toxys®

The value of understanding

Animal-free Developmental Toxicity Prediction Tools

Amer Jamalpoor, PhD, ERT
Scientific Director

NVT Spring symposium - April 18, 2023

Toxys B.V.
Leiden, The Netherlands

Animal testing for DART

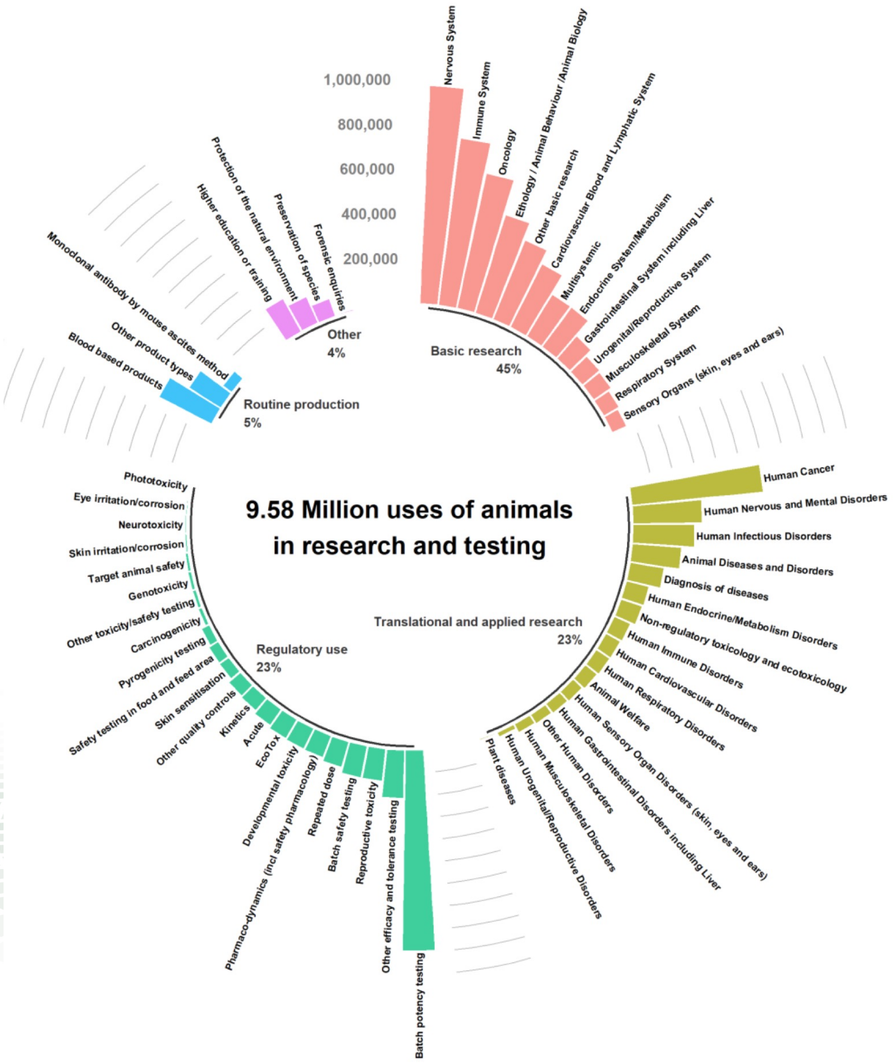
EUROPEAN COMMISSION

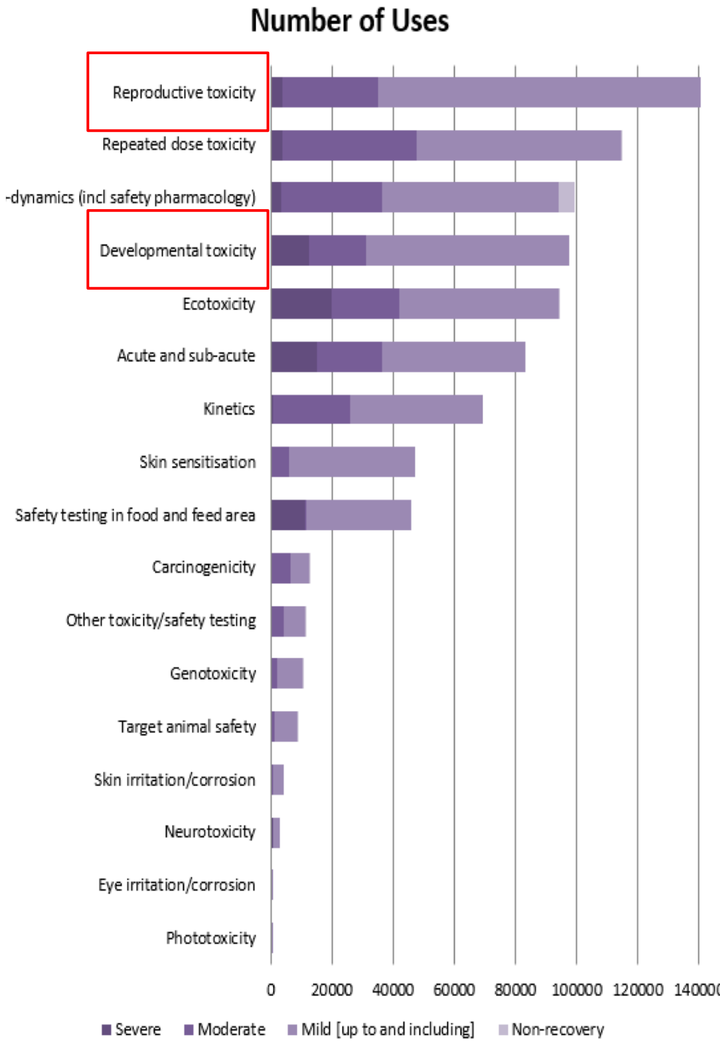
Brussels, 5.2.2020
COM(2020) 16 final

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

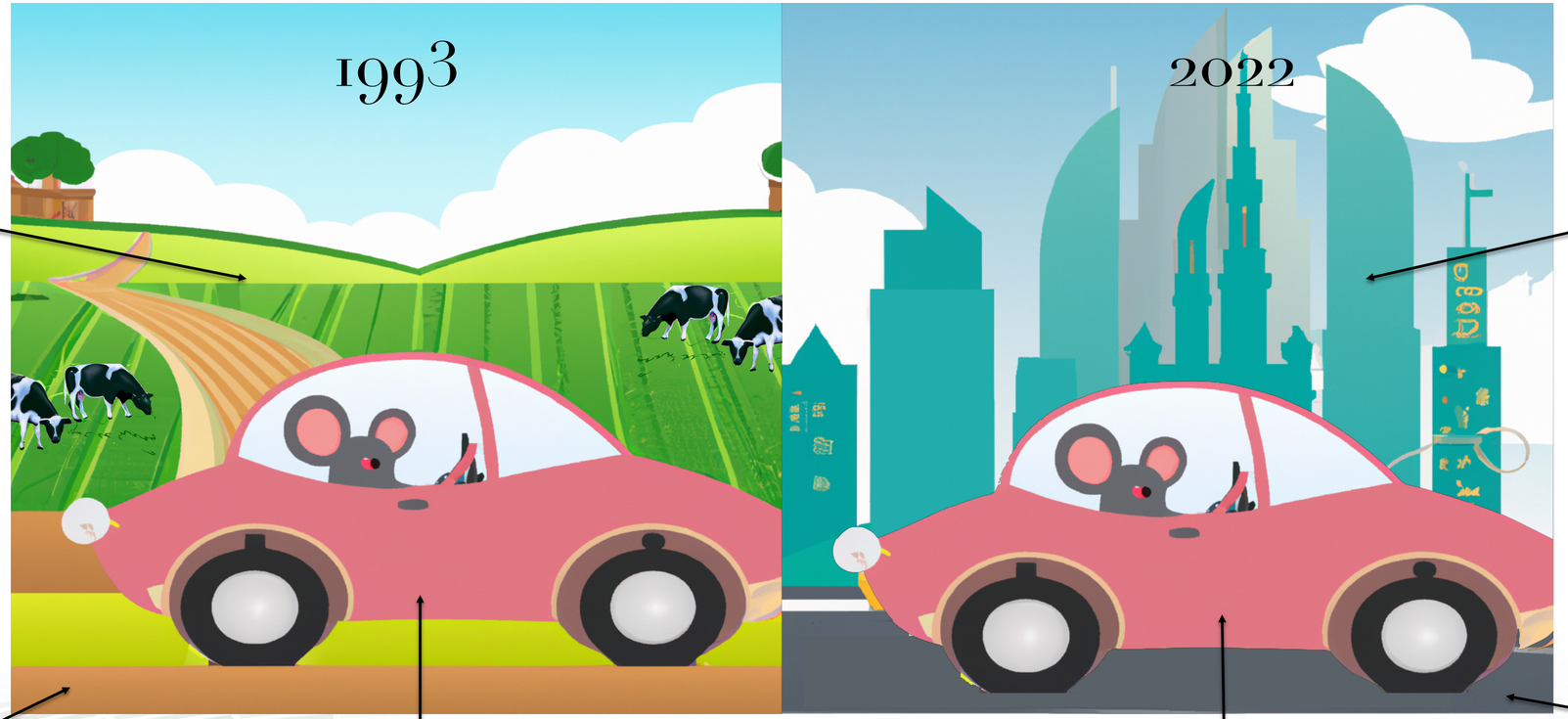
2019 report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017

{SWD(2020) 10 final}





Over 30 years of research and development



Scientific advancement

Scientific advancement

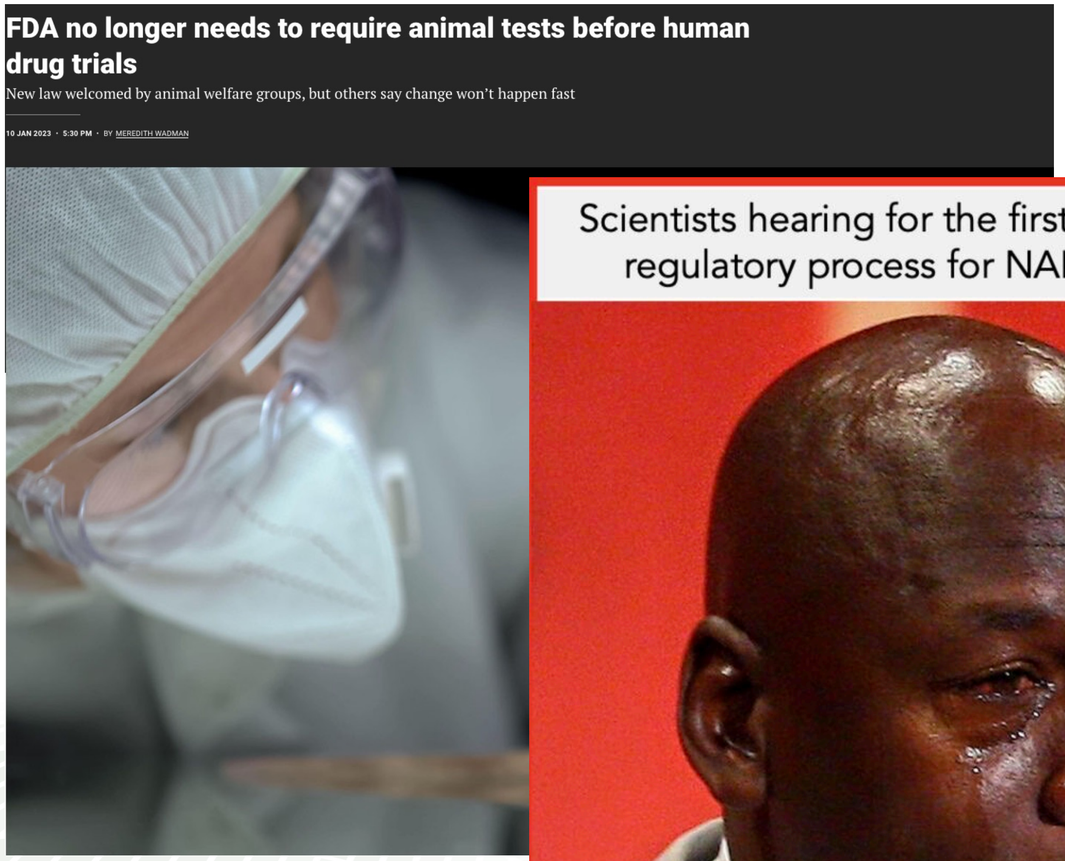
Muddy road:
1) Large # of animals,
2) Tedious,
3) Resource intensive

Regulatory acceptance

Regulatory acceptance

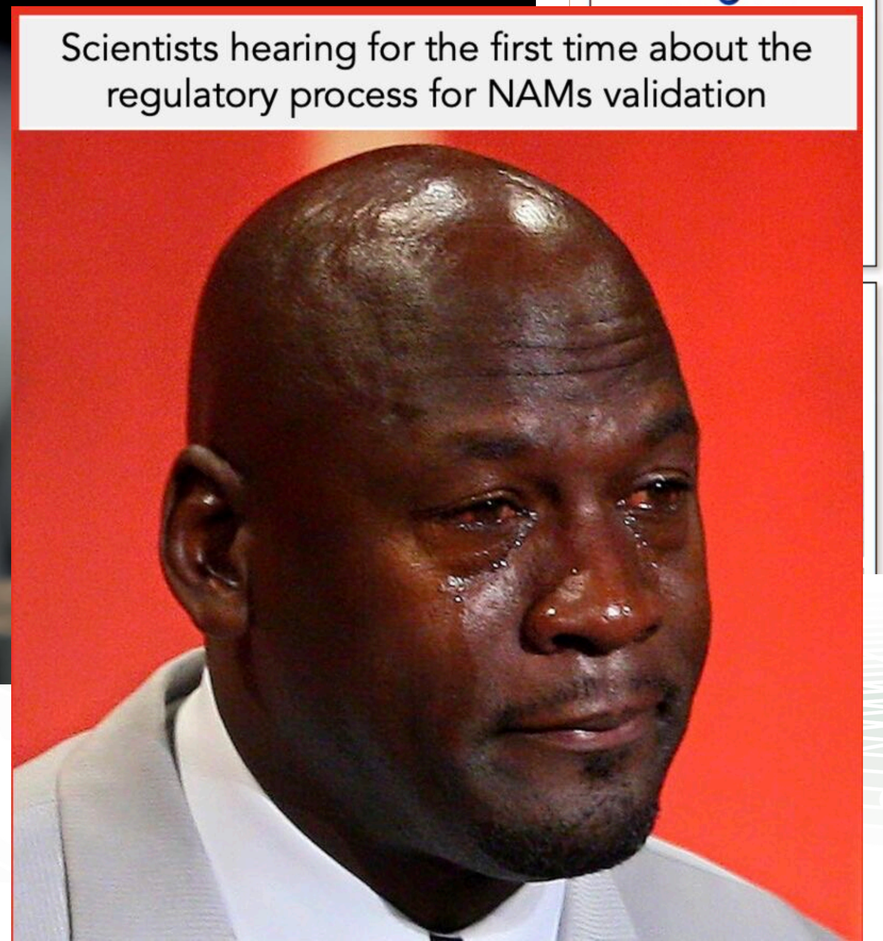
Asphalt road:
1) Refinement
2) Reduction
3) Tedious and resource intensive
4) Ethically debatable

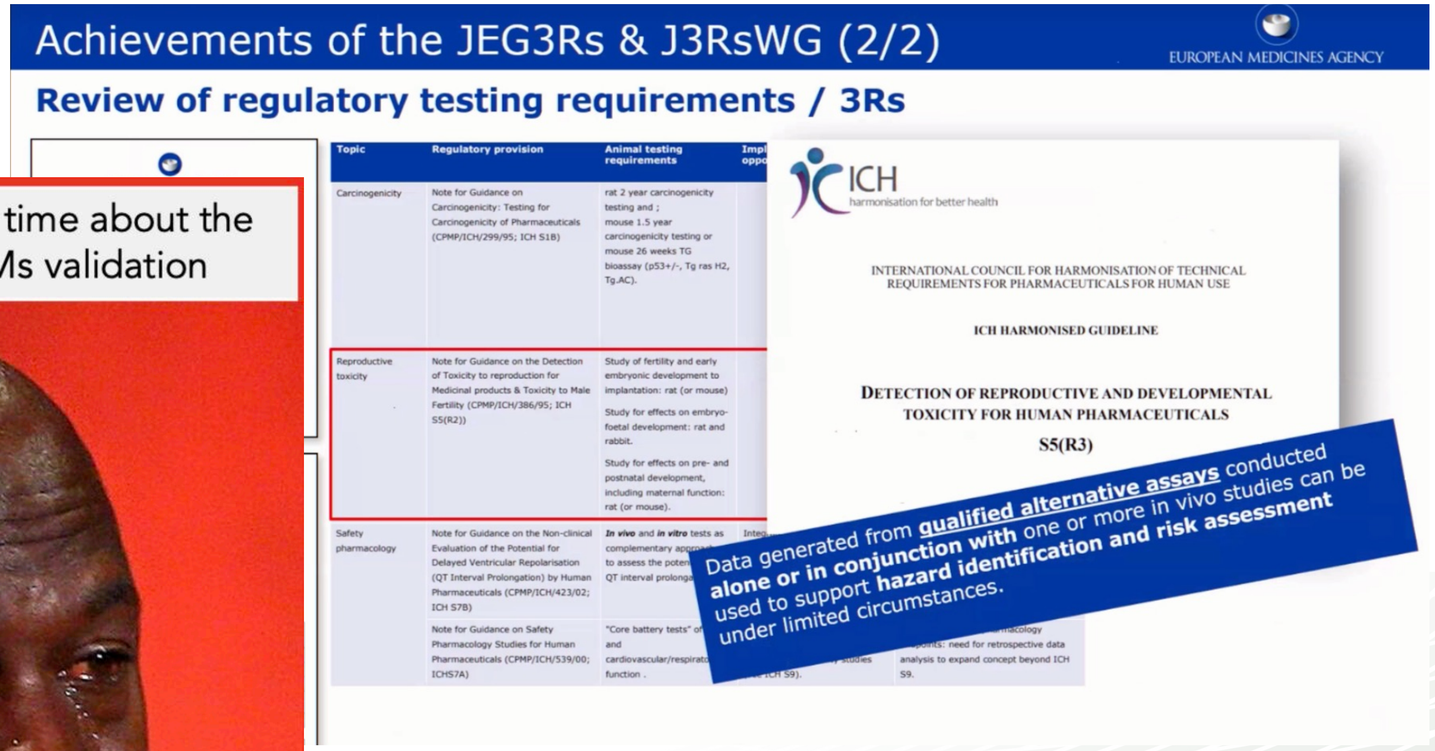
On boarding of animal-free test systems by regulatory agencies


FDA no longer needs to require animal tests before human drug trials

New law welcomed by animal welfare groups, but others say change won't happen fast

10 JAN 2023 · 5:30 PM · BY MEREDITH WADMAN




Achievements of the JEG3Rs & J3RsWG (2/2)

EUROPEAN MEDICINES AGENCY

Review of regulatory testing requirements / 3Rs

Topic	Regulatory provision	Animal testing requirements	Impl oppo
Carcinogenicity	Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals (CPMP/ICH/299/95; ICH S1B)	rat 2 year carcinogenicity testing and ; mouse 1.5 year carcinogenicity testing or mouse 26 weeks TG bioassay (p53+/-, Tg ras H2, Tg.AC).	
Reproductive toxicity	Note for Guidance on the Detection of Toxicity to reproduction for Medicinal products & Toxicity to Male Fertility (CPMP/ICH/386/95; ICH S5(R2))	Study of fertility and early embryonic development to implantation: rat (or mouse) Study for effects on embryo-foetal development: rat and rabbit. Study for effects on pre- and postnatal development, including maternal function: rat (or mouse).	
Safety pharmacology	Note for Guidance on the Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (CPMP/ICH/423/02; ICH S7B)	*In vivo* and *in vitro* tests as complementary approa to assess the poten QT interval prolonga	Integ
	Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (CPMP/ICH/539/00; ICHS7A)	"Core battery tests" of and cardiovascular/respirato function .	ICH S9).

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS

S5(R3)

Data generated from **qualified alternative assays** conducted **alone or in conjunction with** one or more in vivo studies can be used to support **hazard identification and risk assessment** under limited circumstances.

Alternative Developmental Toxicity screening

Various of alternative methods:

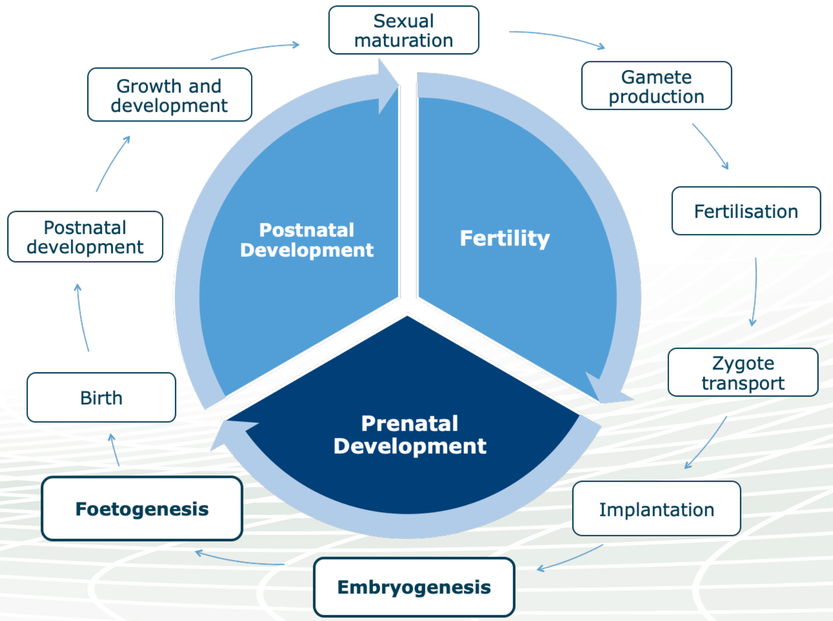
- Cell-based approaches (mouse stem cell tests)
- Whole embryos (rat WEC, ZET, chicken embryo)
- Organ-based (mini brains, liver, placenta)
- In silico approaches (virtual embryo)

Advantages

- Time and cost efficiency
- Insight into the key events and MoA
- Reduction in animal use

Disadvantages

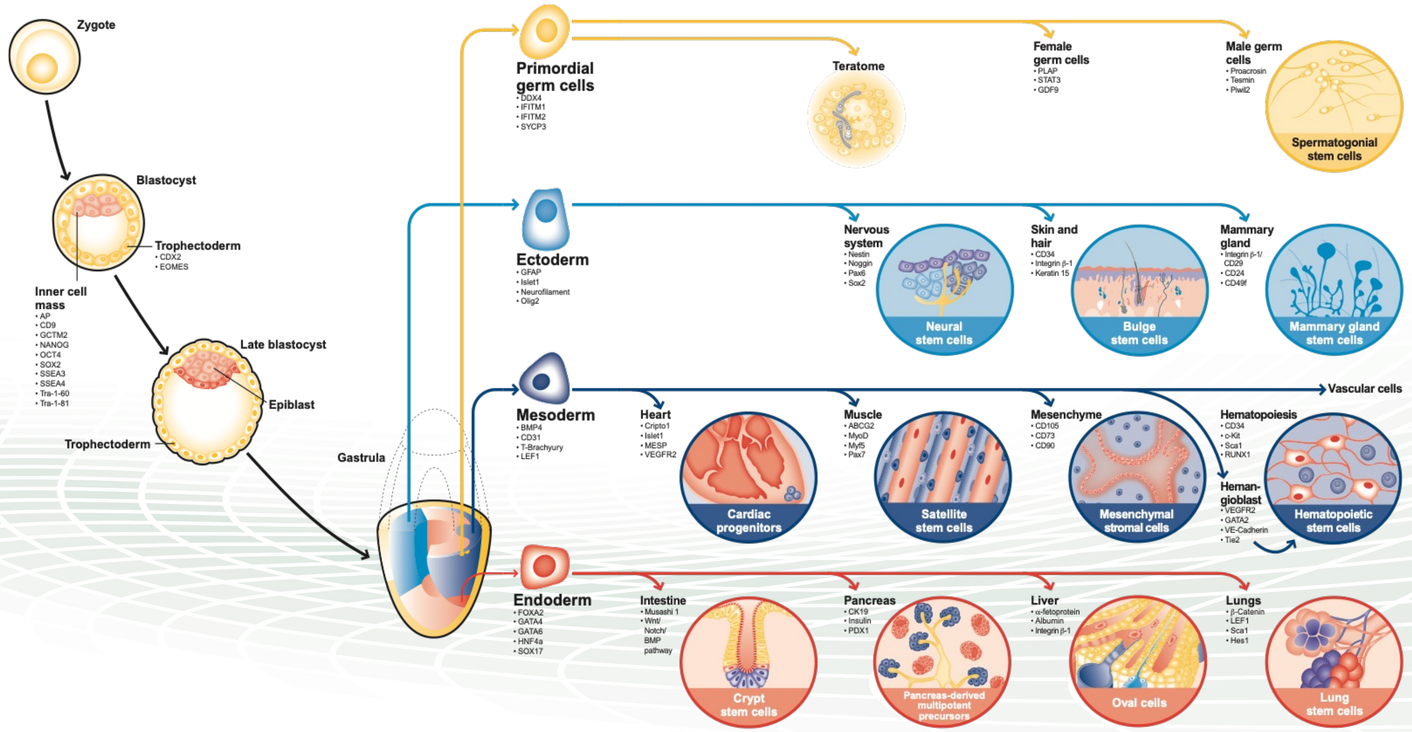
- Restricted duration of exposure
- Simplified biological system
- Interspecies differences



Reproductive cycle

Differentiation of human induced pluripotent stem cells (hiPSCs)

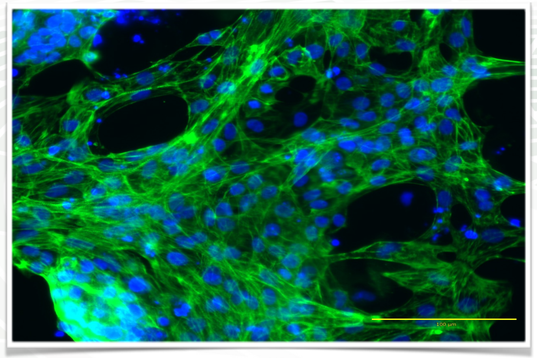
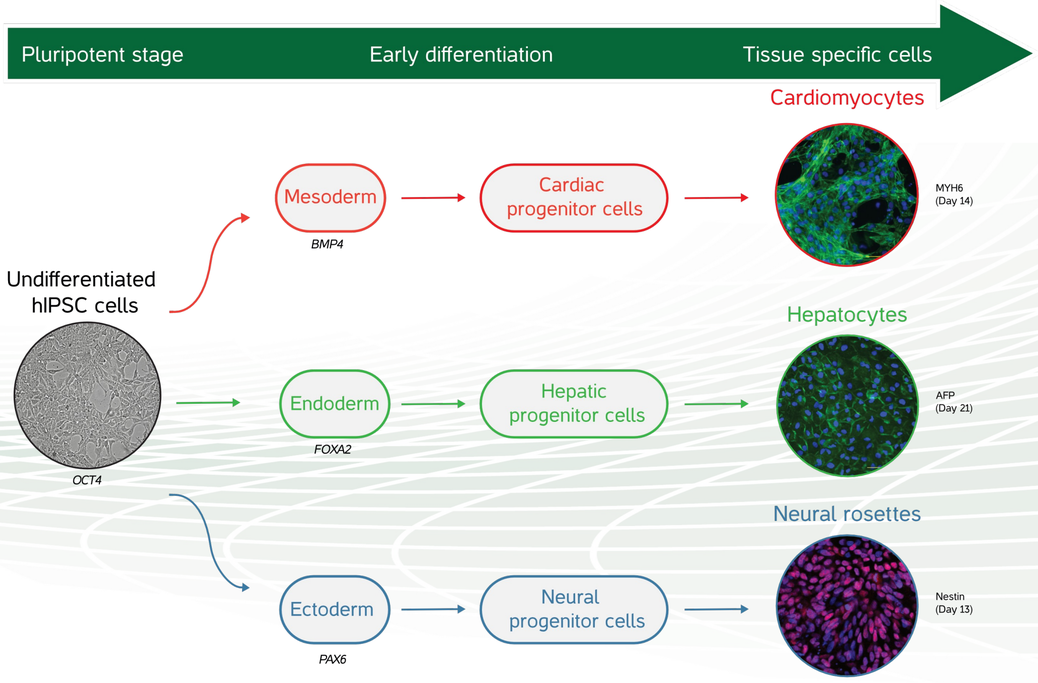
- Human material
- Differentiate into specialized cell lineages and specialized tissues
- Unlike human ESC, hiPSC have no ethical issues
- The principle is that the **adverse effects of chemical exposures on *in vitro* differentiation** are correlated to developmental toxicity.



https://www.abcam.com/research/stem-cells

The ReproTracker® assay

Key features:

- Human test system
- *In vitro* development of functional heart, liver and neural tissues
- Visualization of the key cellular events of early embryonic development
- Detect disruption of developmental program based on morphological and molecular read-out

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