Cambridge Stem Cell Initiative

Anne McLaren Laboratory for Regenerative Medicine

Cambridge **BRC**

Cambridge Biomedical Research Centre

World Stem Cells & Regenerative Medicine Congress 2012.

Wednesday, 23rd of May, 2012

Stratified medicine in a dish using human induced pluripotent stem cells

MRC | Centre for Stem Cell Biology and Regenerative Medicine
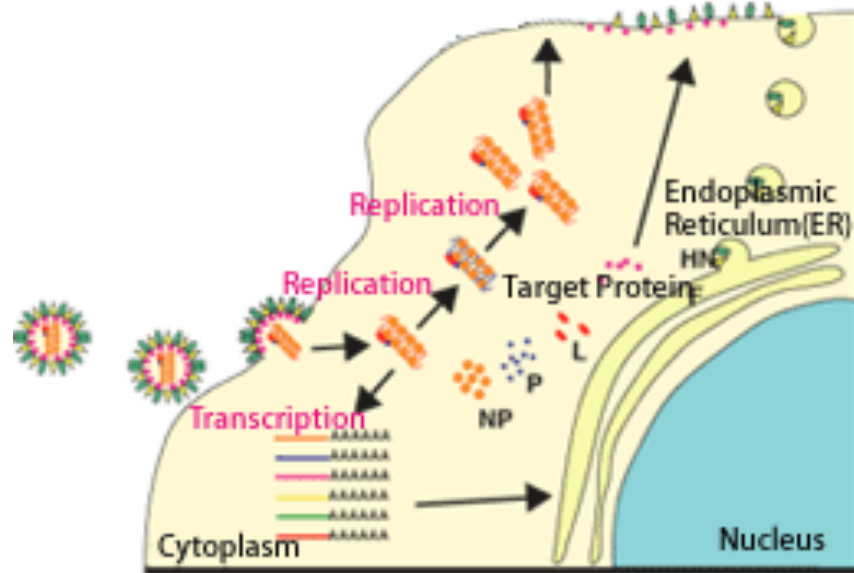
VALLIER Ludovic
lv225@cam.ac.uk

MRC centre for regenerative medicine

Clinical promises of hIPSCs

Sendai Virus to reprogram human somatic cells

Protocol to generate iPSCs from dermal fibroblast cells

Sendai Virus

2-3 wks   1 wk   4-8 wks   4-8 wks

Skin Biopsy ▶ Dermal Fibroblasts ▶ Transduction
Oct-4
Sox2
Klf4
+/- Myc ▶ hIPSCs ▶ Amplification
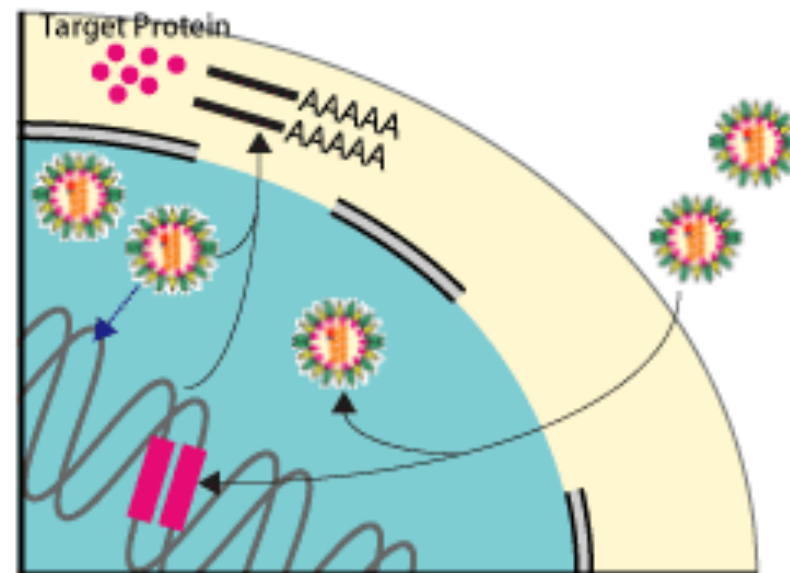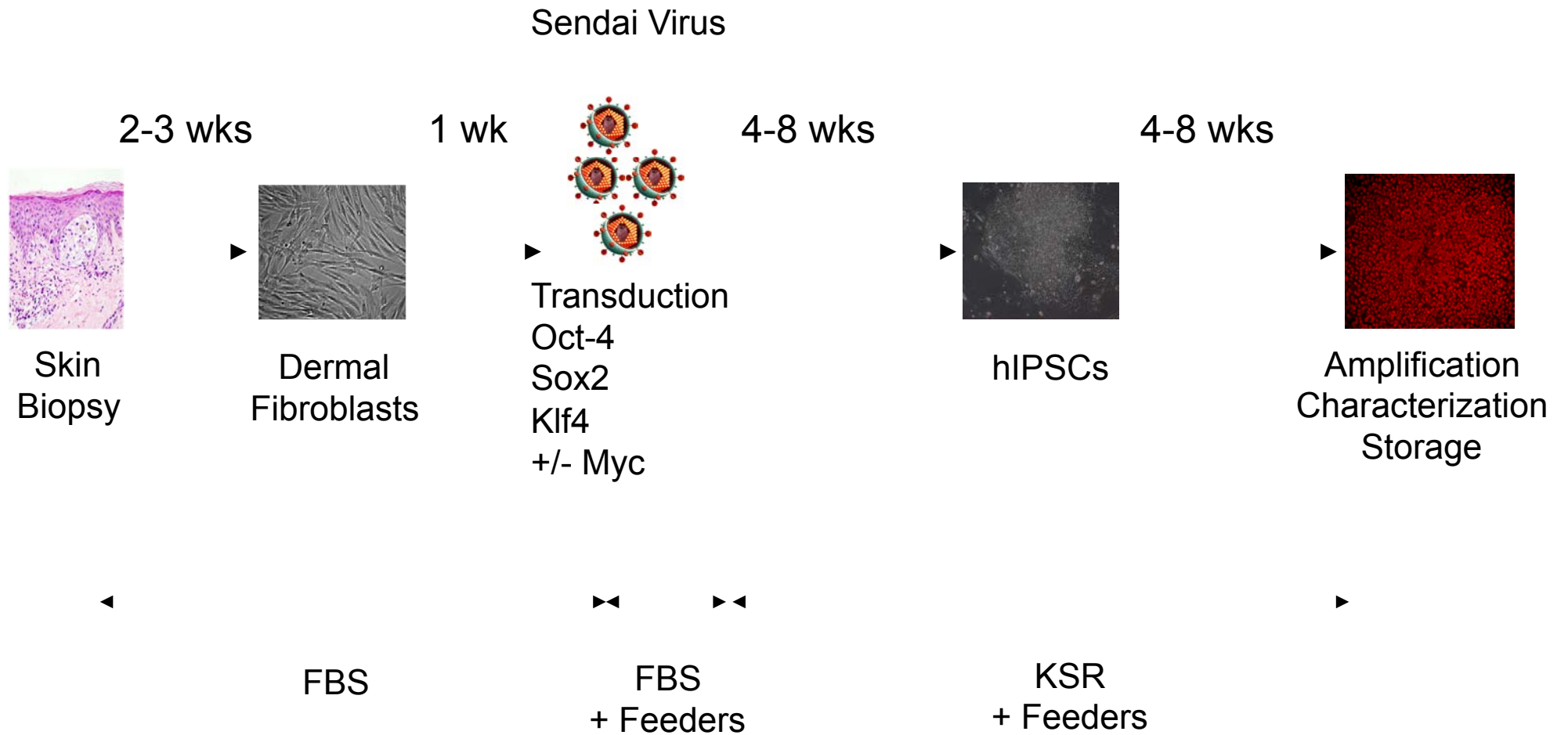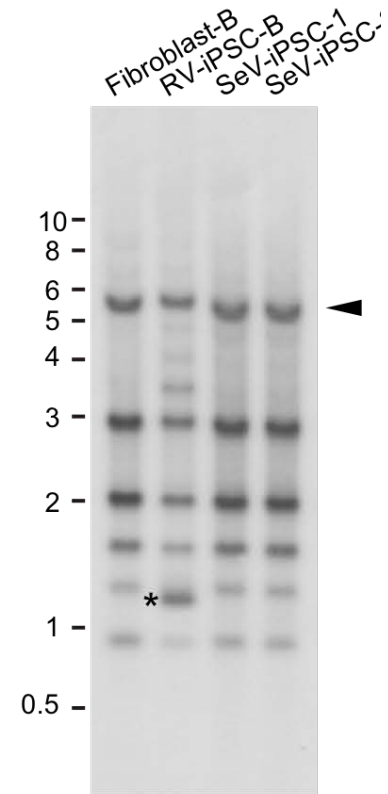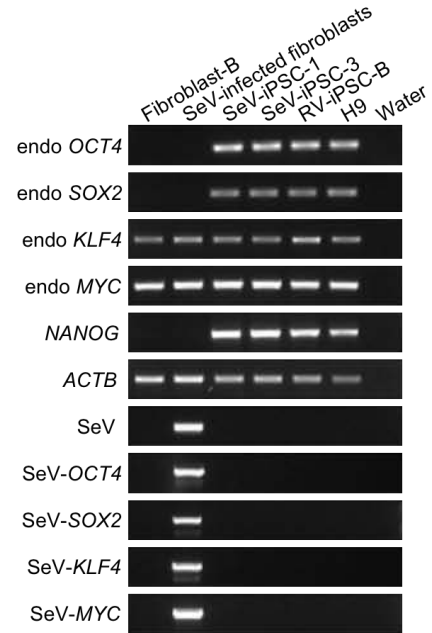Characterization
Storage

FBS   FBS
+ Feeders   KSR
+ Feeders
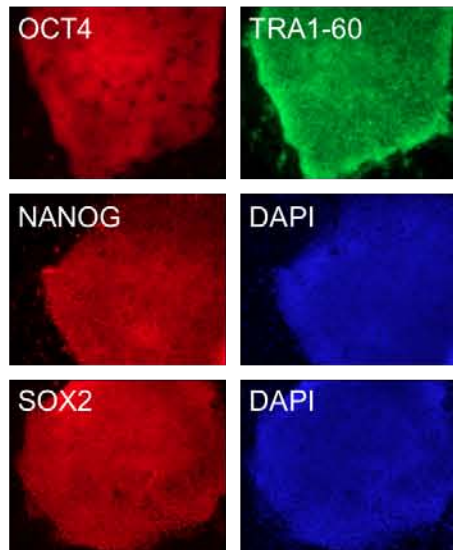
Sendai Virus to reprogram human somatic cells

Sendai Virus to reprogram human somatic cells

Neuroectoderm   Extraembryonic   Endoderm

SOX1   GATA6   SOX17

PAX6   GATA4   EOMES

NCAM   CDX2   FOXA2

SeV-iPSC-3 vs Fibroblast-B

DNAVec, Japan / Kosuke Yusa /Tamir Rashid
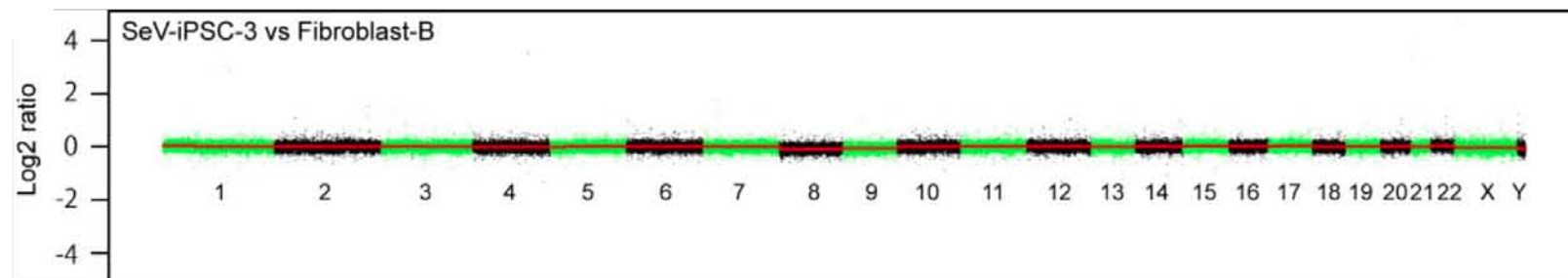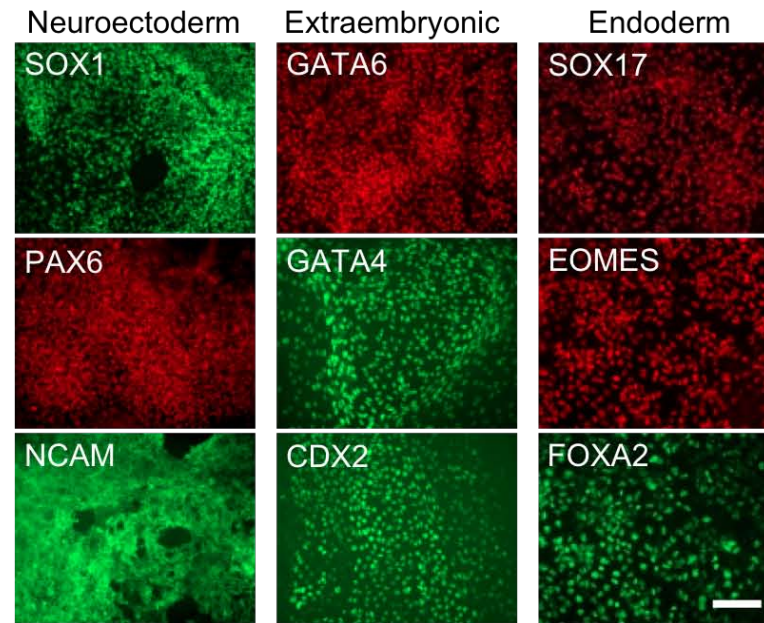
Clinical promises of hIPSCs
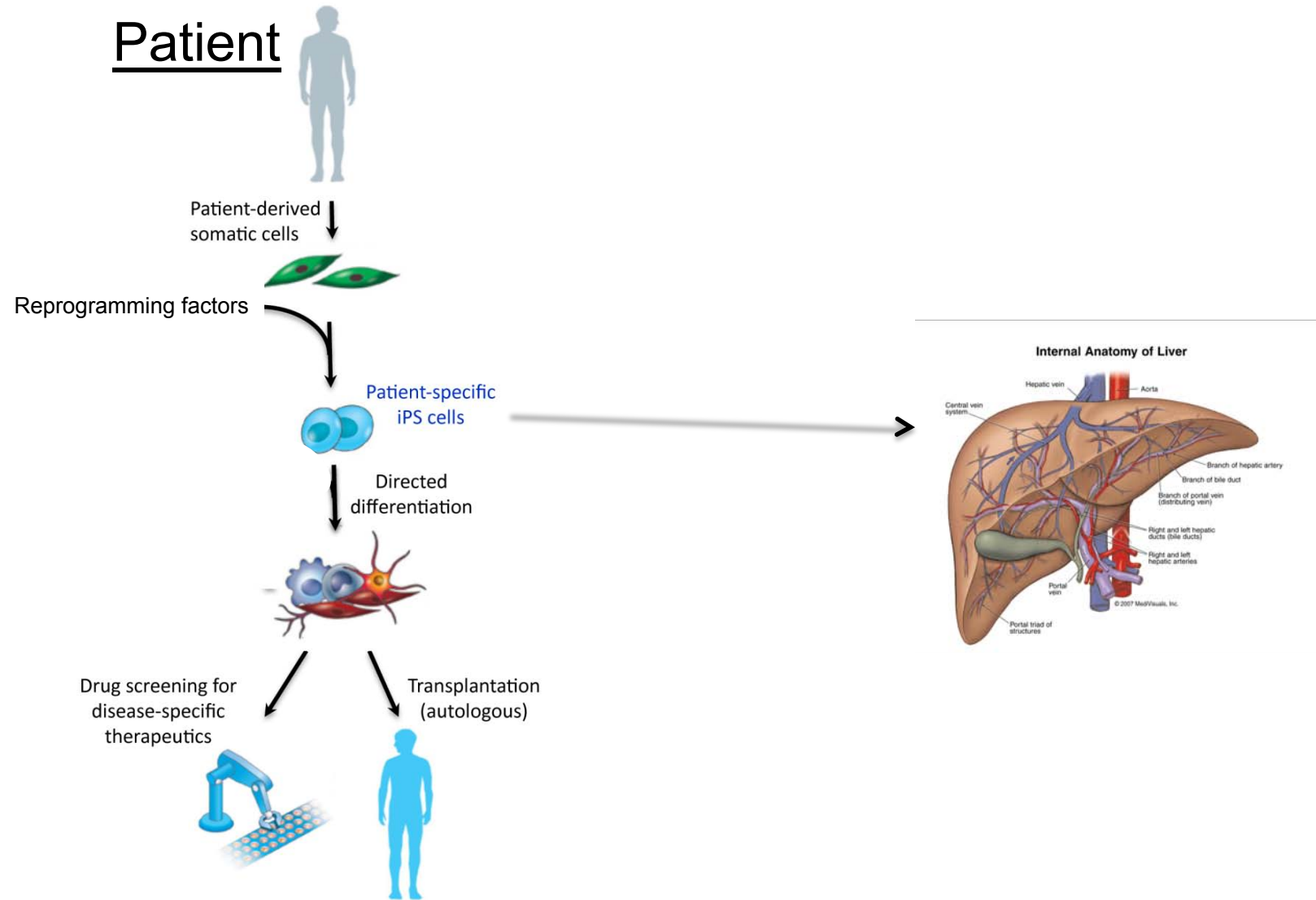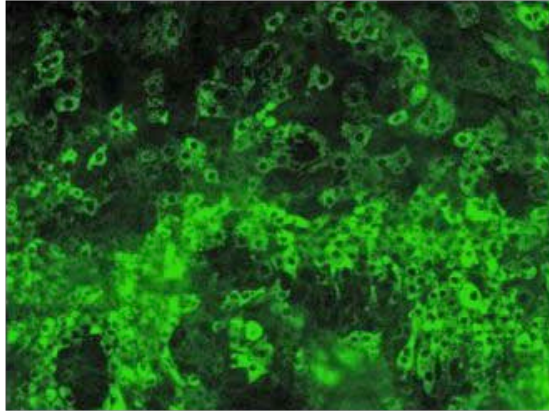
Differentiation of hPSCs in defined conditions allow the generation of near homogenous population of liver cells.
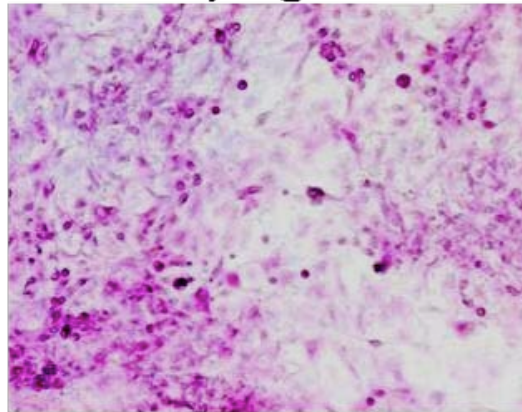
Nick Hannan / Candy Cho / Tamir Rashid
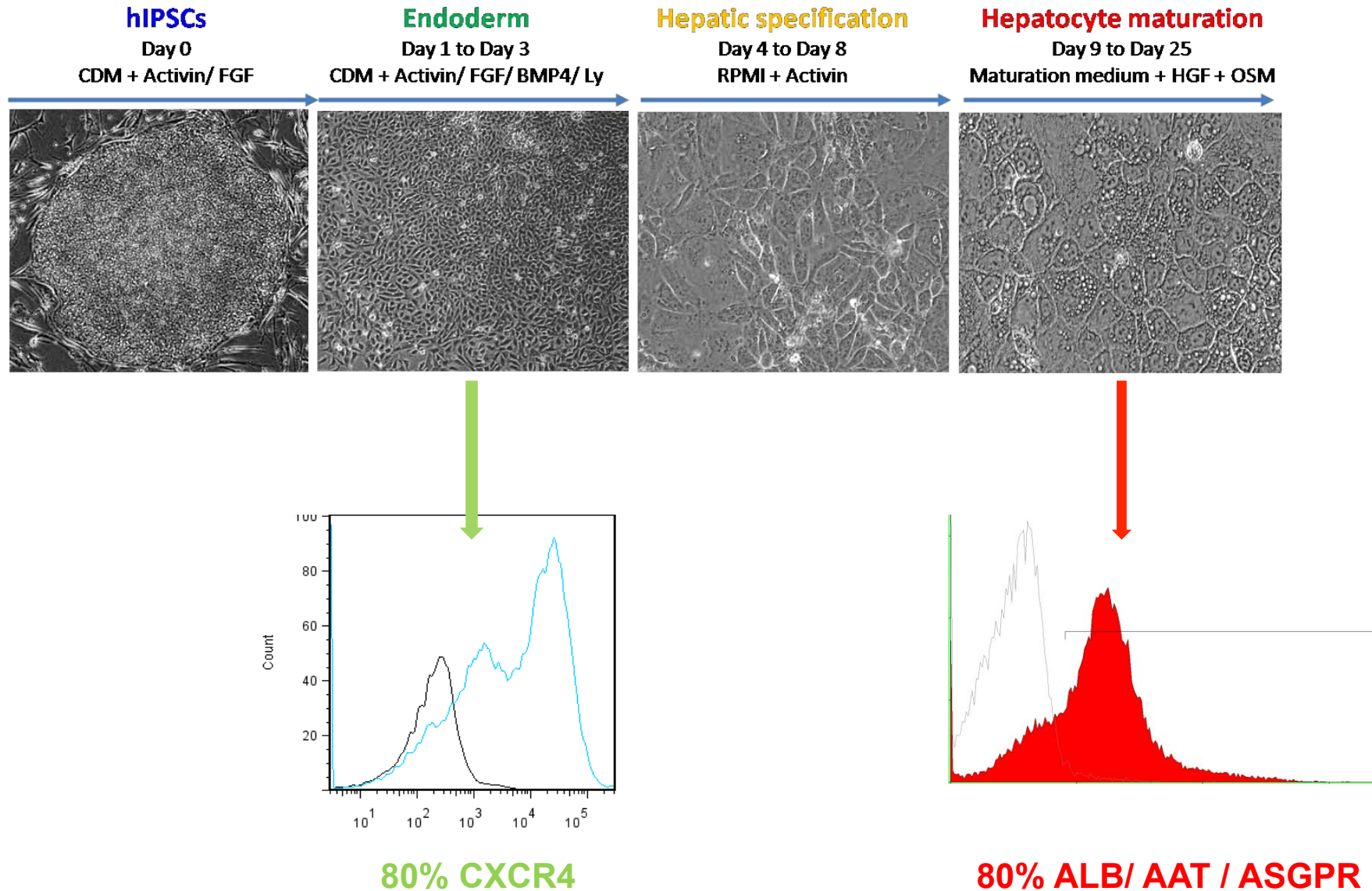
Differentiation of hIPSCs into hepatocyte like cells.

Albumin   Glycogen   LDL incorporation

Alb expression   ATT expression   AFP expression

Relative gene expression

Day 27 — Day 35 — Primary hepatocytes

Charis-Patricia Segeritz /Tamir Rashid
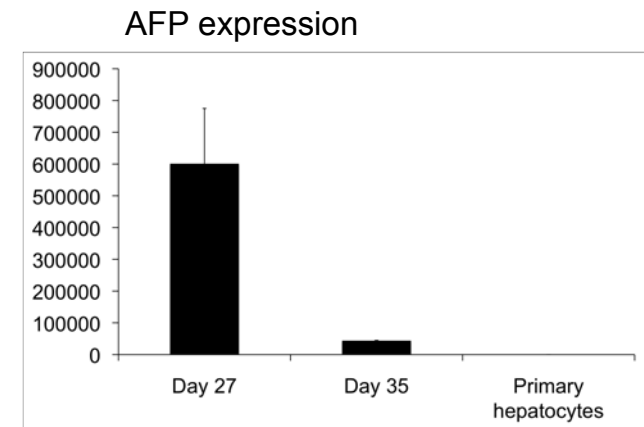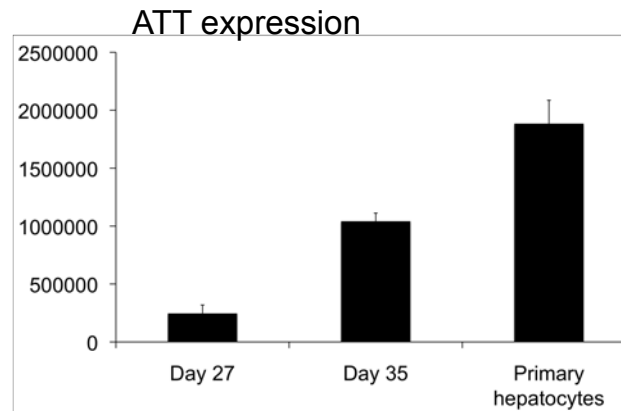
96 wells plate essay using hIPSC derived Hepatocytes

CyP3A4 activity

Miguel Cardoso de Brito

A disease specific hIPSC library

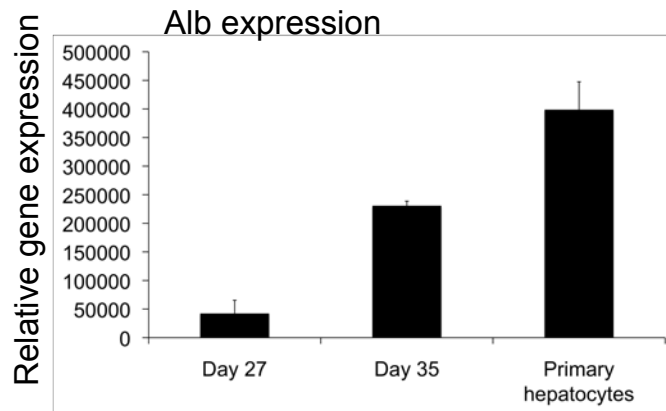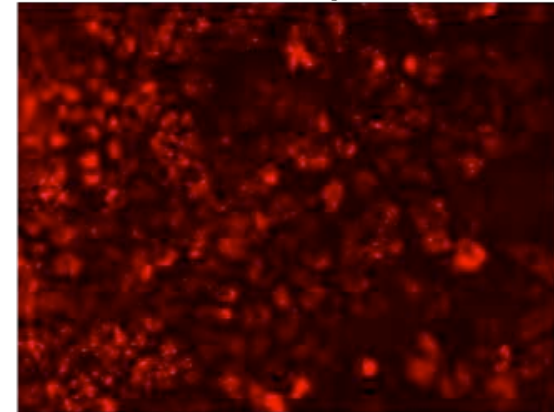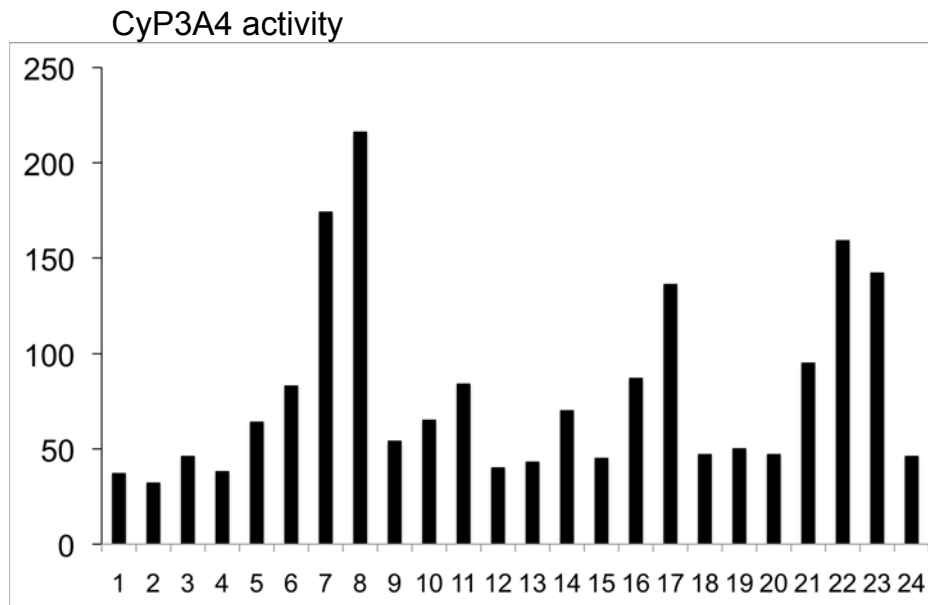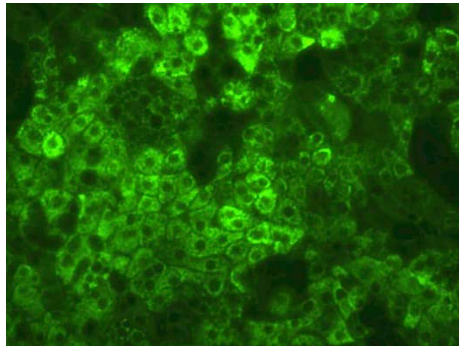| Disease	No. of patients sampled	No.of ips lines derived	No of ips lines characterized	No of ips lines differentiated to hepatocytes
Alpha 1 Antitrypsin deficiency	3	19	6	6
Glycogen storage disease type 1a	1	6	3	3
Familial Hypercholesterolaemia	1	9	3	1
Crigler Najjar Syndrome	1	6	3	1
Hereditary Tyrosinaemia Type 1	1	6	3	1
Control	2	12	6	6

Tamir Rashid

Glycogen Storage Disease Type1a

Tamir Rashid

GSD1a

CONTROL
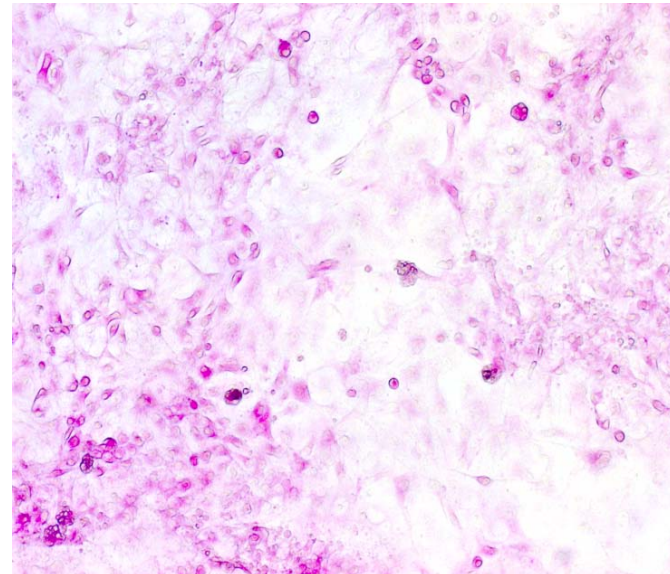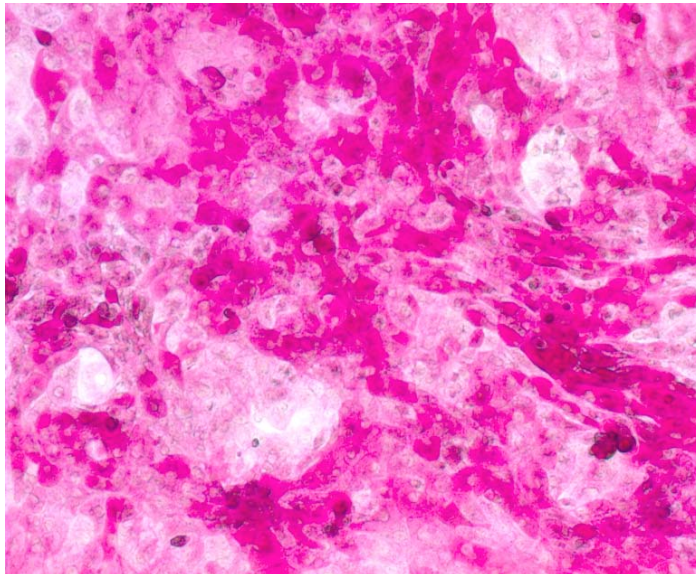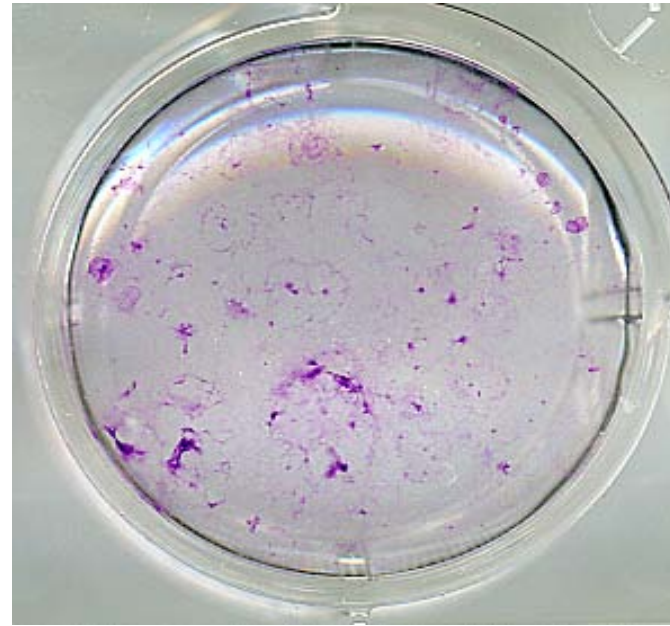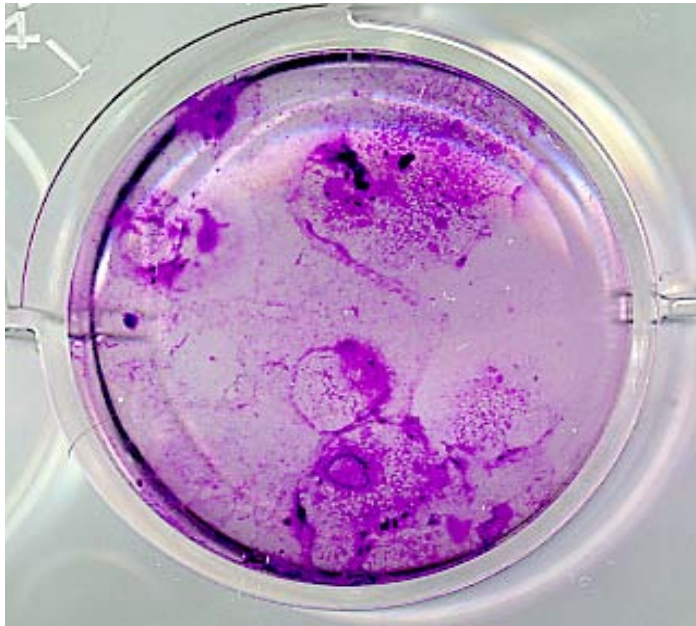
Co – immunostaining for total and polymeric AAT

Z

All AAT   **Polymeric AAT**   **All + Polymeric**

M

Tamir Rashid
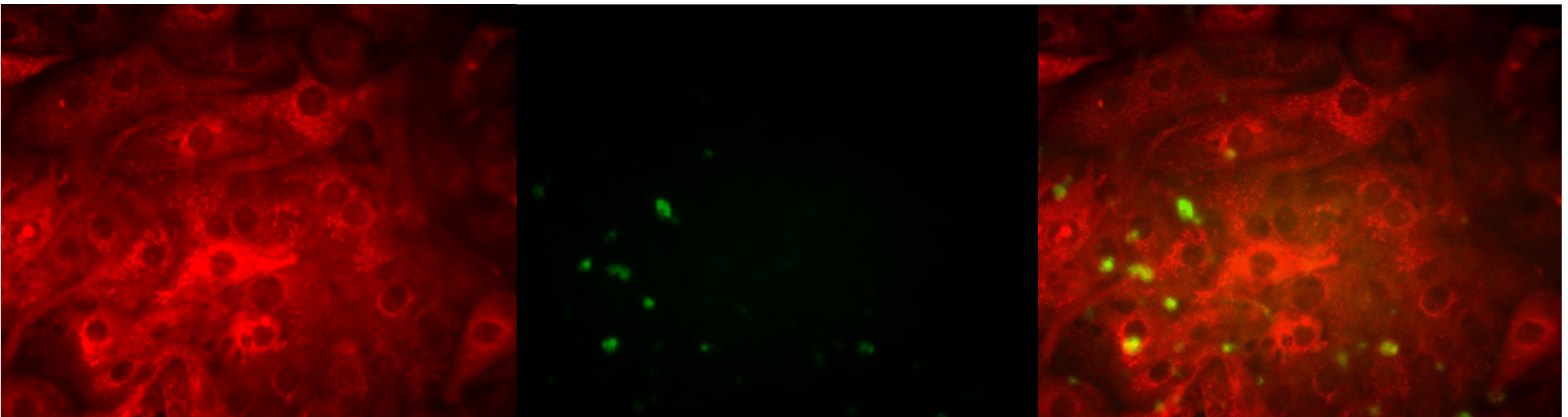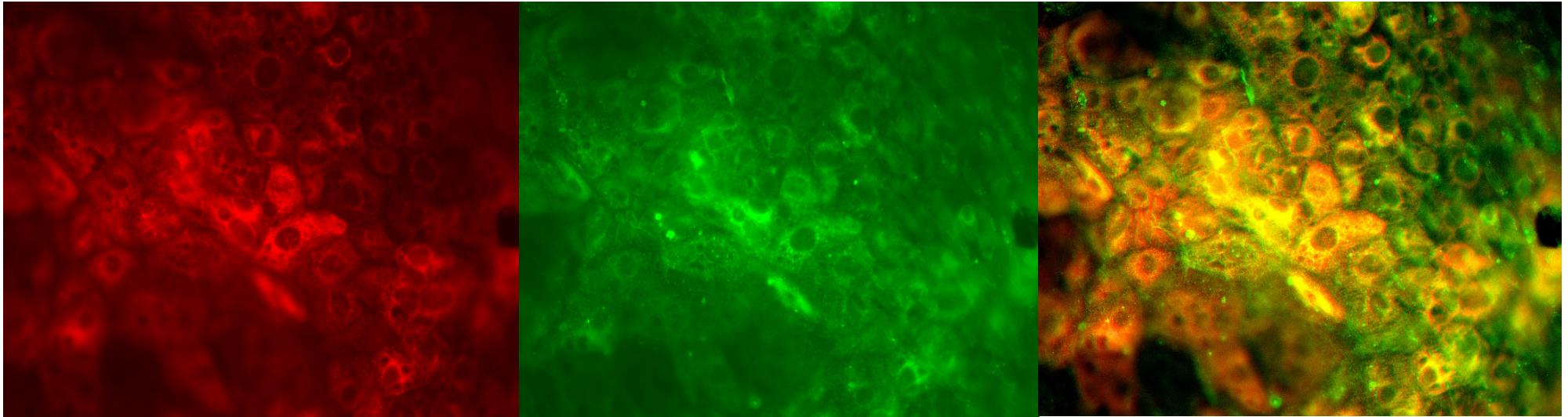
Summary and conclusions
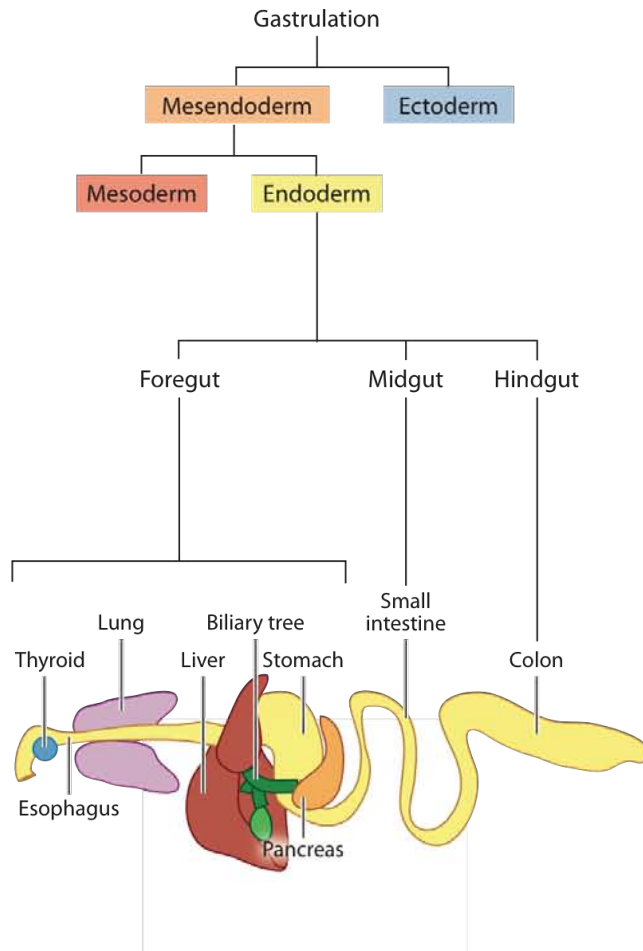
- ➤ Large scale derivation of hIPSC is feasible.

- ➤ A wide diversity of endoderm cells can be generated in vitro.

- ➤ Artificial DE derivatives are similar to their natural counterpart. Important for Regenerative Medicine.

- ➤ Protocol works with a broad number of patients > 60%.

- ➤ Variability between hIPSC lines is not provoked by differences between age, gender, method of reprogramming.

- ➤ Variability between hIPSCs is influence by genetic background of hIPSC and thus could be representative of human genetic diversity.

Launch of DEFINIGEN
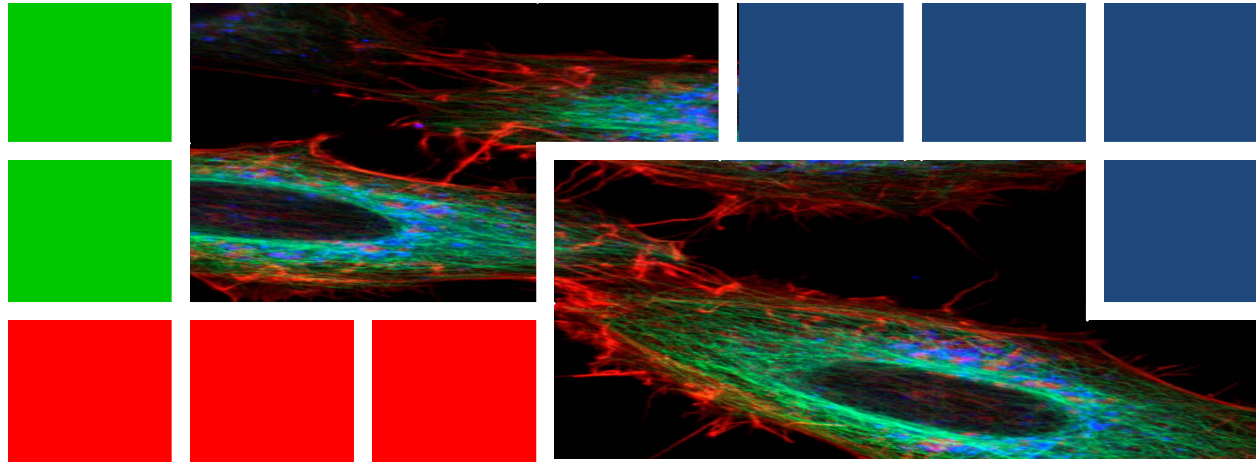
- Proprietary platform technology developed at the University Cambridge.

- Academic Founders: Ludovic Vallier, Tamir Rashid and Roger Pdersen

- CEO: Marcus Yeo

DEFINIGEN MISSION
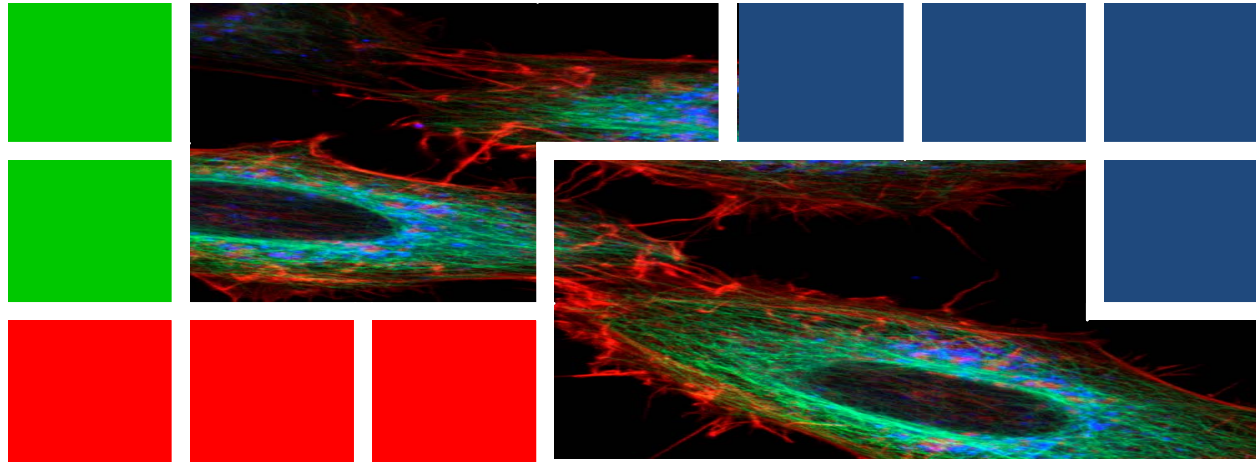
- To decrease costs of bringing drugs to the clinics

- To generate Primary human cells universally recognised as the predictive gold standard model in preclinical development – screening & toxicology

  First product: Hepatocytes for predictive toxicity model

- To meet the unmet need - provision of stem cell products with the functionality of primary cells will significantly improve the efficiency

- To explore Regenerative Medicine application (long Term objectives)

Acknowledgements

Collaborators

Cambridge

LRM
Roger Pedersen
Matthew Trotter
Sanjay Sinha
Kim Jensen
Mark Kotter

Cardio-Vascular
Nick Morell/ Amer Rana

IMS
Rob Semple / Isabelle
Sadaf Farooqi

Medicine
David Lomas

Hematology
Allan Warren
Willem Ouwehand

Oncology
Alex Burna

Biochemistry
Jules Griffin

PDN
Anne Ferguson Smith

<u>Sanger Institute</u>
Allan Bradley / Kasoke Yusa

<u>Manchester university</u>
Neil Hanley

<u>UCL</u>
Stephen Beck

<u>Barcelonea</u>
Jorge Ferrer
Santiago Rodriguez-Segui

<u>Singapore</u>
Ray Dunn/ Adrian Teo
Bing Lim
Leah Verdy

<u>University of Aberdeen</u>
Kevin Docherty/ Hilary Docherty

<u>Universite Paris Sud</u>
Anne Weber

<u>Pasteur Institute</u>
James Di Santo/ Helene Strick Marchand

<u>ENS Lyon</u>
FL Cosset/ Florianne Fusil

<u>Karolinska Institute</u>
Lars Ährlund-Richter
Jessica Cedervall

<u>SCRIPPS</u>
Sheng Ding

MRC | Centre for Stem Cell Biology and Regenerative Medicine

Liv-ES

wellcome trust

Cambridge BRC

BBSRC/TSB