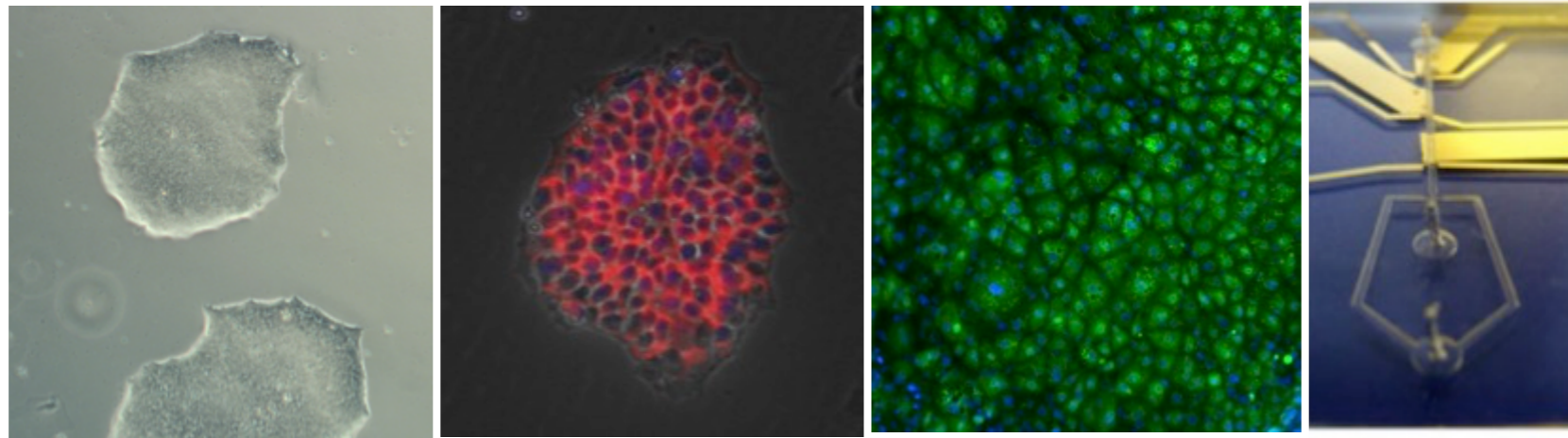




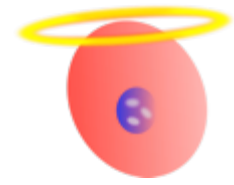
Liver on a chip: Bioengineering for novel drug development



**Dr. Ruchi Sharma
CEO**

Stemnovate Limited
3 Charles Babbage Road
Cambridge CB3 0GT

www.stemnovate.co.uk



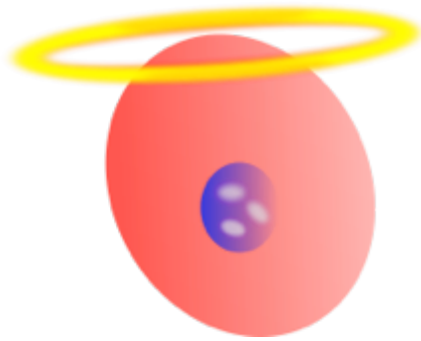
Stemnovate

Your drug discovery partner....

Accelerate drug development

Reduce R&D cost

Improve safety



Stemnovate's compliant platforms integrate somatic stem cell models 'on a chip' as the novel bioengineered solution for drug-screening and safety testing.

Milestones

Startup Founded.

April 2016

Operations Started

June 2017

Secured \$1 Million in Innovate UK grant.

August 2017

Top Pharmaceutical collaboration.

August 2017

Investment Raised

October 2017



Innovate UK

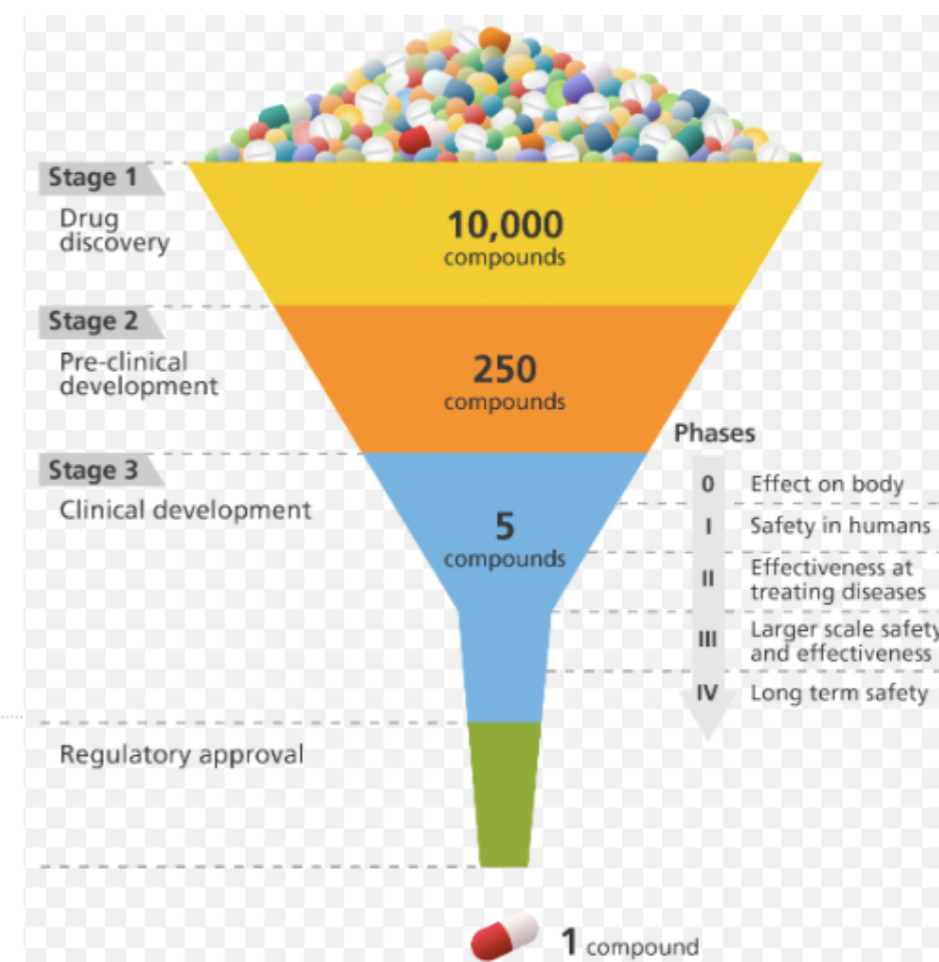


Big Problem : DRUG FAILURE

- ☑ Drug discovery is time consuming
- ☑ Late stage failures are expensive
- ☑ 'One size fits all' risks patient safety

AMERICAN HOLOCAUST – ADVERSE DRUG REACTION (ADR) – PREVENTABLE DEATHS: Public Health Crisis – 440,000 Preventable Medical Deaths Per Year – 4.4 Million Deaths over 10 Years

JANUARY 5, 2014 BY ADMIN



\$2.6 billion

Second Problem: Research Translation

Poorly designed animal experiments in the spotlight

High-status journals or institutions no guarantees of carefully-reported trials.



nature International weekly journal of science

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NATURE | NEWS

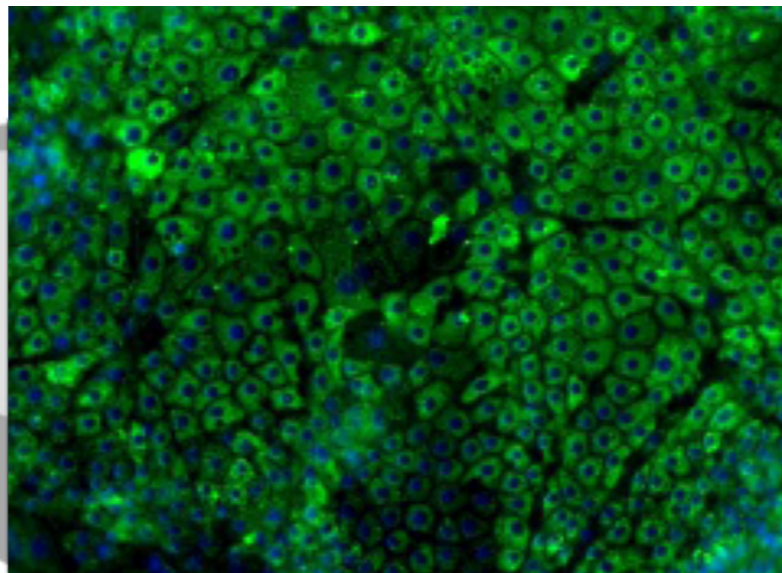
Biotech giant publishes failures to confirm high profile science

Amgen posts three studies at new online channel for discussing reproducibility.

Liver on a chip: Hepatotoxicity

462 medicinal products withdrawn from the market between 1953 and 2013, the most common reason being hepatotoxicity.

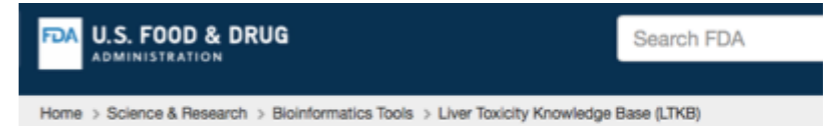
(Onakpoya et al. BMC Medicine, 2016)



38% and 51% of compounds showing liver effects in humans do not present similar effects in animal studies.

(FDA, Guidance for Industry: DILI Premarketing DILI Evaluation)

ADME Toxicology Market
\$ 16.34 Billion (2024)
in vitro ADMET 20% CAGR



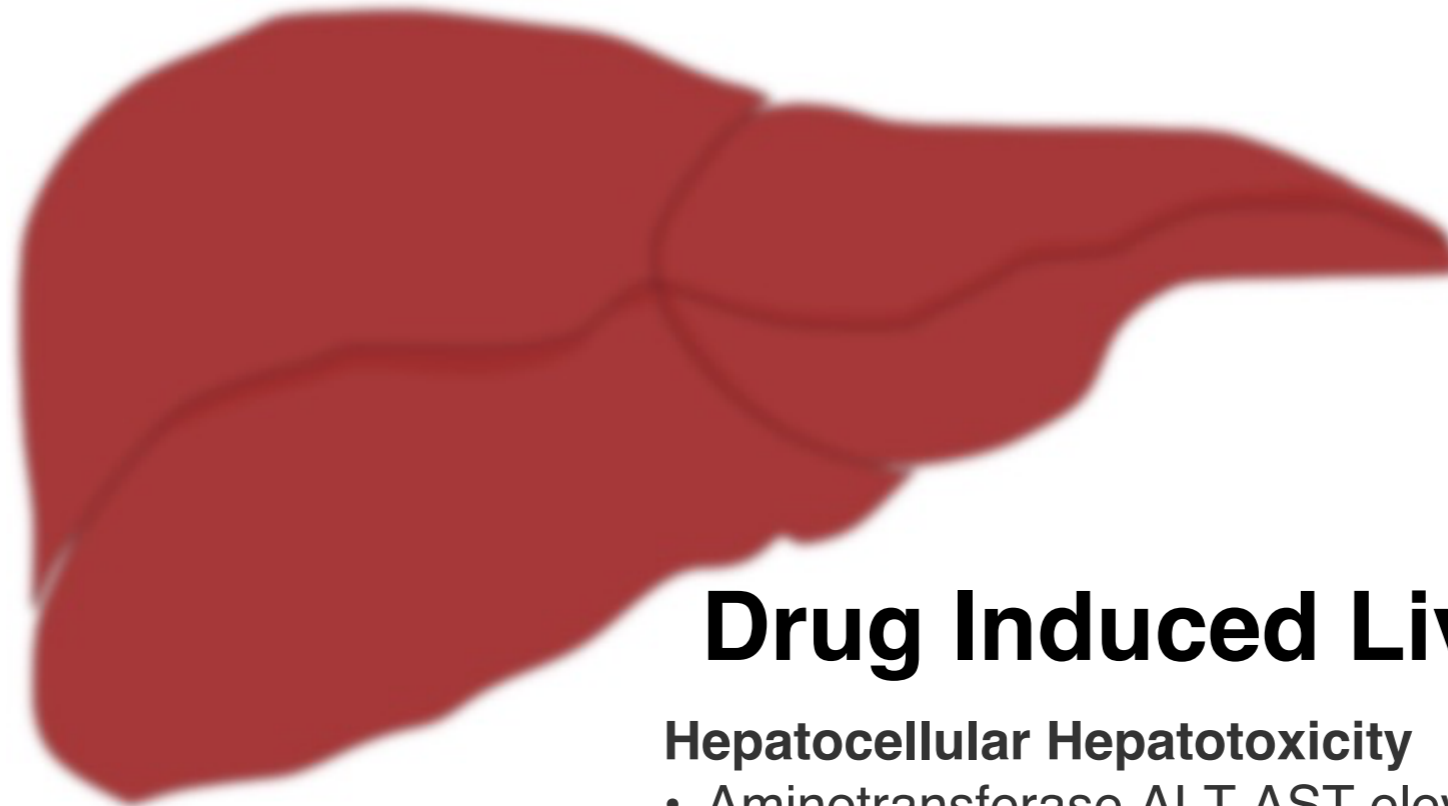
Liver Toxicity Knowledge Base (LTKB)

DILI identified as a key area of focus in FDA's **Critical Path Initiatives**

Liver: Drug Metabolism

Biotransformation : Phase I (Endoplasmic Reticulum) Oxidation & Reduction
Phase II (Cytosol) conjugation

Cytochrome P450
eg. CYP1A2
Induction Smoking
Inhibitor Grapefruit



Drug Induced Liver Injury

Hepatocellular Hepatotoxicity

- Aminotransferase ALT,AST elevated
- Hepatocellular jaundice, mortality 50%
- Jaundice, encephalopathy, liver transplantation
eg: acetaminophen and isoniazid

Cholestatic hepatotoxicity

- Pruritus
- Jaundice elevation in alkaline phosphates
eg: Amoxicillin and Chlorpromazine.

DILI & Drug withdrawal

Withdrawn from Marketplace

- **Bromfenac** painkiller
- **Troglitazone** anti diabetic
- **Pemoline** attention deficit disorder and narcolepsy
- **Felbatanol** anti epileptic



Limitations of use because of hepatotoxicity

- **Felbamate (Felbatol)**, an antiepileptic
- **zileuton (Zyflo)**, asthma
- **Tolcapone (Tasmar)**, Parkinson disease
- **Trovafloxacin (Trovan)**, antibiotic
- **Benoxaprofen** NSAID
- **Tienilic acid**, a diuretic

FDA Drug Safety Communication: New Boxed Warning on severe liver injury with propylthiouracil

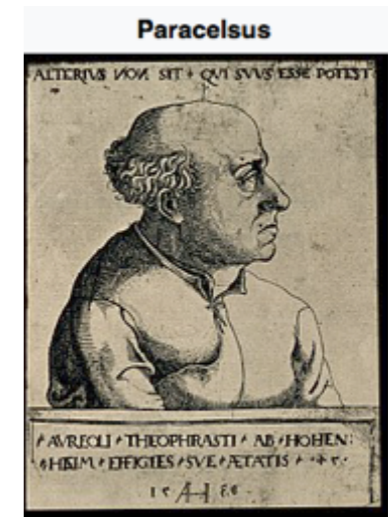
Drug Induced Liver Injury

Is It a Bad Drug?

‘Sola dosis facit venenum’

The dose makes the poison

- Paracelsus



Is It a Susceptible Patient?

- Responsiveness to certain drugs is different for men and women
- Elderly are more susceptible than young



57 genes encode Cytochrome P450

CYP2D6 is highly polymorphic: 3 phenotypes

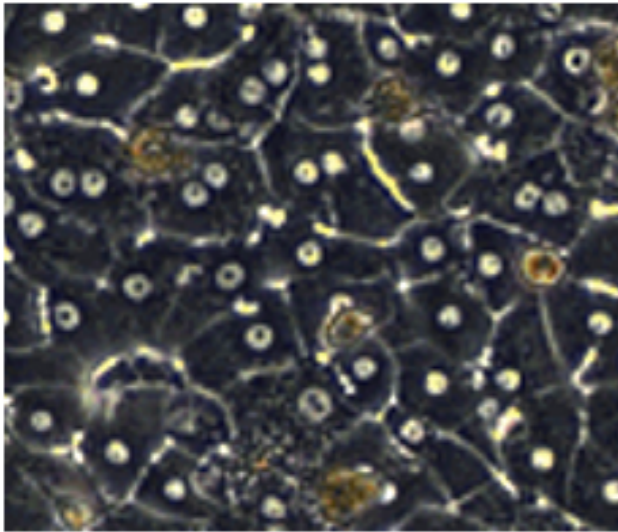
- **Extensive metabolizers** have functional enzyme activity
- **Intermediate metabolizers** have diminished enzyme activity
- **Poor metabolizers** have little or no activity

eg. 5-10% of Caucasians and 1-2% of Asians



Is It the testing?

Primary human hepatocytes



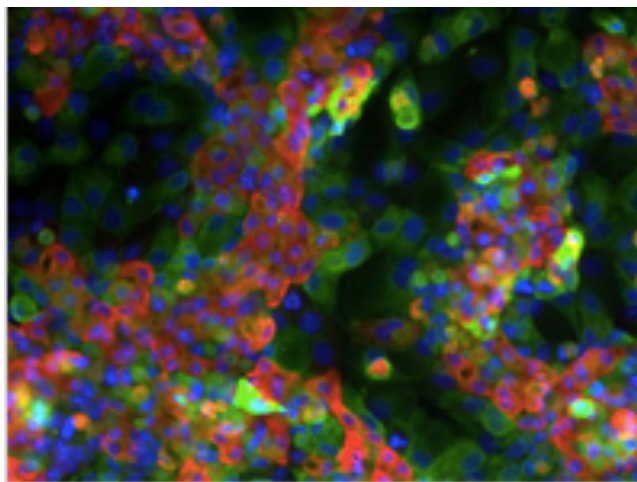
The supply of(PHHs) is limited and sporadic.

- Little growth capacity, have a short lifespan
- Lose their differentiated functions when cultured even for a few days.
- Large donor variations, especially CYPs.



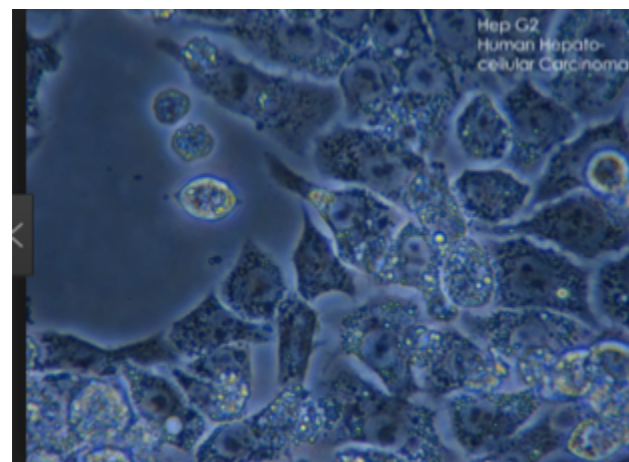
Scientists Have Conducted Decades of Research on Mislabeled Cell Lines

September 8, 2016 // 08:00 AM EST



HepaRG

- **Tumor derived line** (female patient chronic hepatitis C infection and hepatocarcinoma)
- Ductular structure cells rather than mature hepatocytes or bile ducts

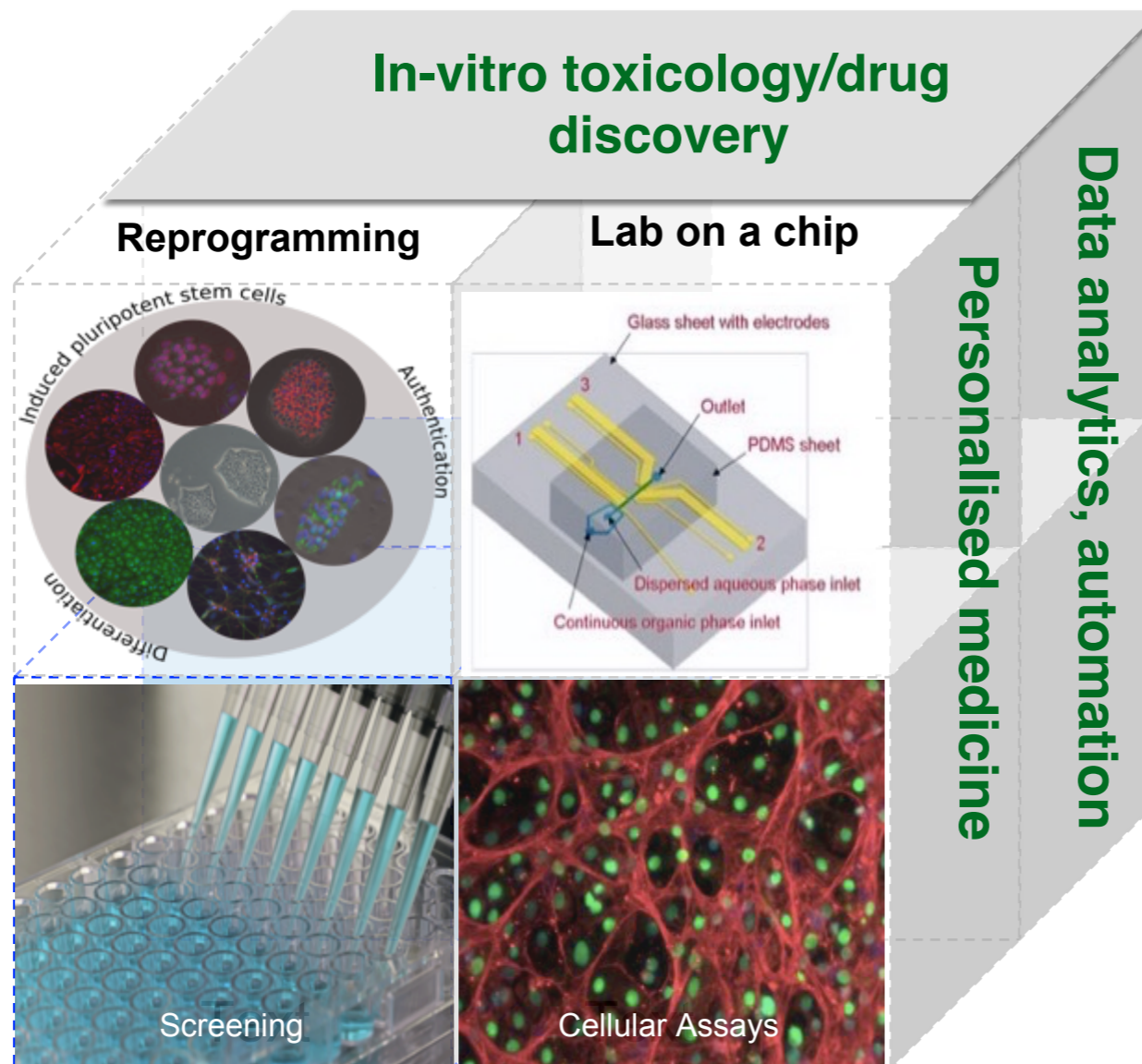


Hep G2

- **Tumor derived line** (15-year-old Caucasian American male hepatocellular carcinoma)
- Chromosome number 55

Stemnovate's solution

'Liver on a chip' is aimed to deliver an in-vitro testing platform that could show the liver response to evaluate predictable and unpredictable hepatotoxins over the breadth of the genetically diverse human population.



- ✓ Mass production
- ✓ Quality Control/assurance
- ✓ Regulatory Compliance

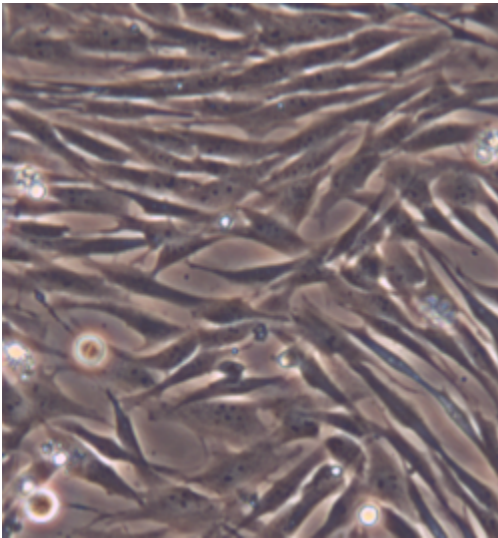
Applications

- ✓ Profiling
- ✓ Hit to Lead
- ✓ Lead Optimisation
- ✓ Preclinical
- ✓ Clinical R&D

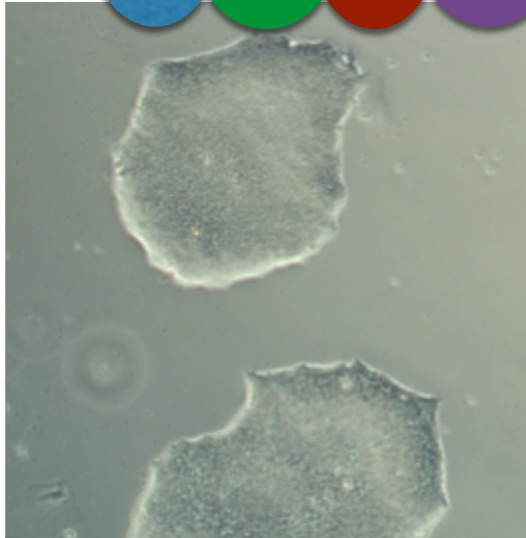
Liver on a chip: Creating human organ microsystem



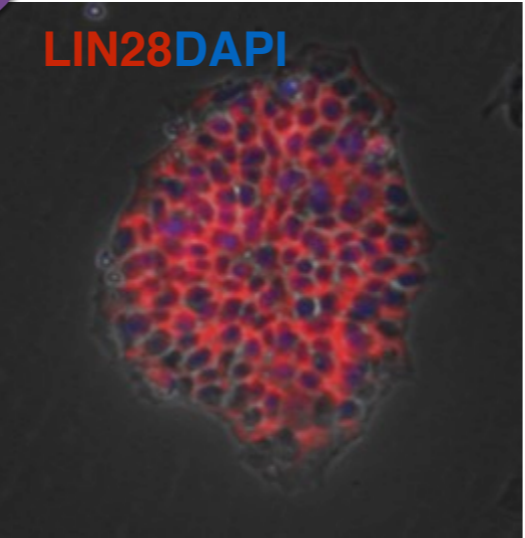
Non-integrating reprogramming technique



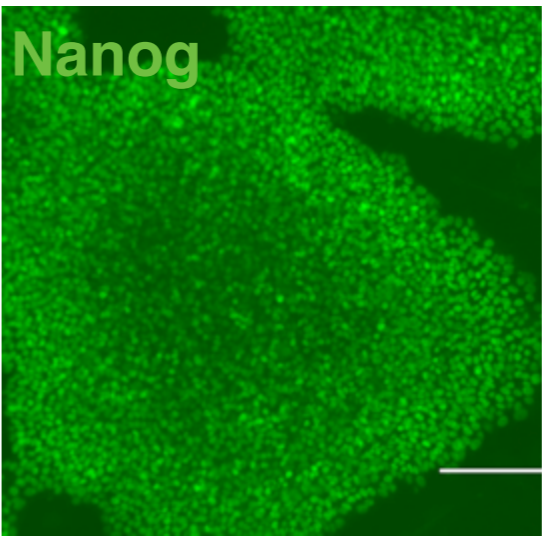
Fibroblasts



IPSC Colonies

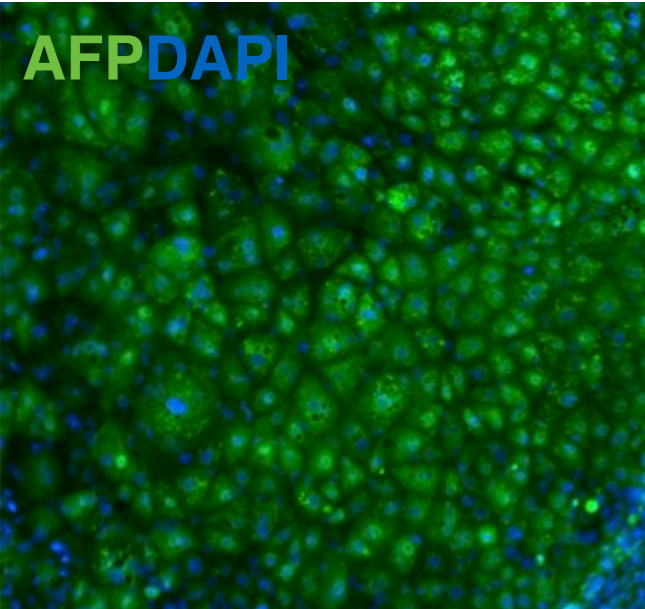


Pluripotent IPSC line



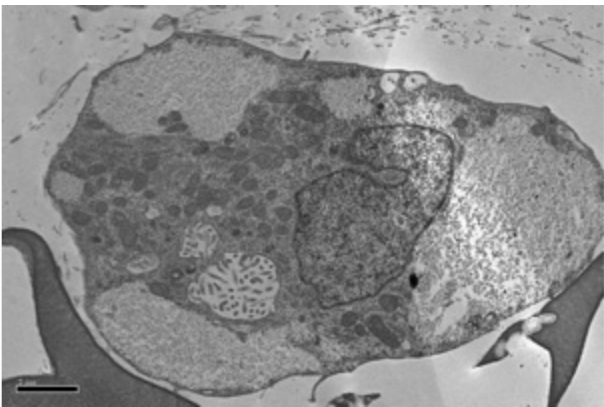
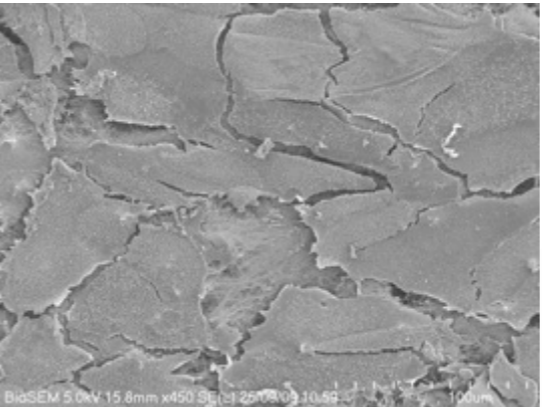
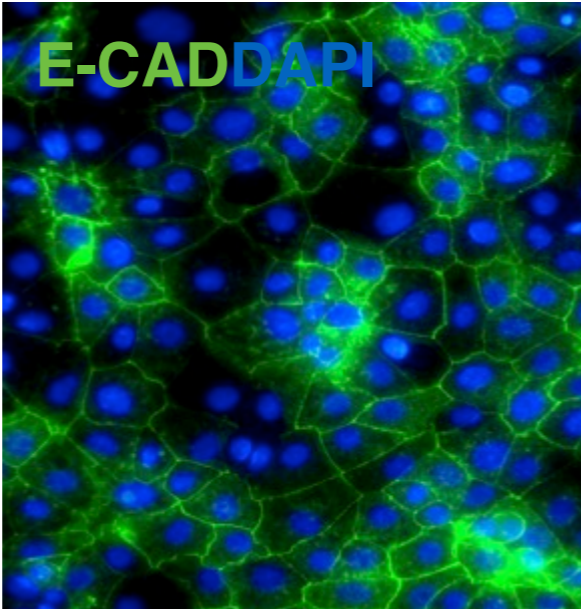
1

Representative human genomic variability



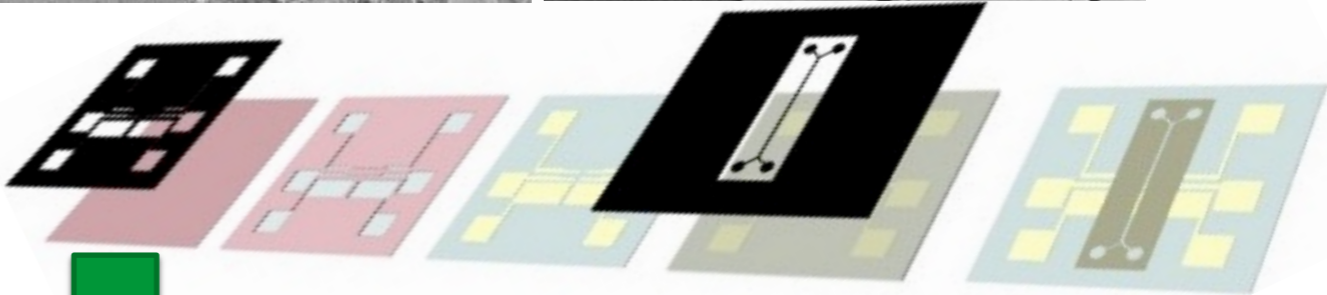
2

Renewable source of functional Hepatocytes



3

Microphysiological modelling

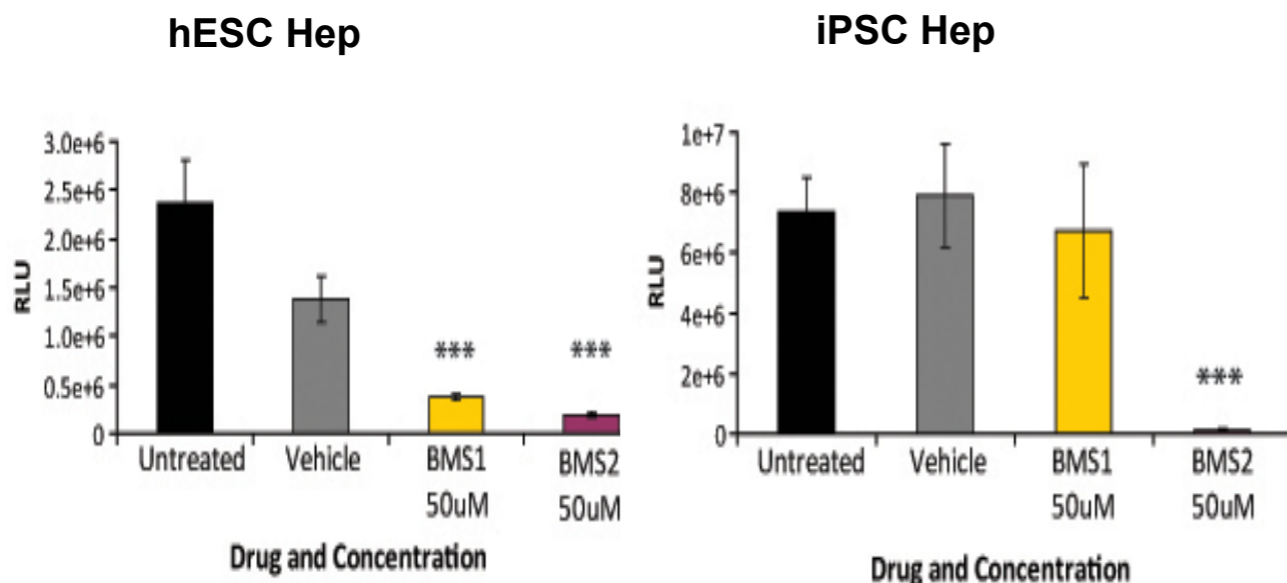


Background to our 'Liver-on-chip' technology



First report, Industrial Validation in collaboration with Bristol Mayer Squibb that hepatocytes derived from pluripotent stem cells have functionality equivalent to cryopreserved hepatocytes

Latest report, Hepatocytes derived from Pluripotent stem cells showed similar patterns of gene expression and also arranged themselves to form complex structures that are found in liver tissue'



IC50 Values similar to primary hepatocytes

Metabolite Induced Toxicity

Medine et al 2013, Stem Cells Translational Medicine

MRC Medical Research Council
Leading science for better health

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Home > News > News and features > Liver cell therapies closer as study reveals key to mass production

NEWS

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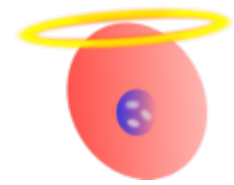
Video & audio

Contact the Press Office

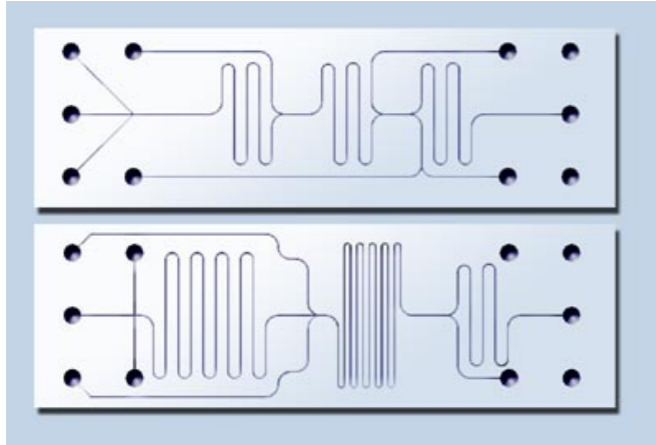
Liver cell therapies closer as study reveals key to mass production

Mass Production

<http://www.mrc.ac.uk/news/browse/liver-cell-therapies-closer-as-study-reveals-key-to-mass-production/>



Liver on a chip: Microfabrication



Materials

- PDMS (Polydimethylsiloxane)
- Glass

Thermoplastics :

- PMMA Polymethyl methacrylate (Plexiglass).
- PC Polycarbonate (Lexan)
- PS PolyStyrene (Tissue culture Plastic)
- COC Cyclic Olefin Copolymer
- COP Cyclic olefin polymers

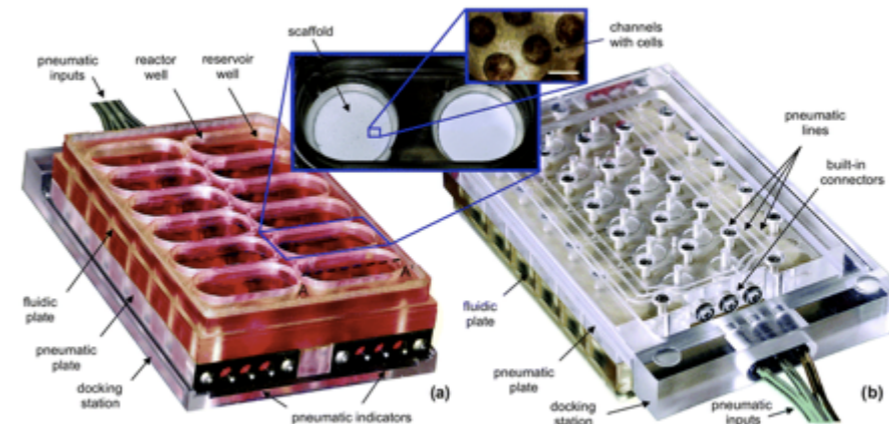
Hydrogels

Techniques

- Photolithography
- Soft lithography
- Micro contact printing
- Micromolding

Models

- Multiwell 2D pattern
- 3D Micro-pillar sinusoids
- Hepachip: Dielectrophoresis
- Liver slice in microfluidics



Domansky et al 2010

Microfluidics is the study of systems that manipulate or process small amounts of fluids within geometries measuring tens to hundreds of microns



Commercial Challenges and Opportunities

Compliance

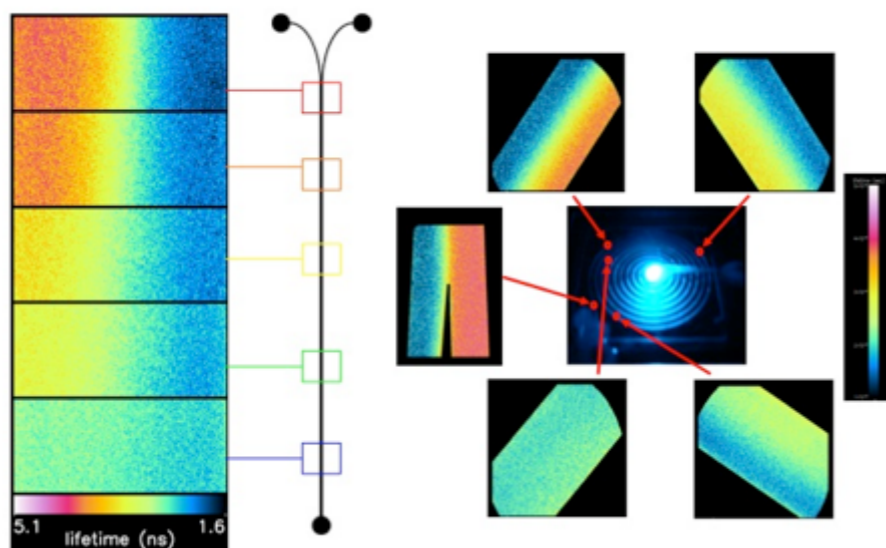
Consent
License
Patents

Designs

Material
Matrix
Cost

Assays

Functionality
Period of study
Industrial validation



Hepatotoxicity Mechanisms

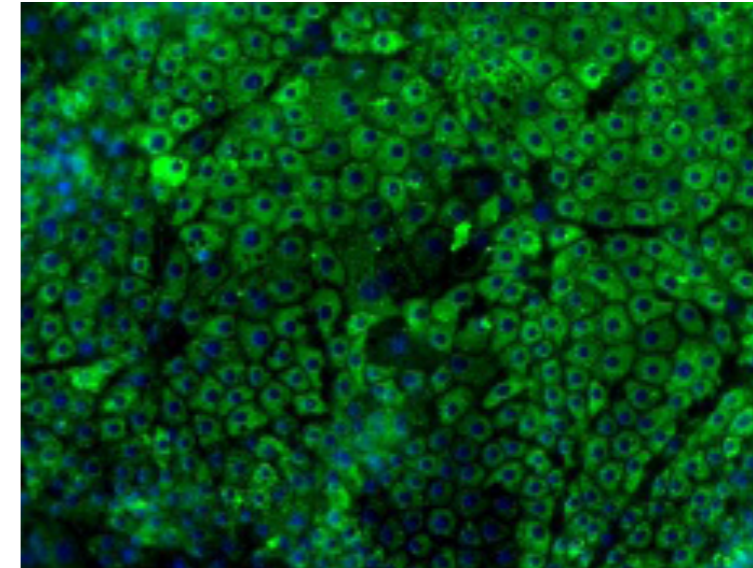
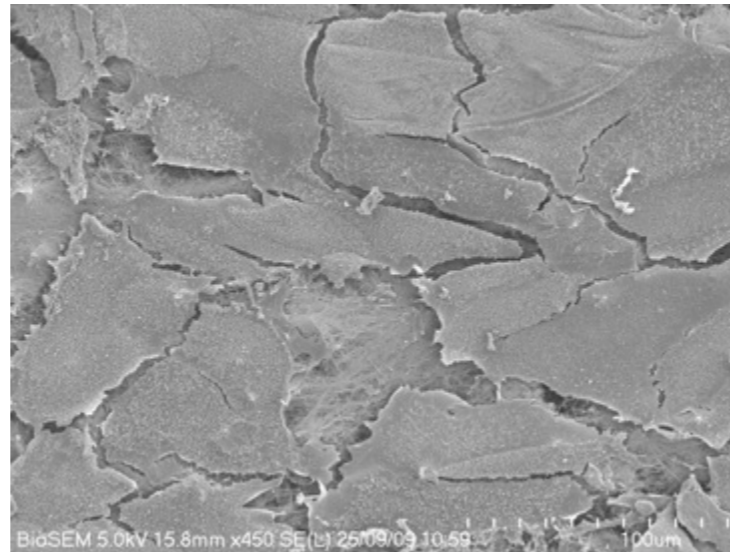
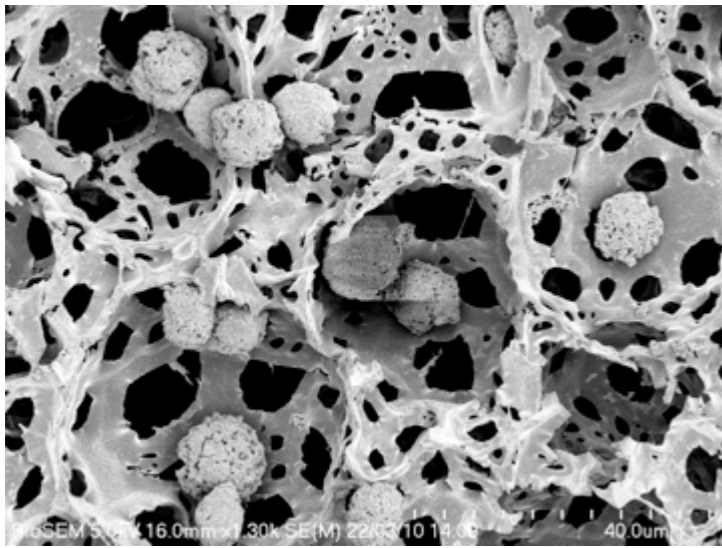
- Disruption of the hepatocyte
- Disruption of the transport Proteins
- Apoptosis of hepatocytes
- Mitochondrial Disruption
- Covalent binding to P450

A metabolic-idiosyncratic reaction

- Indirect metabolite.
- Variable response (within a week or up to one year later).

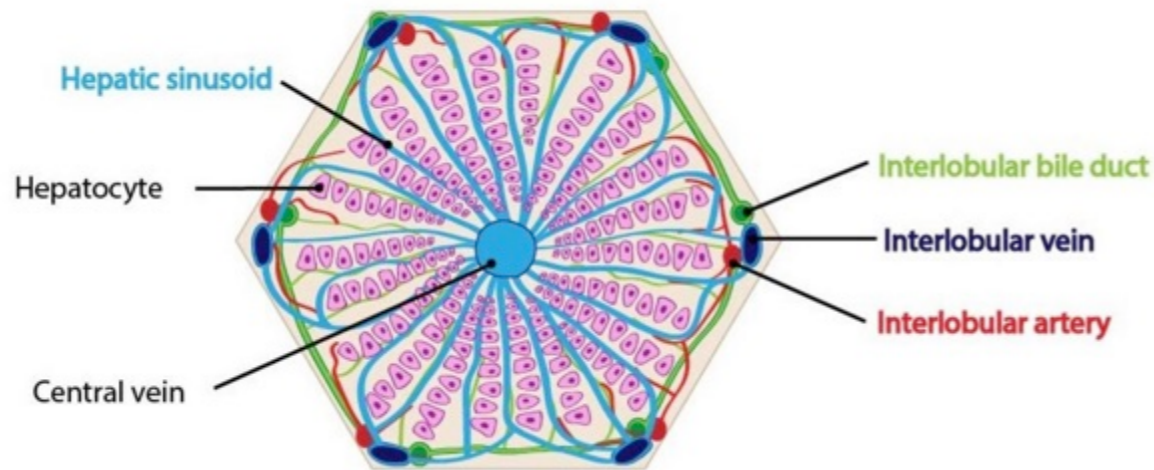
Microphysiological Modelling

Creating human organ microsystem for fast and effective evaluation of safety and efficacy in candidate therapeutics

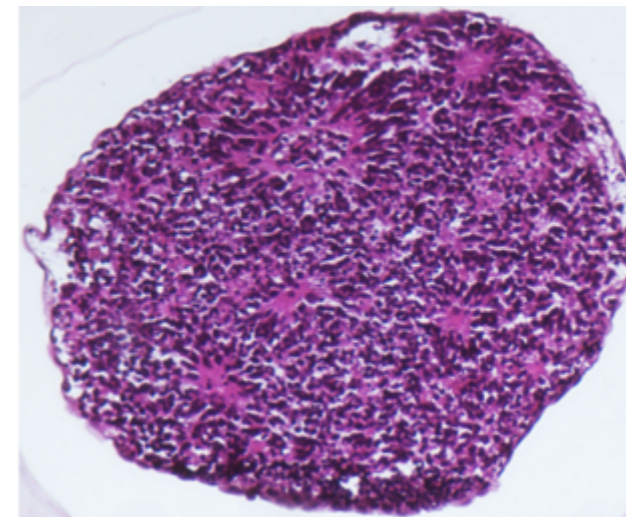


Primary Hepatocytes

Hepatocyte like cells



Hepatic lobule diagram



Spheroid culture

Unpublished

Team

iPSCs Research (8+)



Ruchi Sharma
PhD

Reprogramming, disease modelling, operations management commercialisation and regulation.

Founder|CEO

Hepatocyte Research (15+)



David Hay
PhD

Stem cell research, Hepatocyte differentiation, disease Modelling

Co-Founder|Director



THE UNIVERSITY
of EDINBURGH

Microengineering (20+)

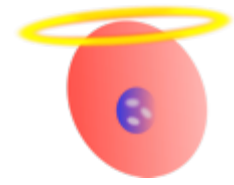


Dr. Adrian Fisher
D.Phil

Design, development and application of integrated microsystems.
Leading Electrochemical Multi-scale Science, Engineering and Technology or EMSET at Singapore

Co-Founder|Director





 **Cambridge**

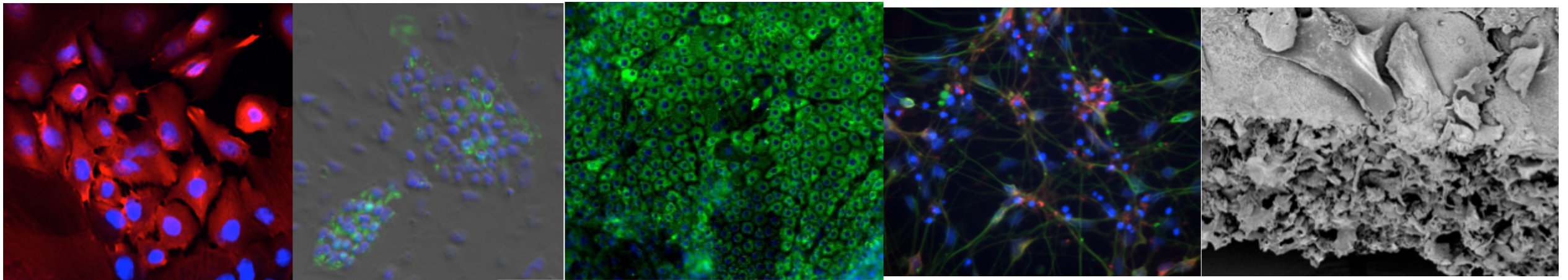


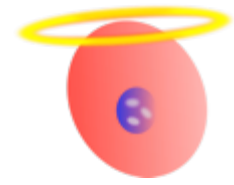
Babraham Research Campus

3, Charles Babbage Road

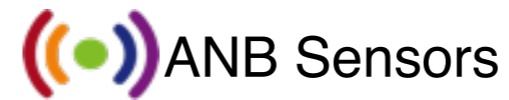
Summary

Innovative technologies for drug screening and safety testing provided by Stemnovate will improve drug development with an integrated personalised approach.





Collaborations



Grants

Innovate UK



Thank You

Stemnovate is the trading name of Stemnovate Limited, a business registered in England & Wales registered number 10140603.

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