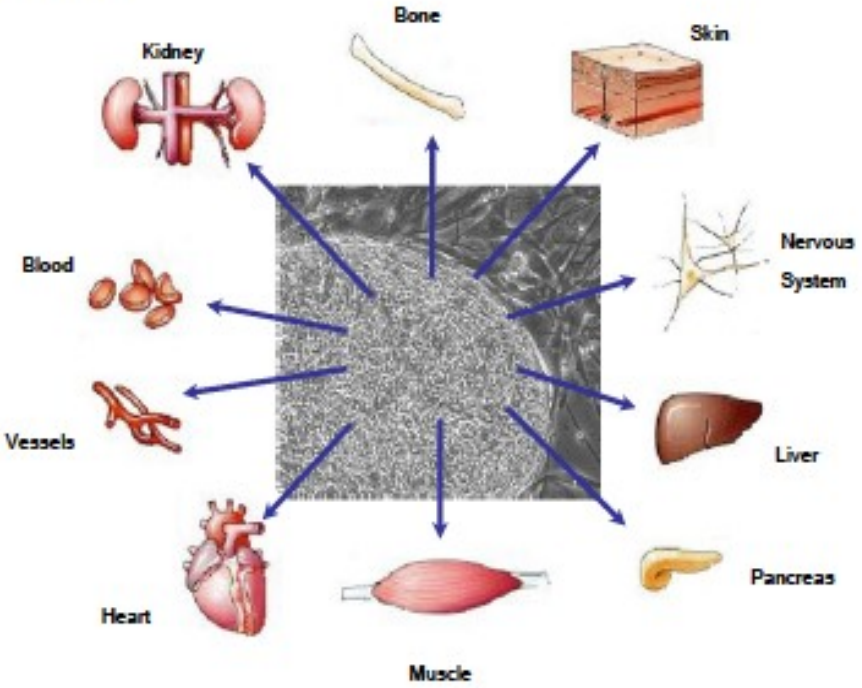
Dialogue with Regulatory Agencies established

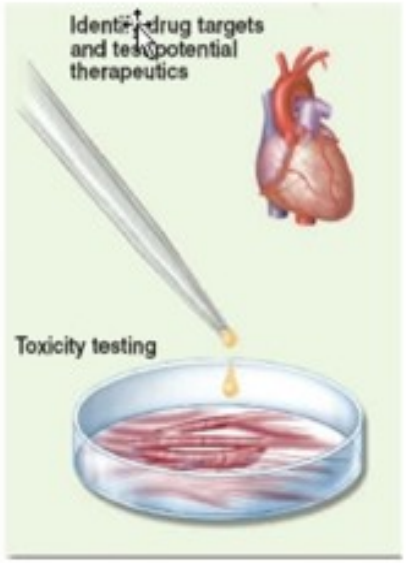
- Providing access to a huge amount of most relevant clinical safety data across all pharmaceutical companies and all major drug classes
- A drug safet signal detection system across globel regulatory data is being set up initially with EMA data, driven by IMI and EFPIA

STEMBANCC: Stem Cells in Safety Assessment



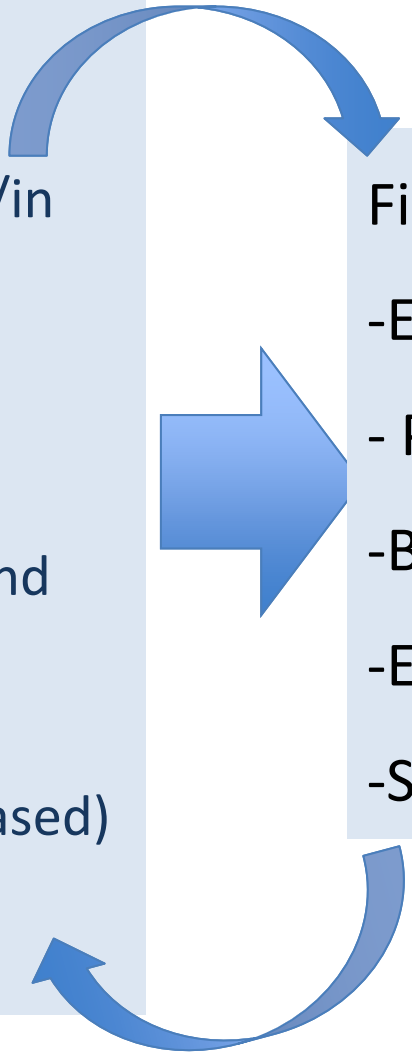
hESCs and iPSCs are Pluripotent: They have the potential to differentiate into all tissue of an adult.





Science is Pushing Paradigm to Shift

- Molecular attributes
- Pharmacology / Target
- Pharmacokinetics (in vitro/in silico)
  - -absorption
  - -transport
  - -metabolism
- Toxicity prediction (MoA and QSARS)
- Toxicity testing
- In vitro systems (human based)
  - - healthy condition
  - - disease condition



First in Human study

-Exploratory approaches

- PK / PD characterization

-Biomarkers Based

-Efficacy

-Safety

Which Paradigm Shift?

Discovery & Screening

In silico

Databases on QSAR; Modelling & Simulation
Omics integration; Systems Biology

In vitro

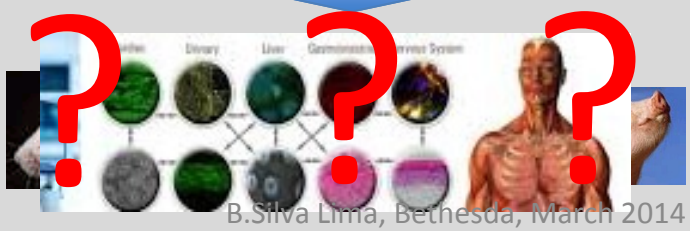
Mutagenicity(Ames) ; hERG assay

In vitro

iPSCs
Human cell systems
3D cultures
Organs in Chip

In human
Exploratory Trials
(ICH M3R2)

Lead Candidate Selection



Paradigm Shift: Which Path to Take?

- **From observational/reactive approach –**

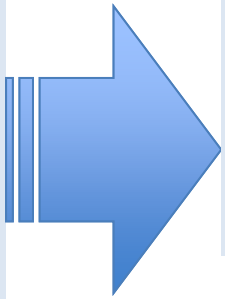
  General toxicity studies in animals then mechanistic

- **Into Predictive/proactive approach:**

  integrated MoA/in silico/in vitro / (in animal) / in human

A Scientists Drive...

- Scientist profile also changing
  - Scientific Cross Talk
    - Physics
    - Medicine
    - Engeneering
    - Electronics
    - Computer systems



Regulators

Regulatory Scientists

Impact on Regulatory Framework

- **Current situation:**

  multiple safety guidelines for multiple endpoints (mainly animal based)

- **The future: strategy oriented guideline (s)**

  (integrating omics/in silico/in vitro/in human) nonclinical / clinical cross talk

How to "Validate" a New paradigm?

- **Test by test?**
- **Innovative tests vs animal tests?**
- **Outcomes?:**

  innovative program vs human

How to "Validate" a New paradigm?

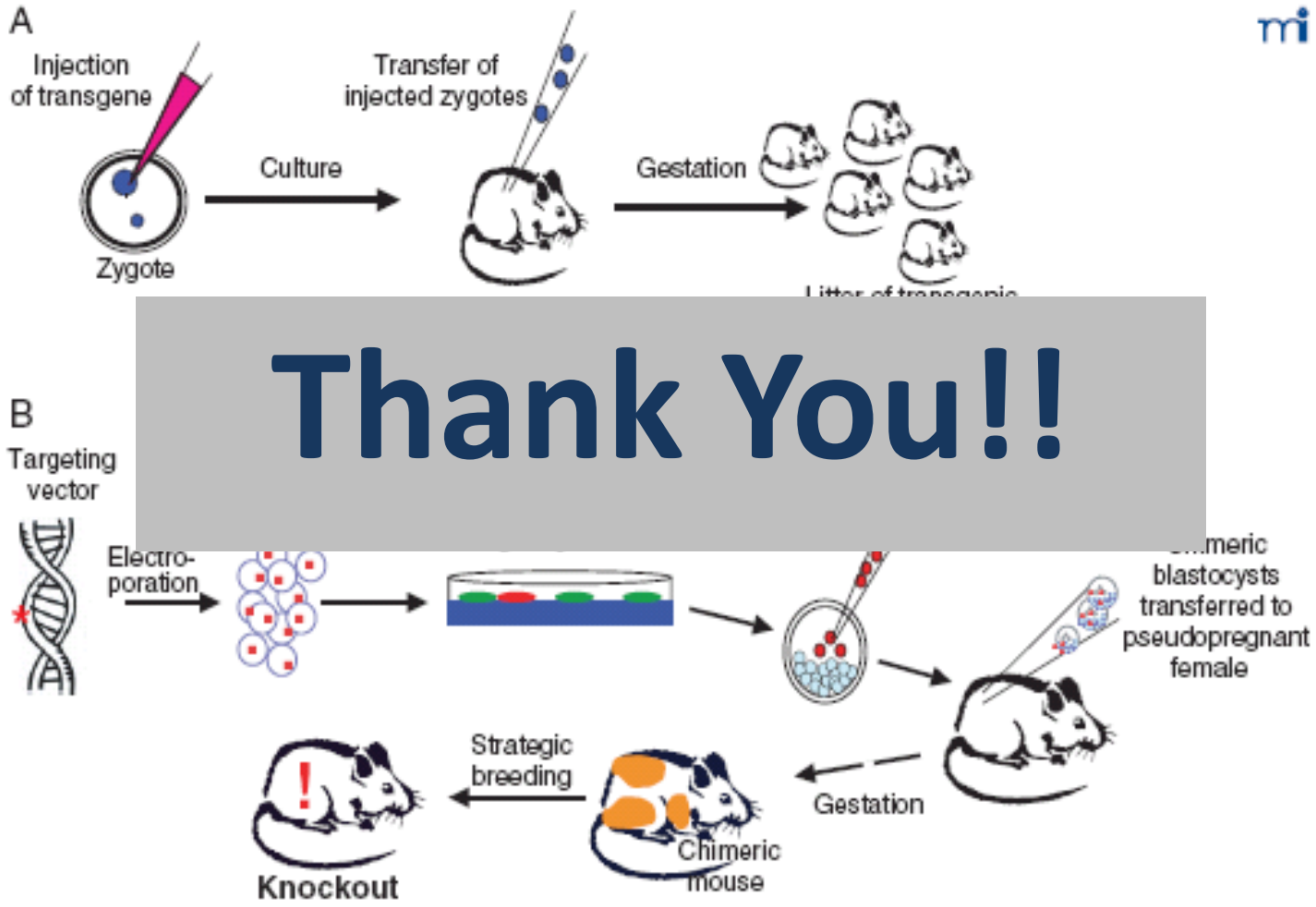
Outcomes:

i) **know molecules:**

innovative program vs human

ii) new molecules (pilot exercises)

"Paralel Path" : both classical and new paradigm


A
Injection of transgene
Zygote
Culture
Transfer of injected zygotes
Gestation
B
Targeting vector
Electro-poration
blastocysts transferred to pseudopregnant female
Strategic breeding
Gestation
Chimeric mouse
Knockout

Thank You!!