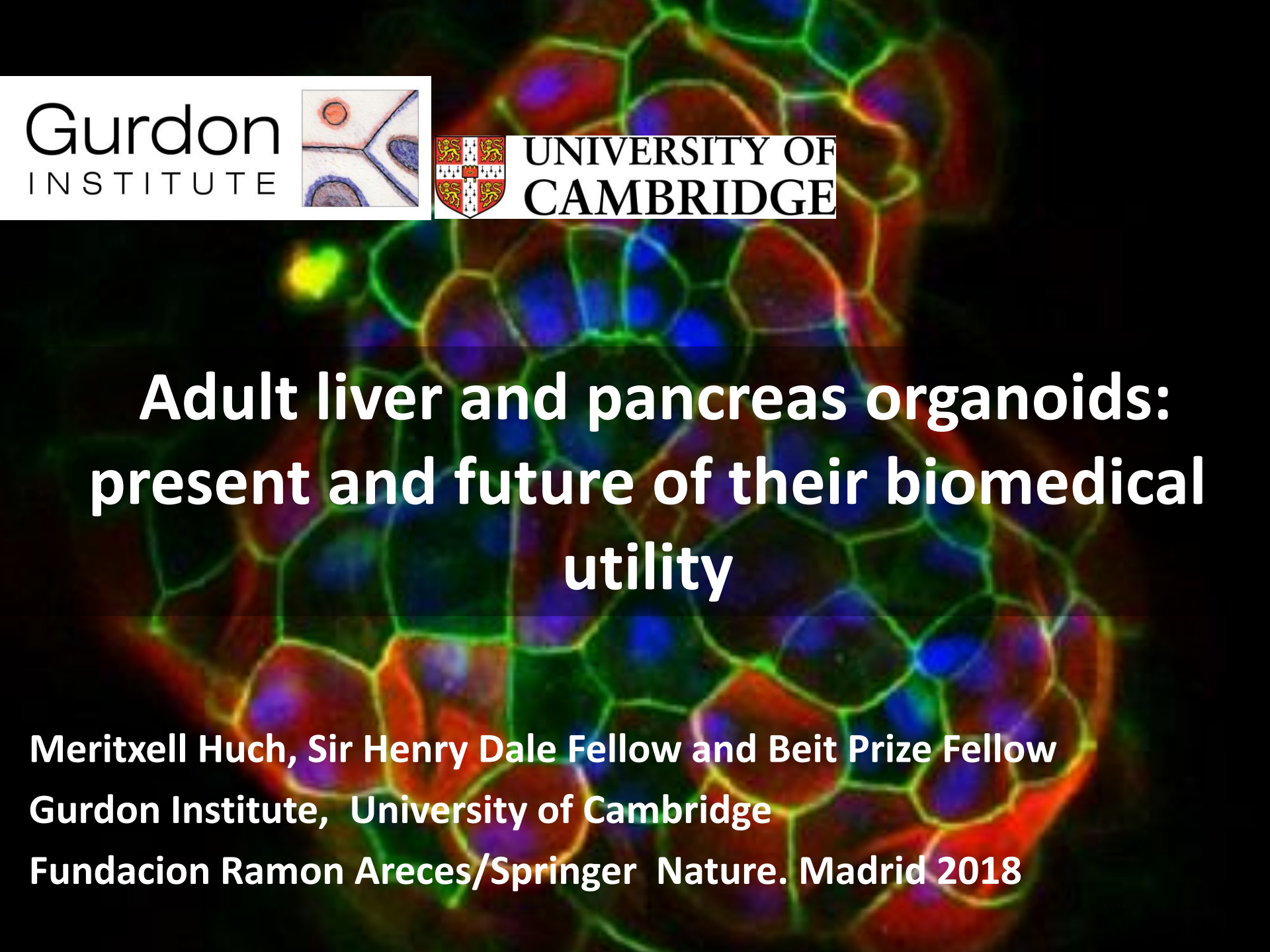


Gurdon INSTITUTE

UNIVERSITY OF CAMBRIDGE

Adult liver and pancreas organoids: present and future of their biomedical utility

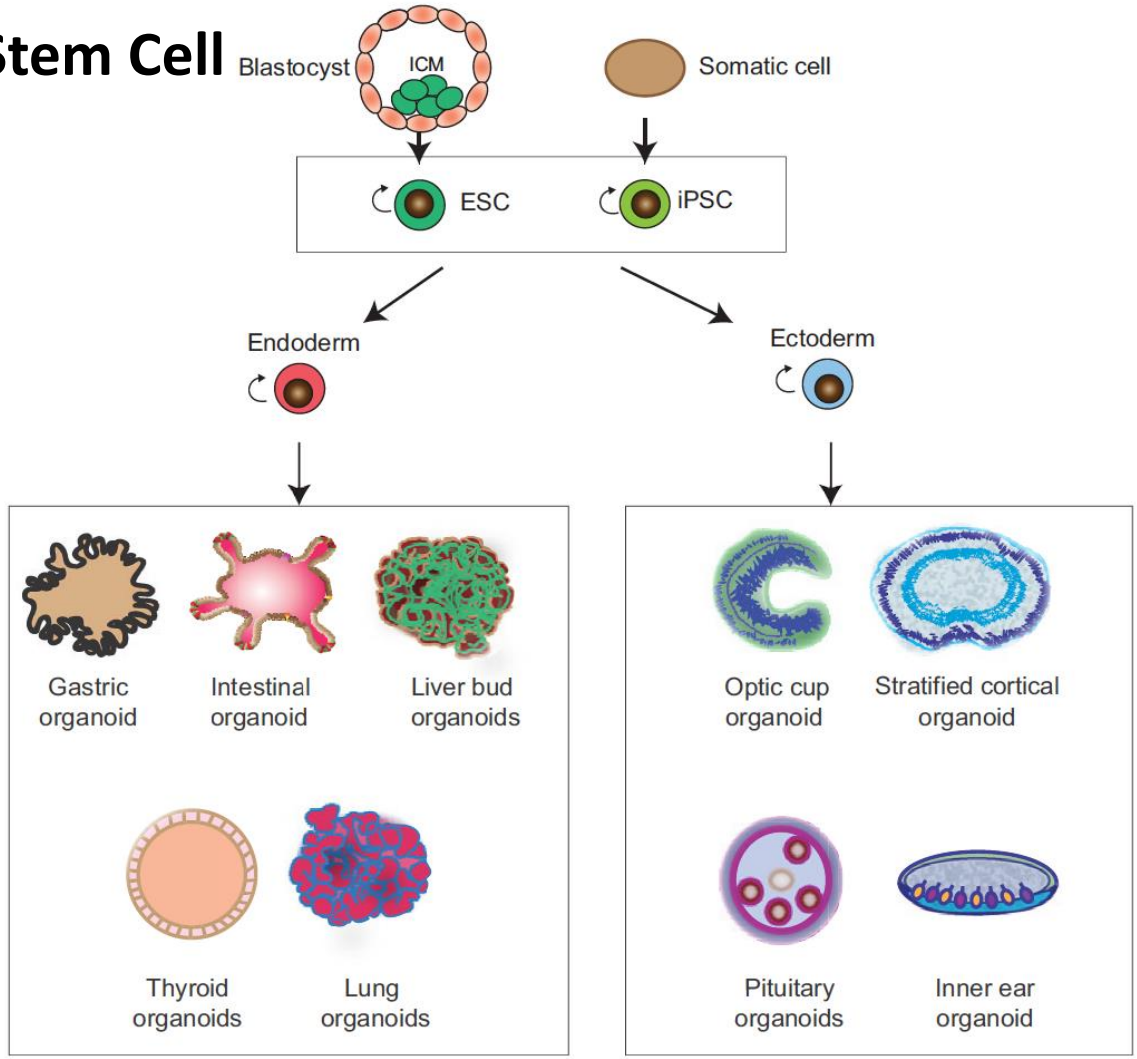
Meritxell Huch, Sir Henry Dale Fellow and Beit Prize Fellow

Gurdon Institute, University of Cambridge

Fundacion Ramon Areces/Springer Nature. Madrid 2018

Generation of functional tissue ex-vivo:

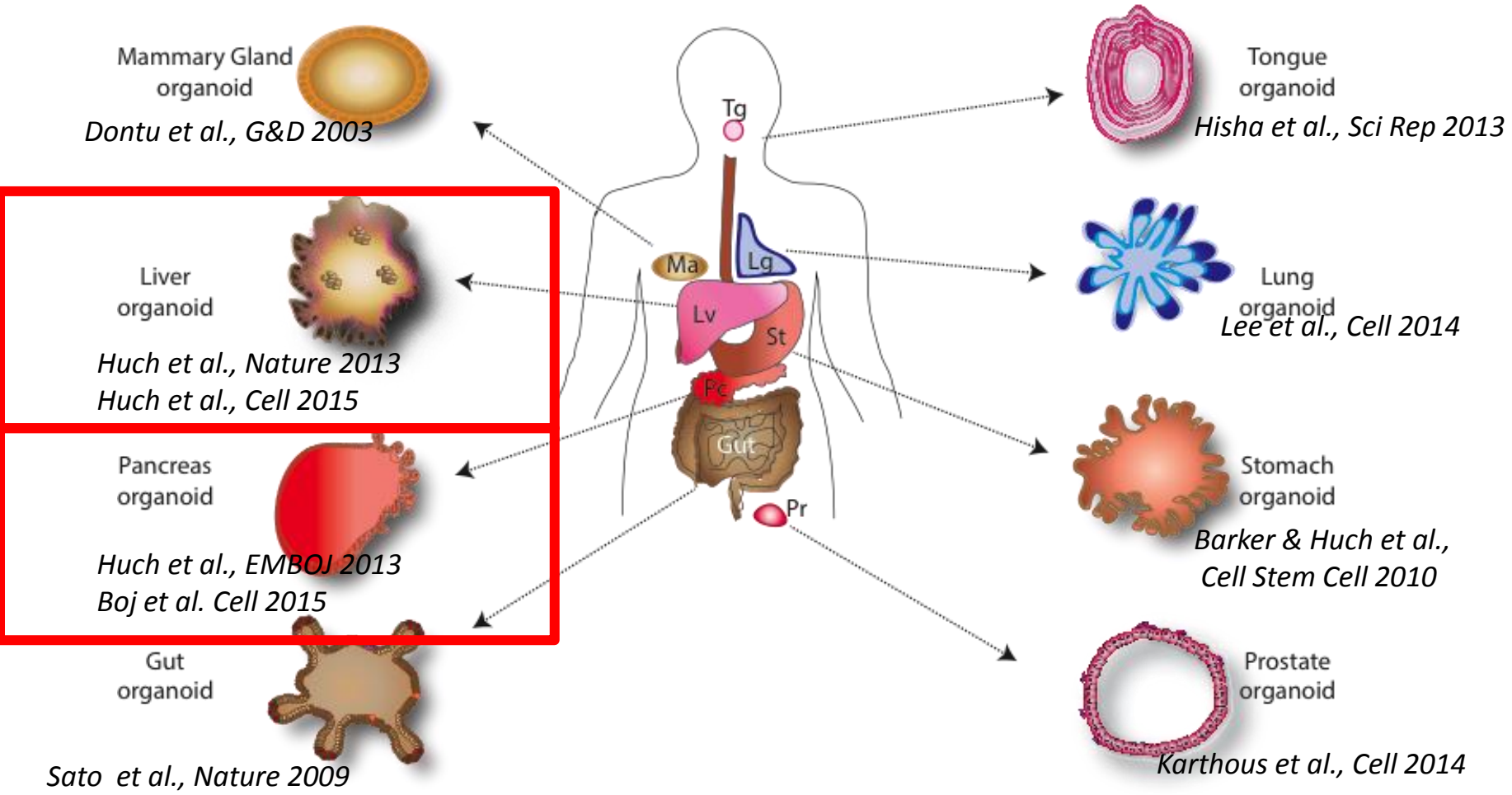
Pluripotent Stem Cell
ESC, iPSC



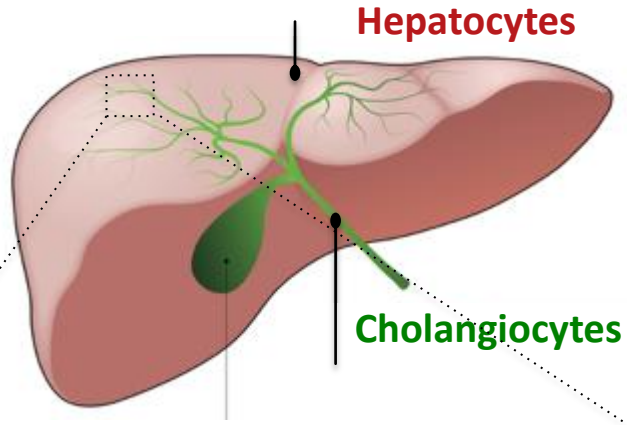
Huch and Koo, *Development*, 2015

Generation of functional tissue ex-vivo:

Adult tissue cells/ stem / progenitors

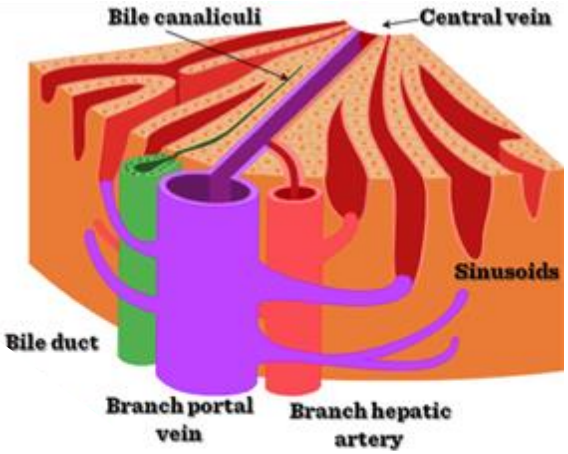


Liver anatomy

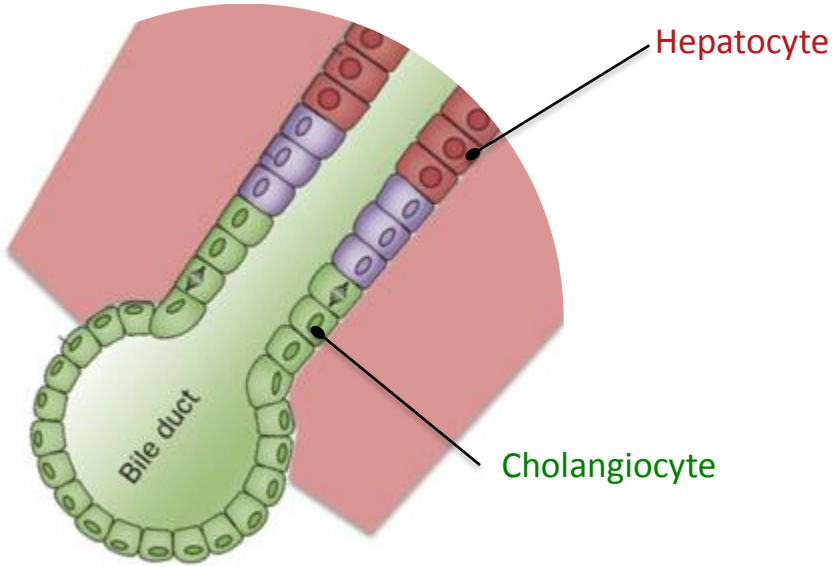


- 70-85% of the liver's mass
- Functions *Detoxification, Digestion (bile production), Storage (glycogen, aa…), Blood glucose regulation…*

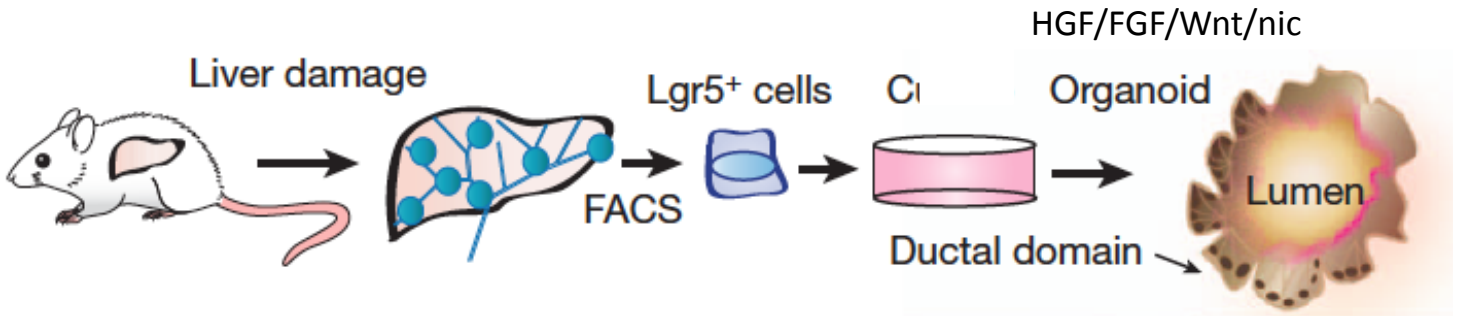
- Drain Bile



Endothelial
Mesenchymal
Resident Macrophages

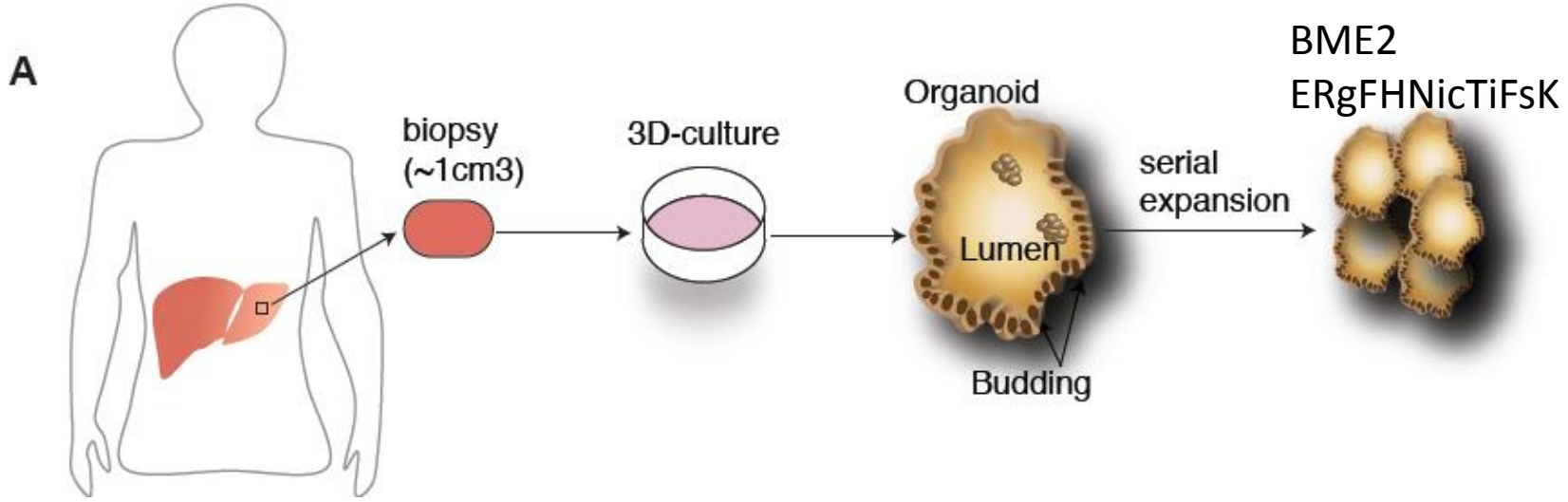


Mouse liver cells generate self-sustaining liver organoids *in vitro*



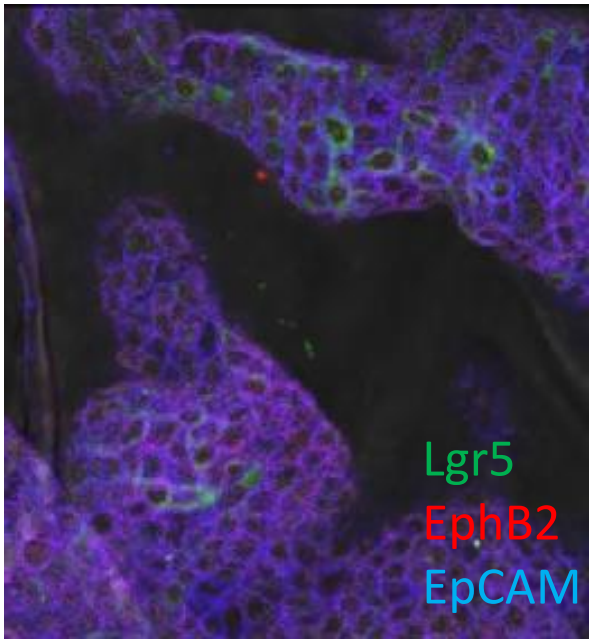
Huch et al.., *Nature* 2013

Human liver organoids expand long term in culture

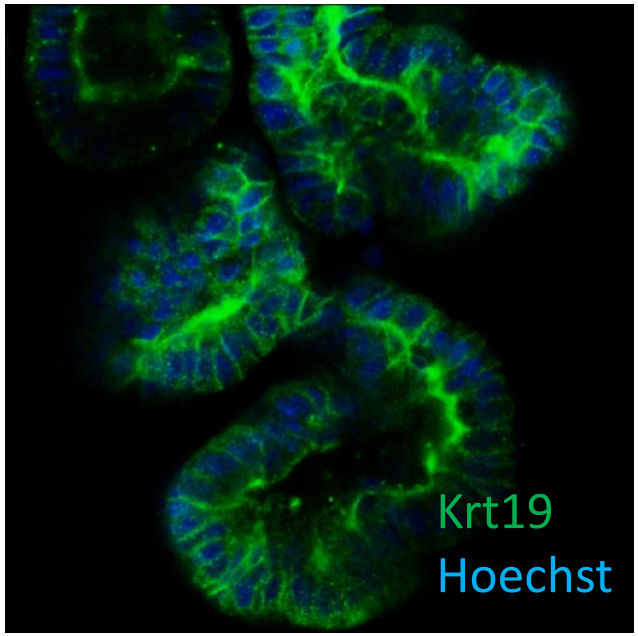


Human liver organoids express ductal and progenitor markers

STEM CELL

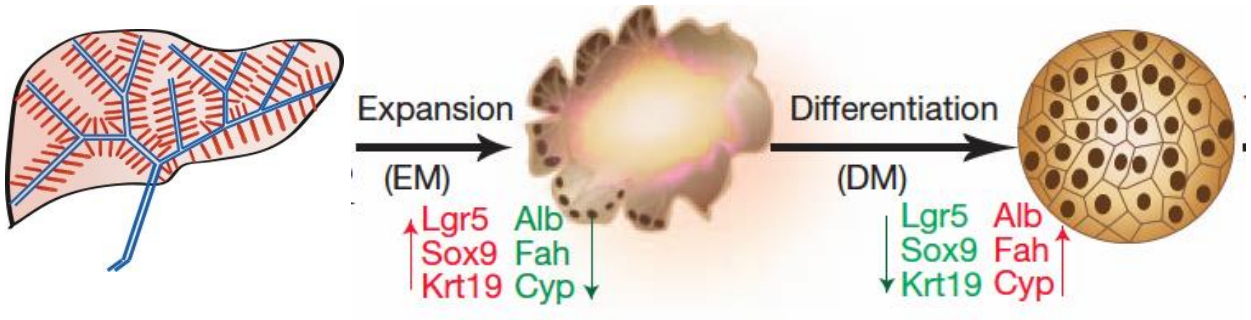


DUCTAL

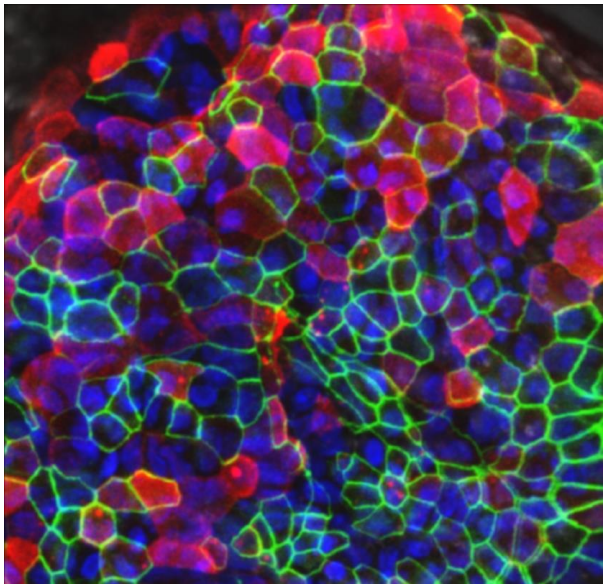


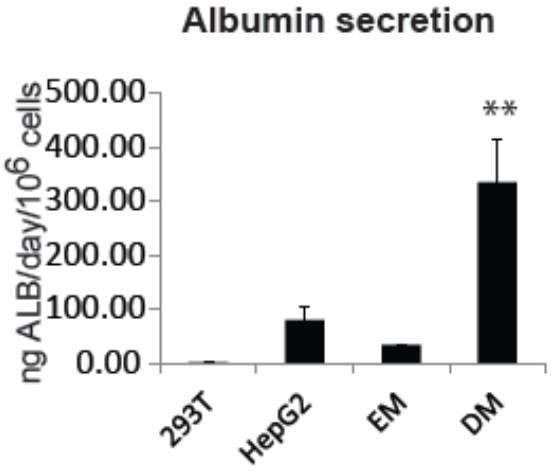
Huch et al., *Cell*, 2015

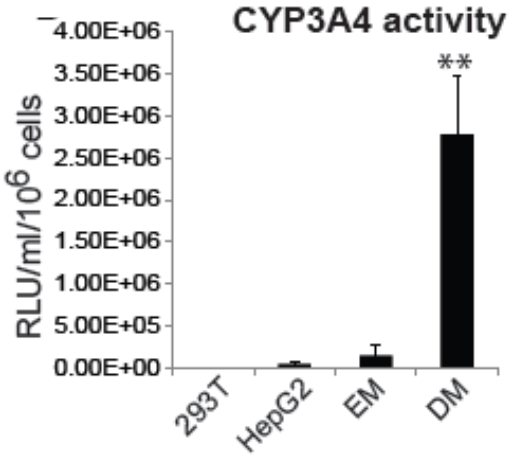
Liver organoids express HEPATOCYTE genes upon DM



ZO1 Alb Hoecsht



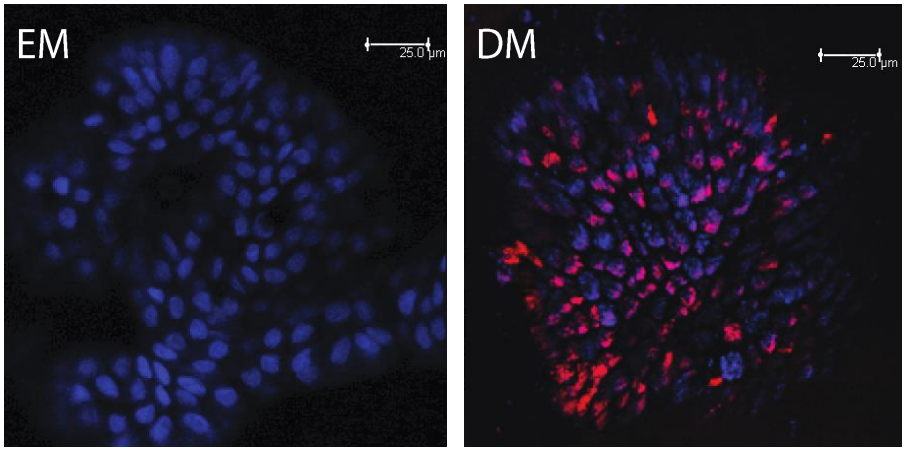


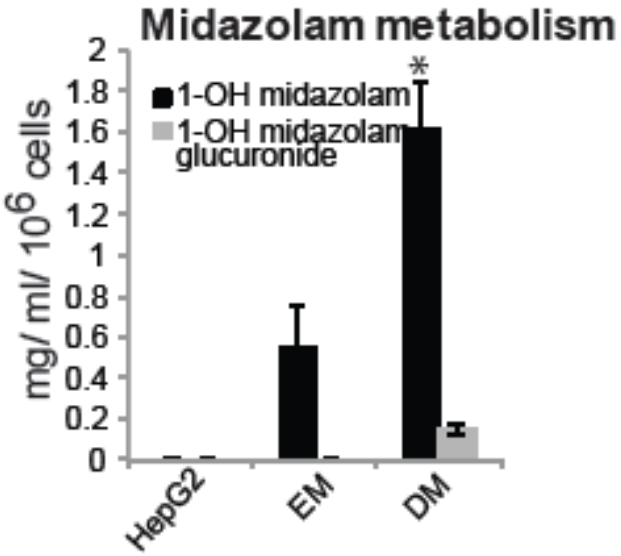


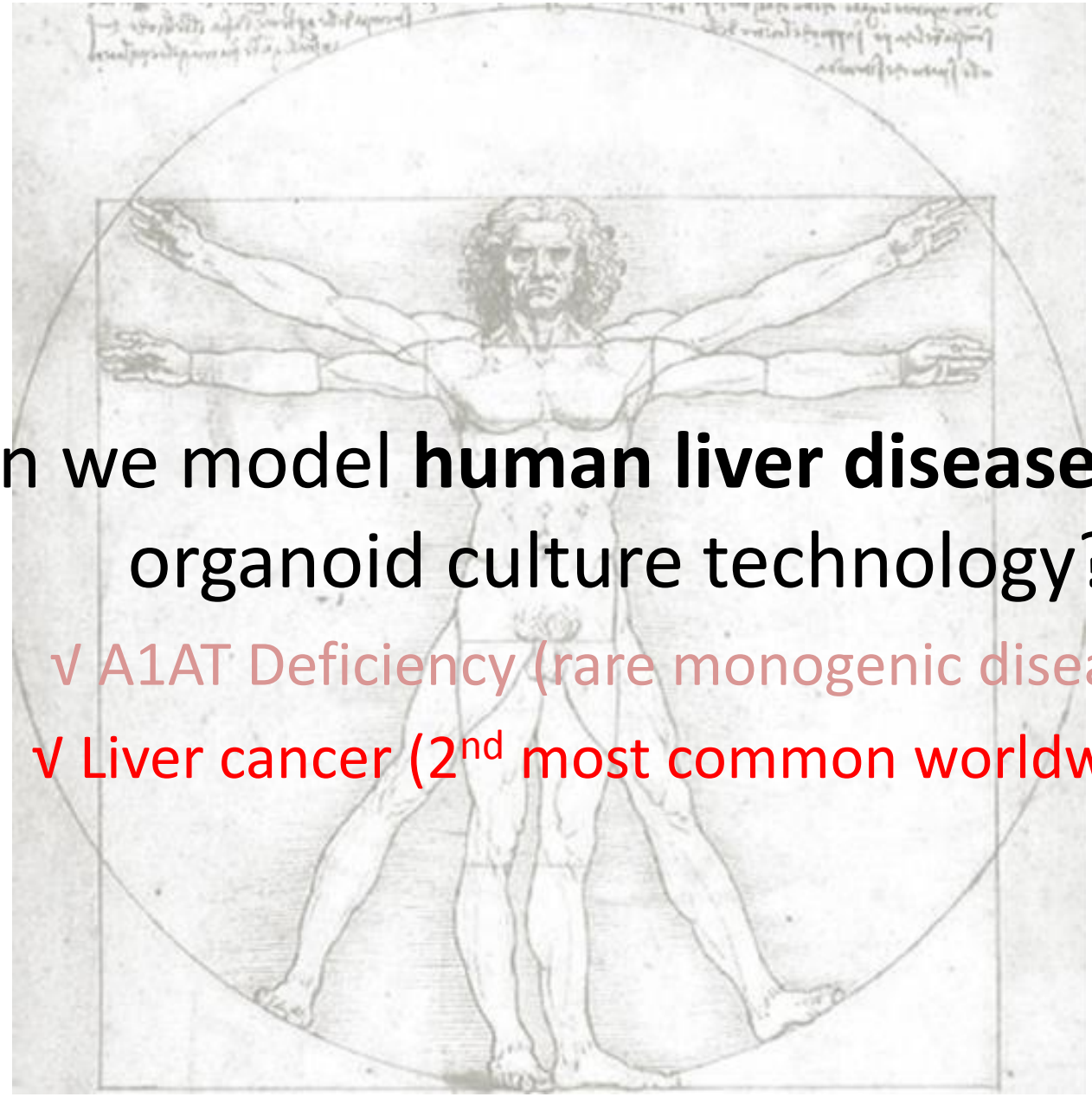
Huch et al.., *Cell* 2015

Human liver organoid cultures differentiate into functional hepatocyte-like cells *in vitro*

LDL-uptake





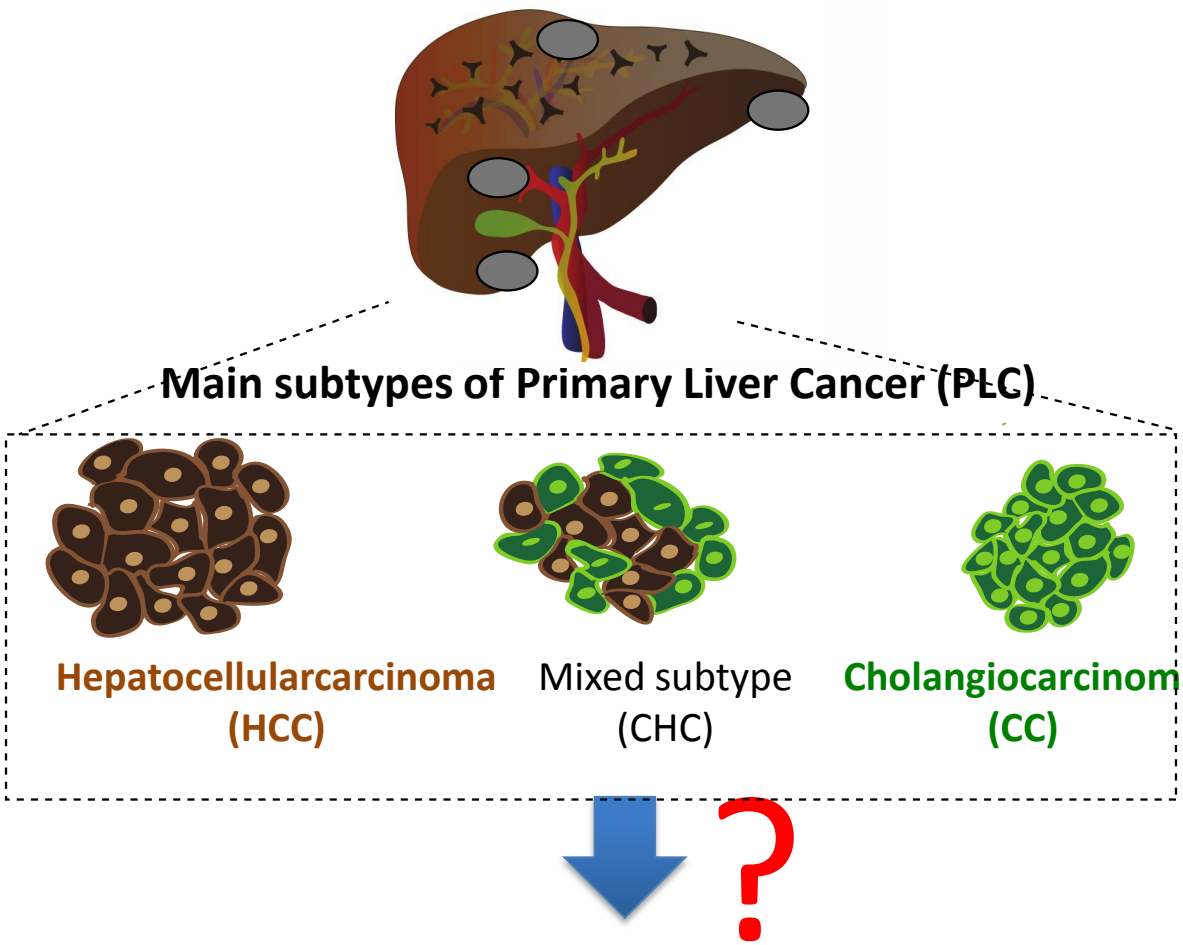


Can we model **human liver diseases** using organoid culture technology?

√ A1AT Deficiency (rare monogenic disease)

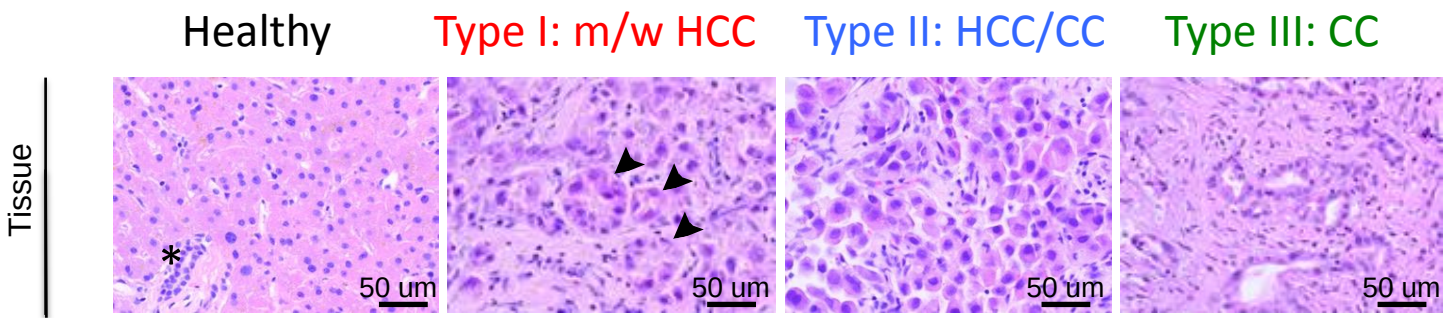
√ Liver cancer (2nd most common worldwide)

Can we model Primary Liver Cancer using patient-derived organoids?



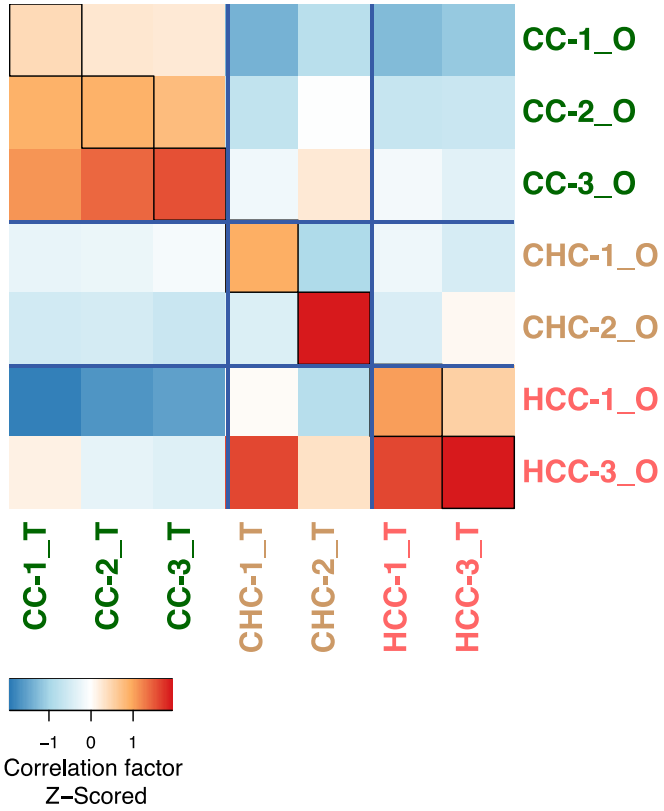
Tumour organoids that retain the patient and subtype specific features?

Human Liver Tumouroids EXPAND long term in vitro while retaining **the histological architecture** of the tumour sub-type

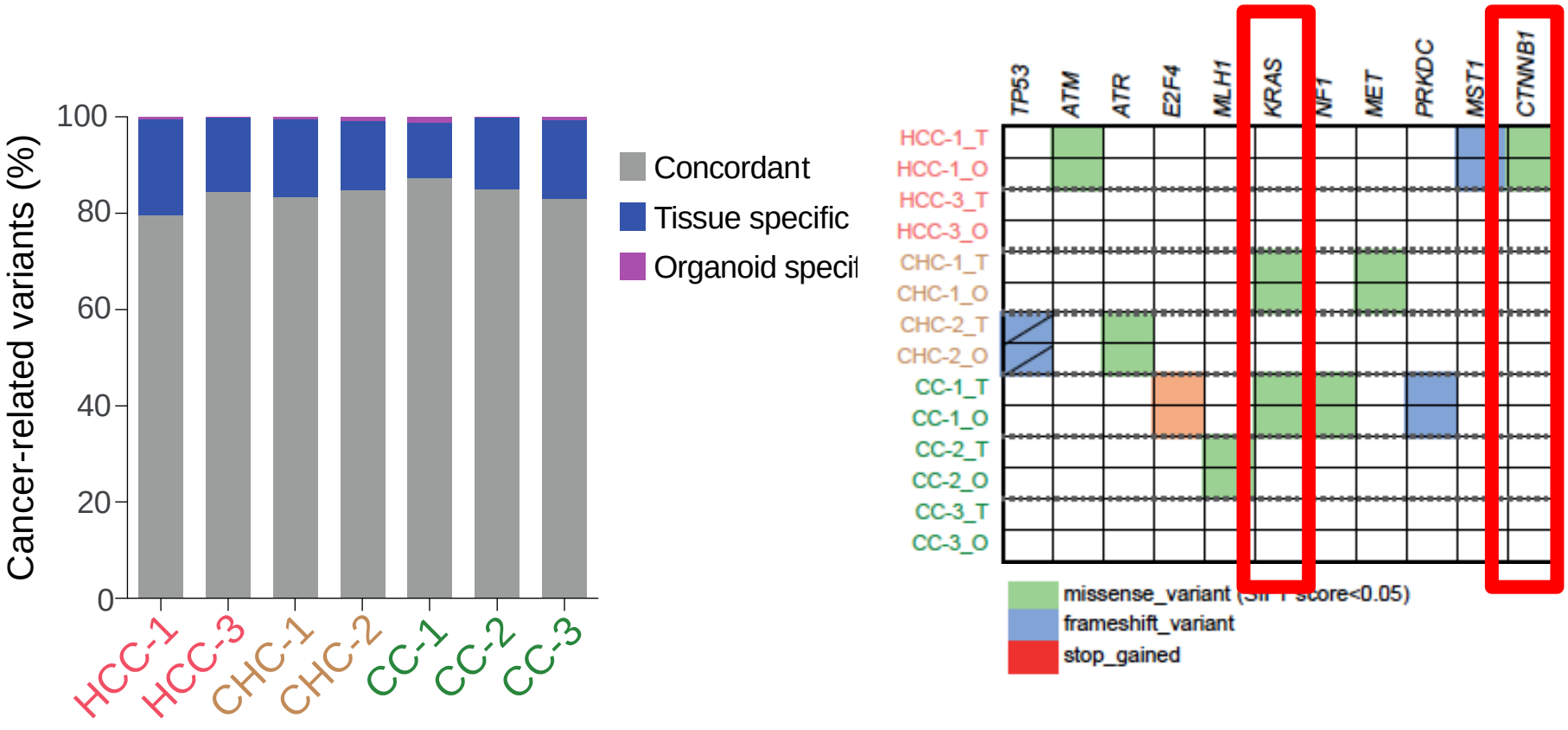


Broutier et al., *Nature Medicine 2017*

Liver tumoroids **expression profile** correlates with the profile of the patient's tumour-of-origin

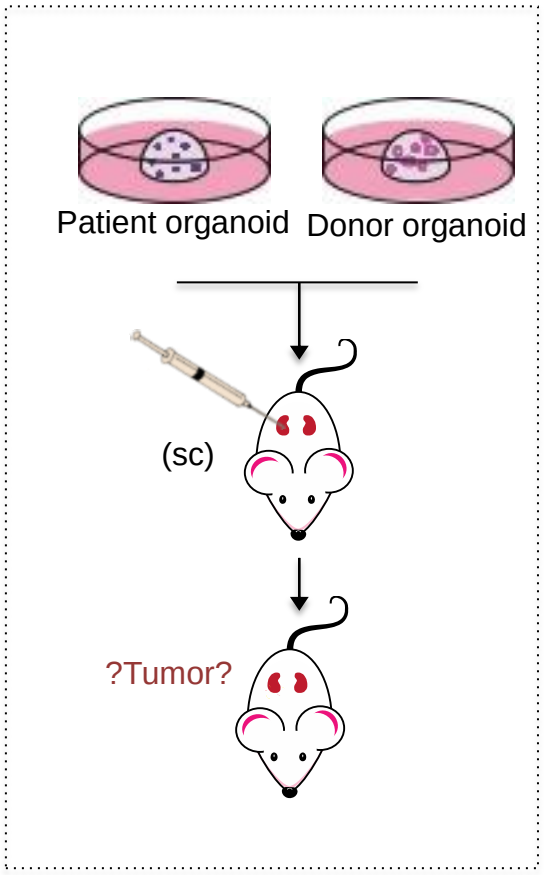


Tumoroids recapitulate the **genetic alterations** present in the original tumour specimen



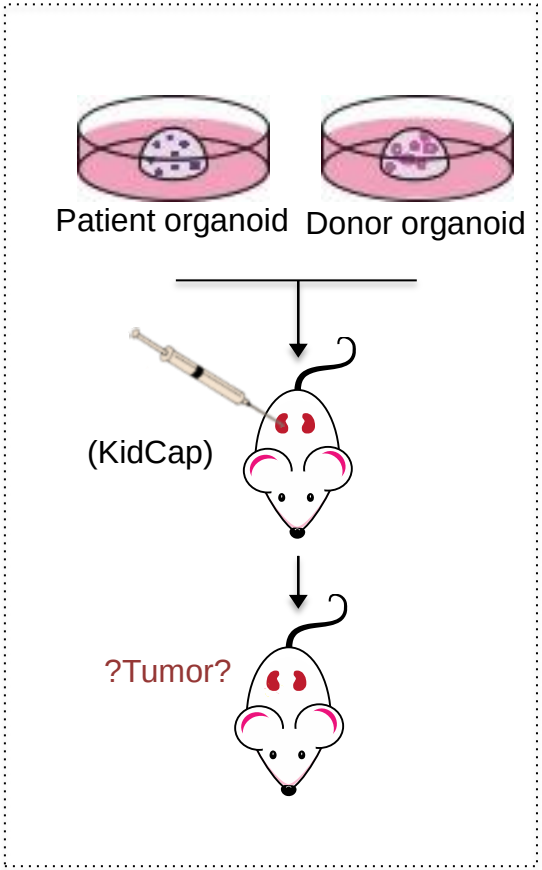
~**84%** of the **cancer-related somatic variants** present in the patient's original tissue were **retained** in the corresponding tumouroid cultures.

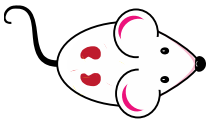
Do expanded tumor-organoids resemble the original tissue ?



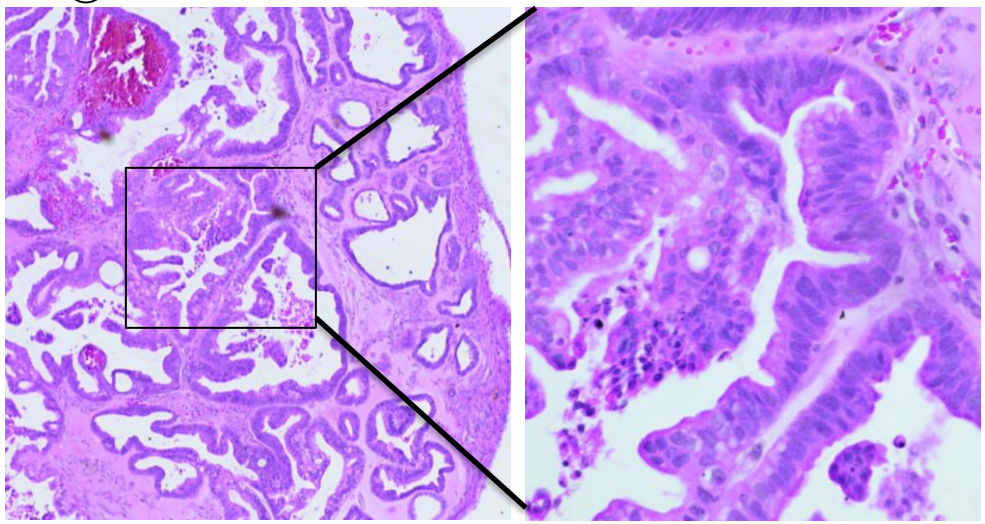
CC- derived organoids **resemble the original** tissue upon transplantation

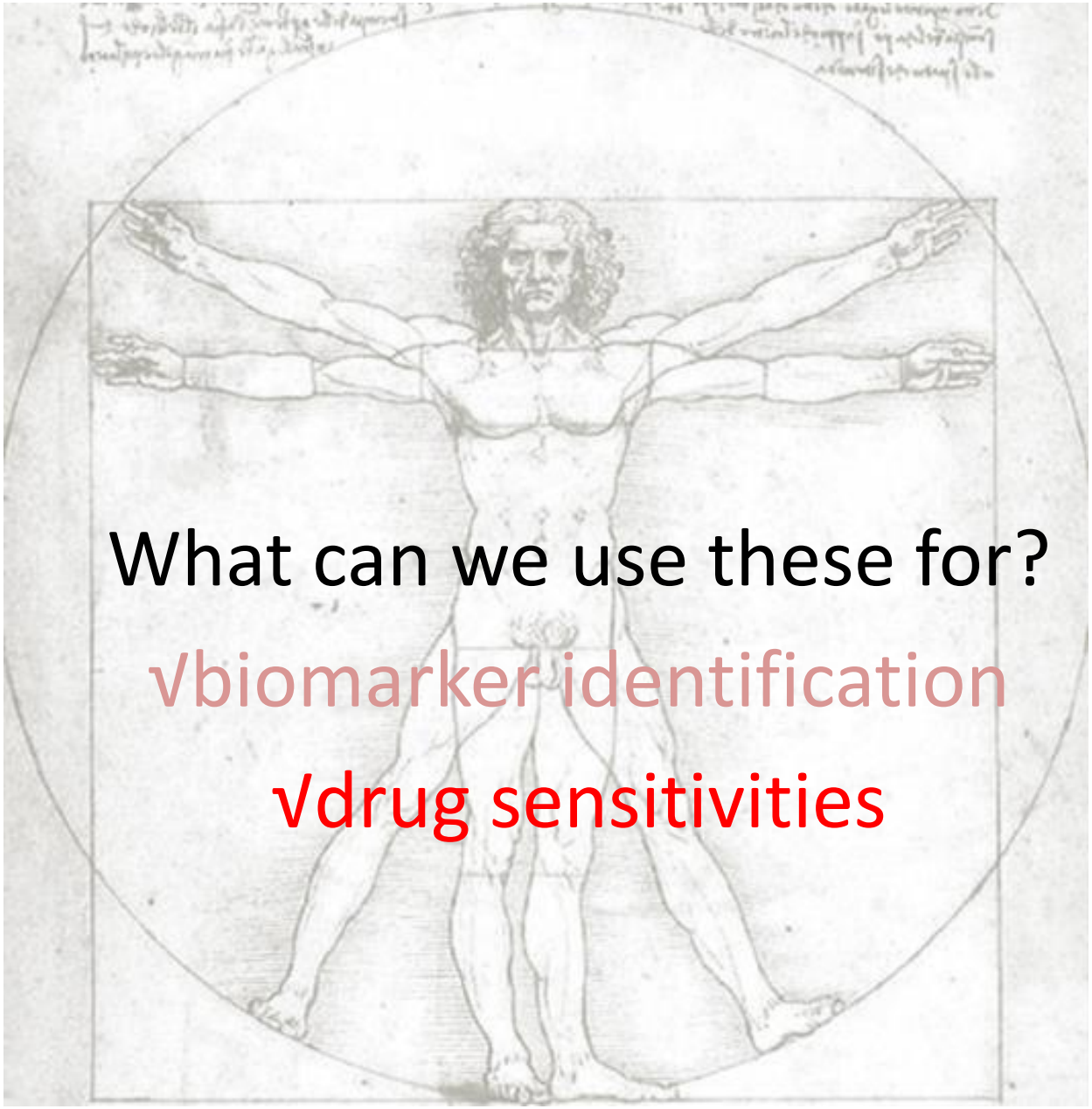






CC-derived tumoroids





What can we use these for?

√biomarker identification

√drug sensitivities

PLC-organoids as platforms for personalized drug testing?

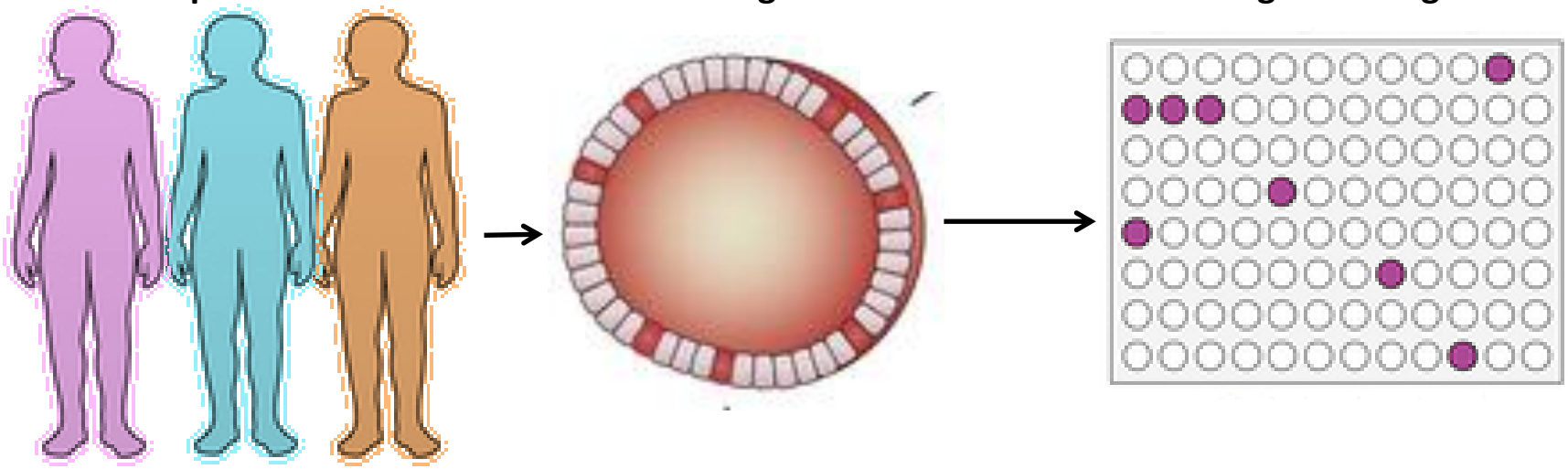
wellcome trust sanger institute

Dr Mathew Garnett
Dr Hayley Francies

PLC patients

PLC-Organoids

Drug screening



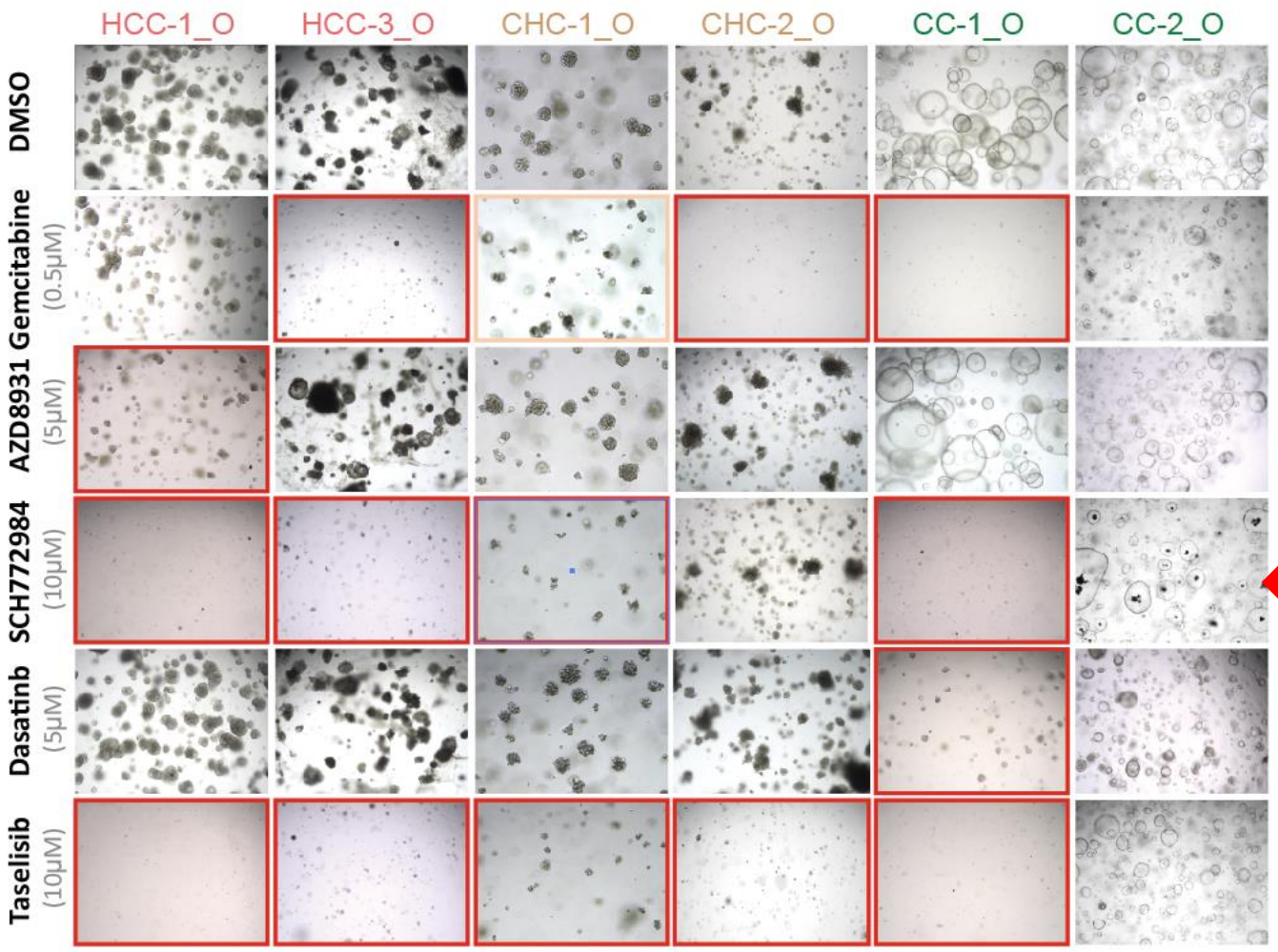
Liver tumouroids are a valuable resource for drug screening and allow **the identification of novel drug sensitivities**

Pathway	Drug Name	Target	HCC-1	HCC-3	CHC-1	CHC-2	CC-1	CC-2
Cell cycle/ DNA damage and repair	Cisplatin	DNA crosslinker						
	Olaparib	PARP1, 2						
	KU-55933	ATM						
	5-Fluorouracil	antimetabolite					■	
	Doxorubicin	DNA replication		■				
	Gemcitibine	DNA replication		■		■	■	
RTKi	Axitinib	PDGFR…						
	PD-173074	FGFR1, 3						
	Sorafenib	PDGFR..		■	■	■	■	
	AZD8931	ERBB1, 2, 3	■				■	
	Lapatinib	ERBB2, EGFR		■			■	
	CH5424802	ALK						
	EMD-1214063	MET					■	
MAPK, PI3K, AKT, mTOR	Trametinib	MEK1/2					■	
	Dabrafenib	BRAF						
	SCH772984	ERK1/2	■	■	■		■	
	Deltarasin	KRAS		■	■			
	MK-2206	AKT1, 2						
	Taselisib	PI3K	■	■	■	■	■	
	OSI-027	mTORC1/2					■	
Other	Vorinostat	HDAC		■	■	■	■	
	BIRB 0796	p38, JNK2						
	Nutlin-3a	MDM2		■				
	PD-0332991	CDK4, 6						
	LGK974	PORCN		■		■	■	
	LY2109761	TGFB1						
	GSK126	EZH2						
	BIBR-1532	TERT						
	Dasatanib	ABL…					■	

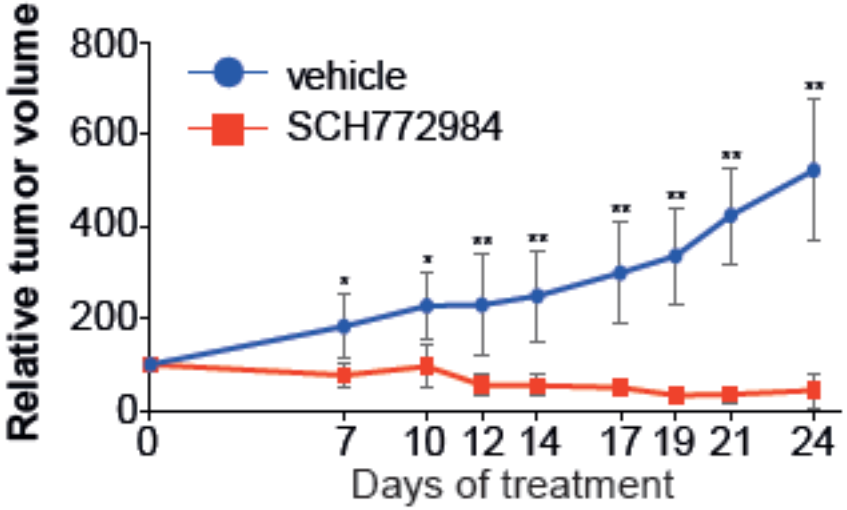
■ sensitive

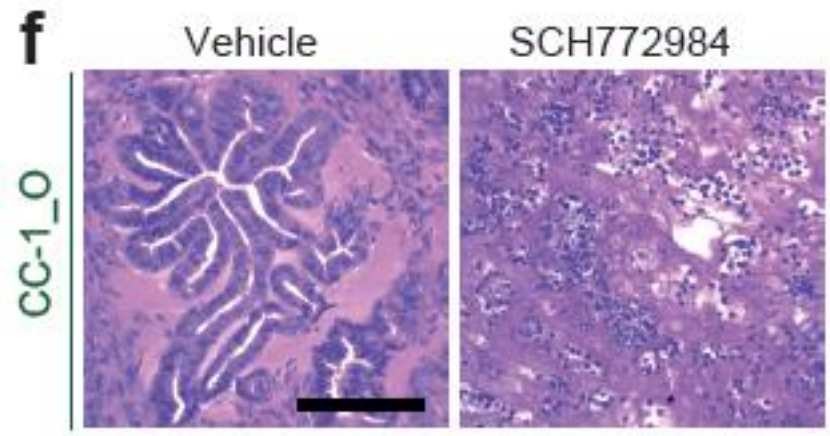
□ resistant

Liver tumouroids are a valuable resource for drug screening and allow the identification of novel drug sensitivities



Liver tumouroid lines are a valuable resource for drug screening and allow the identification of novel drug sensitivities



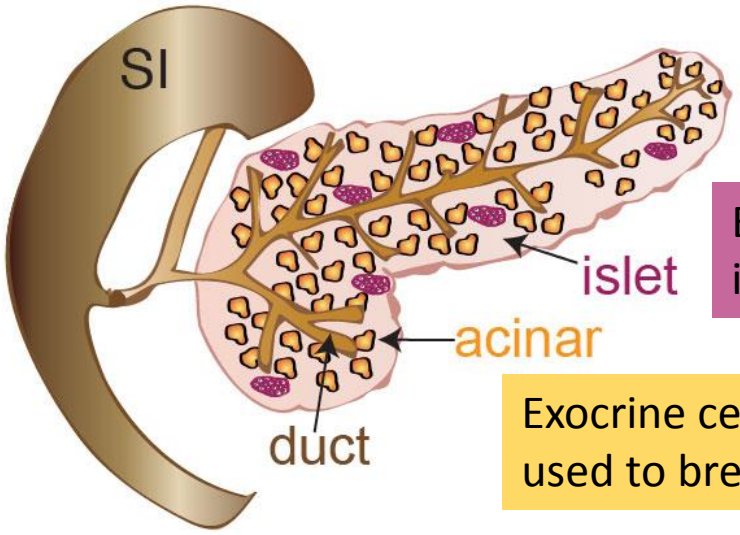


?

Pancreas

Why focus on the pancreas?

The pancreas is an exocrine and endocrine tissue.

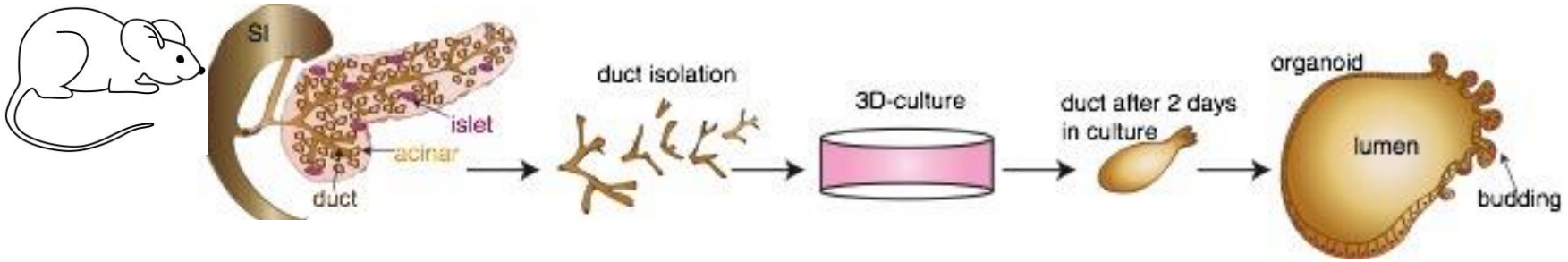


Endocrine cells secrete hormones (e.g. insulin) that control blood sugar levels.

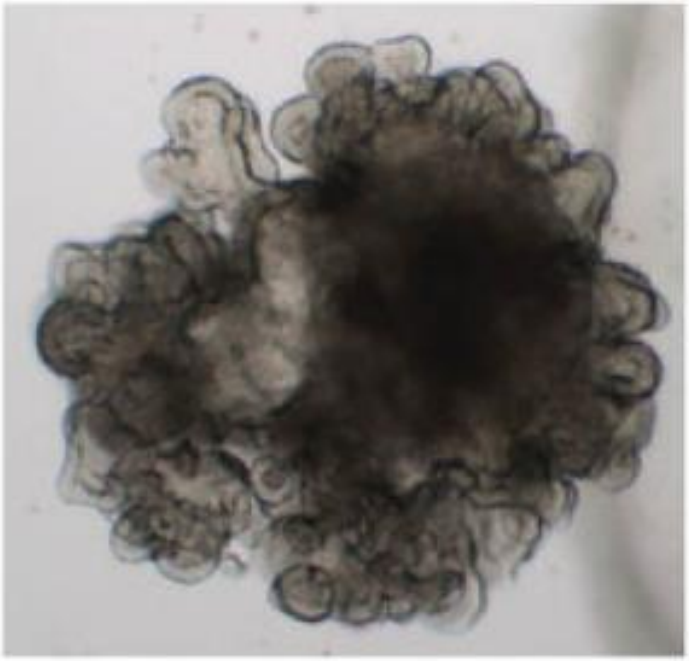
Exocrine cells produce enzymes used to breakdown food.

Complications lead to debilitating diseases including Diabetes and Pancreatic cancer.

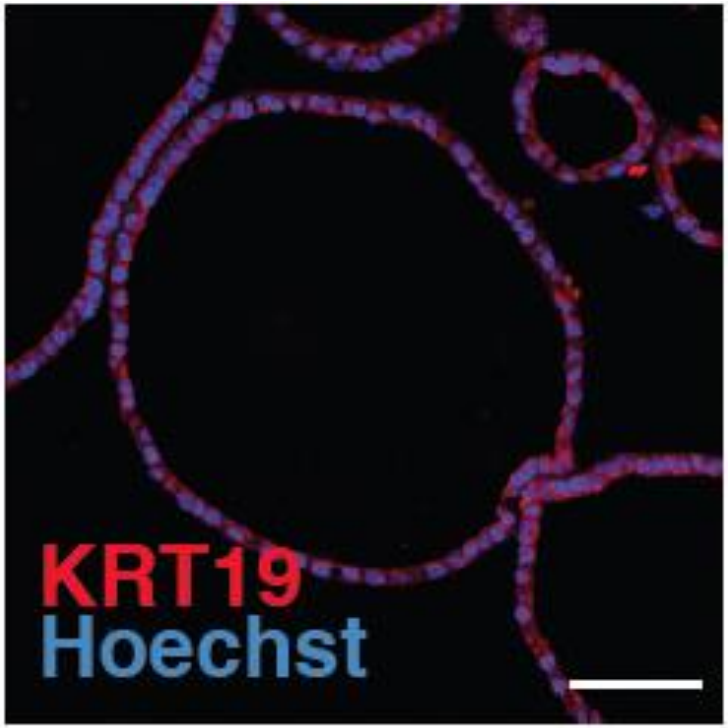
Pancreas ducts grow into pancreas organoids with ductal phenotype



1 month

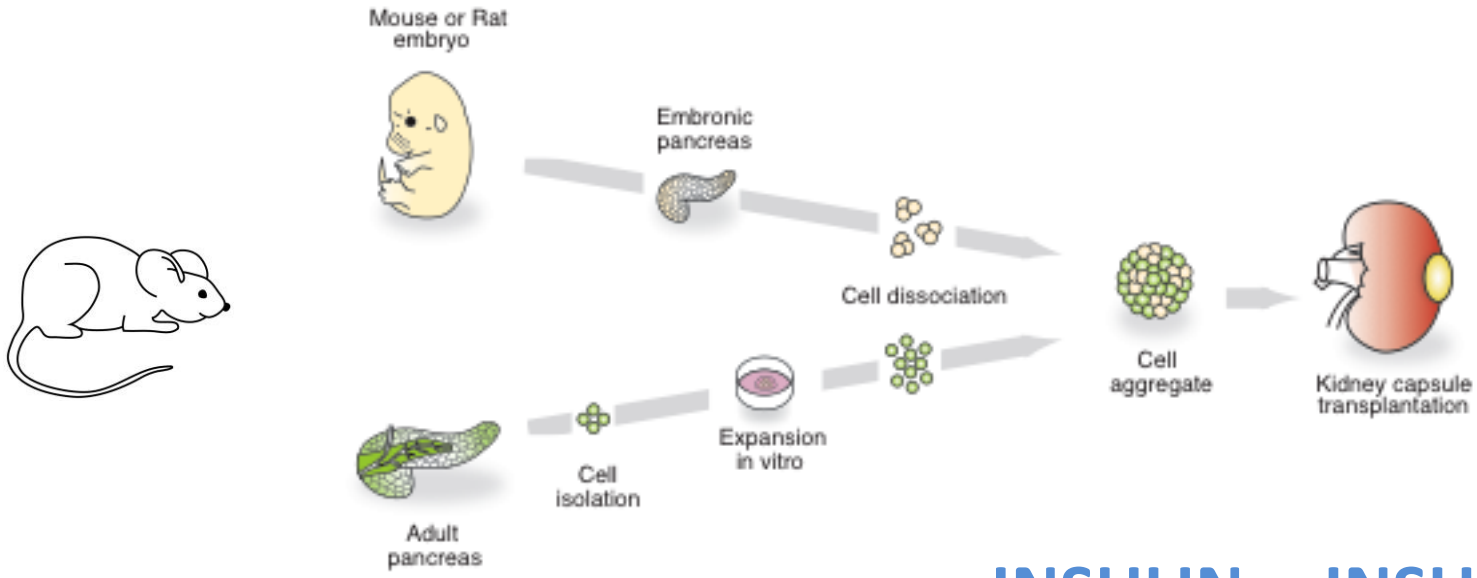


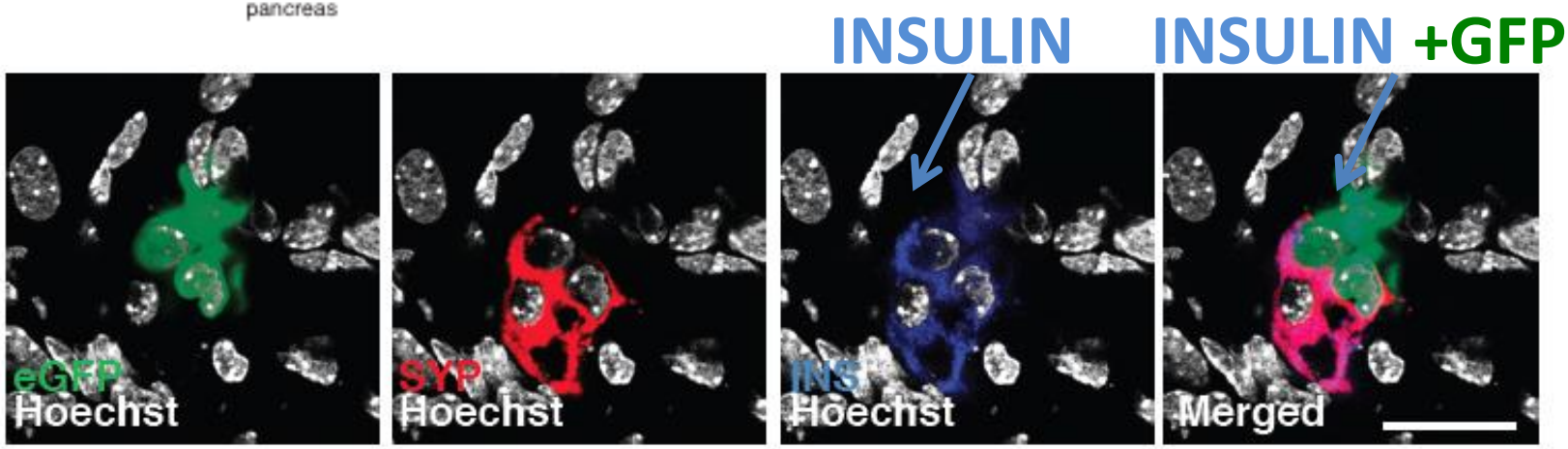
DUCTAL



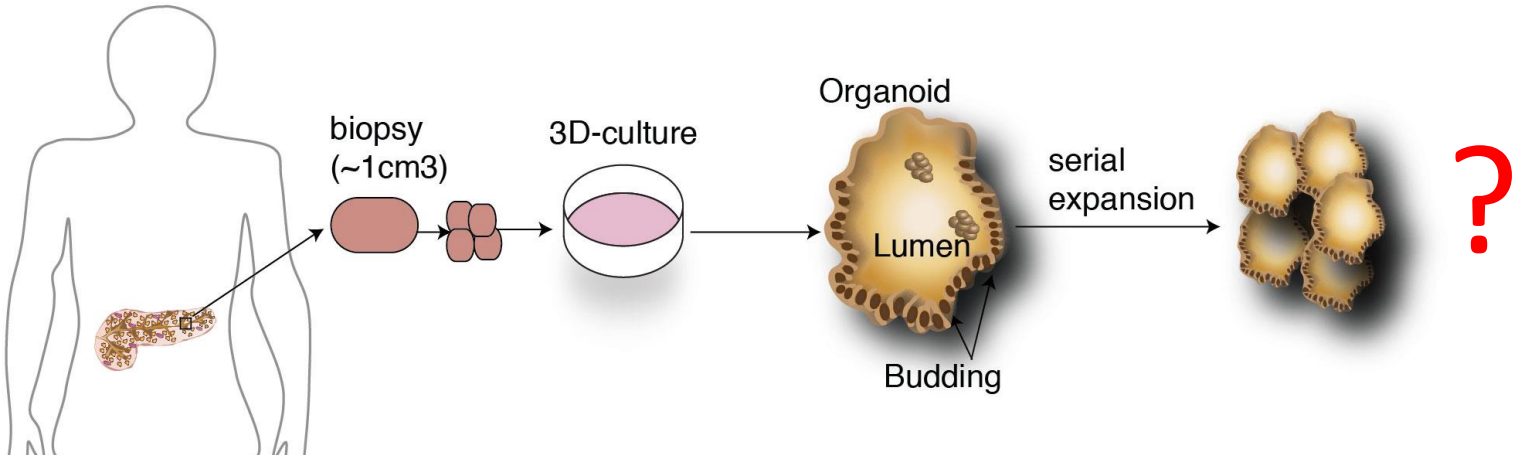
Huch & Bonfanti & Boj et al., EMBO J 2013

Pancreas organoids differentiate towards mono-hormonal endocrine cells *in vivo*



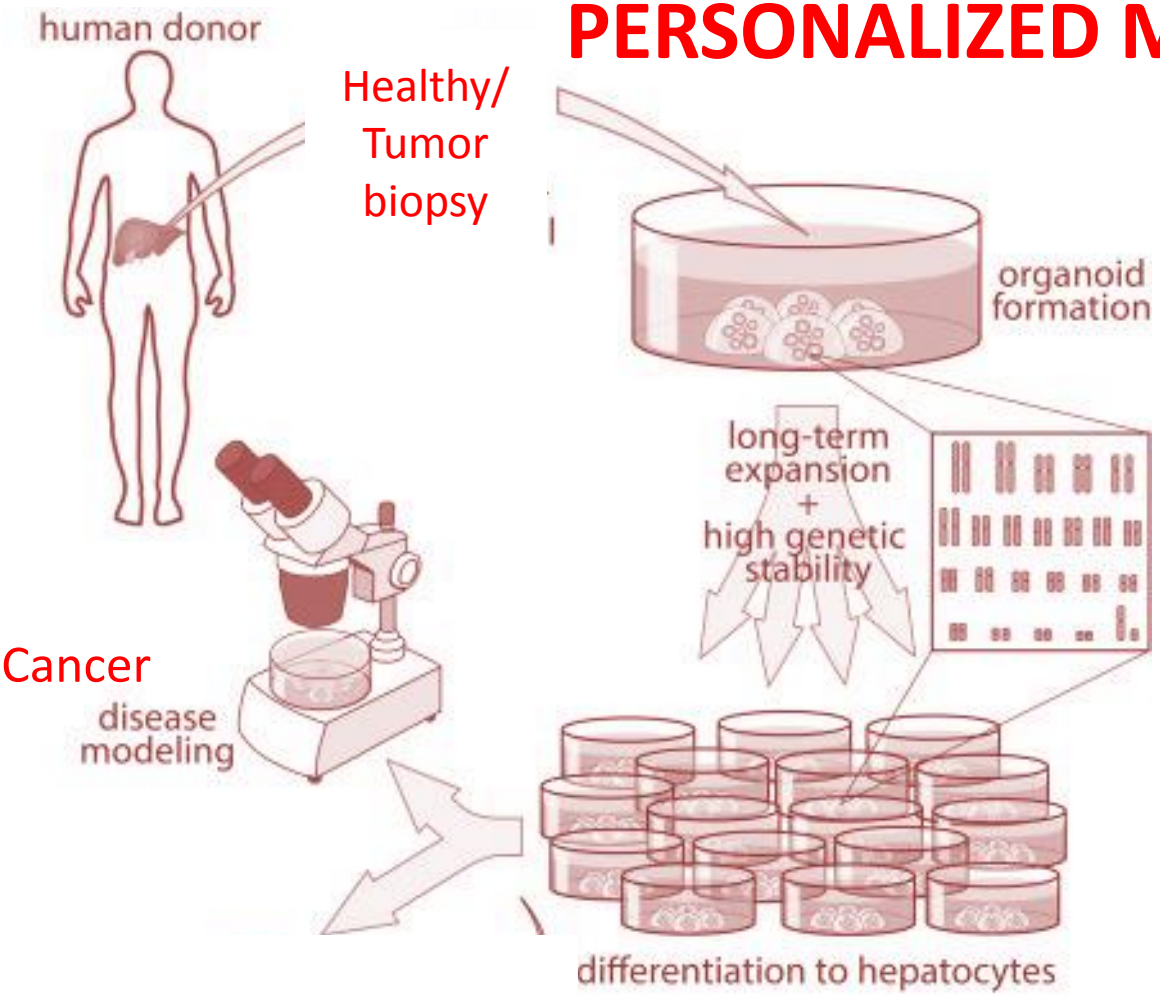


HUMAN Pancreas organoids derived from human pancreas biopsies expand long term in culture



Summary

PERSONALIZED MEDICINE?



Model
Primary Liver Cancer

Long term expanded in vitro

Acknowledgements

Gurdon INSTITUTE

UNIVERSITY OF CAMBRIDGE

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Cambridge Stem Cell Institute

Huch lab

- Laura Broutier
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- Lucia Cordero
- Robert Arnes
- Nicole Prior
- Gianmarco Mastrogiovani
- Olga Sidorova

Collaborators

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- Kourosh Saeb Parsy, Nikitas G (Addenbrokes hospital, Cambridge)
- Dr Susan Davies (Pathologist, Addenbrokes)
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- Steve Wigmore (Edinburgh)

Funding

THE ROYAL SOCIETY

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

wellcome trust

Fellow
Wellcome-Beit Prize

EMBO excellence in life sciences

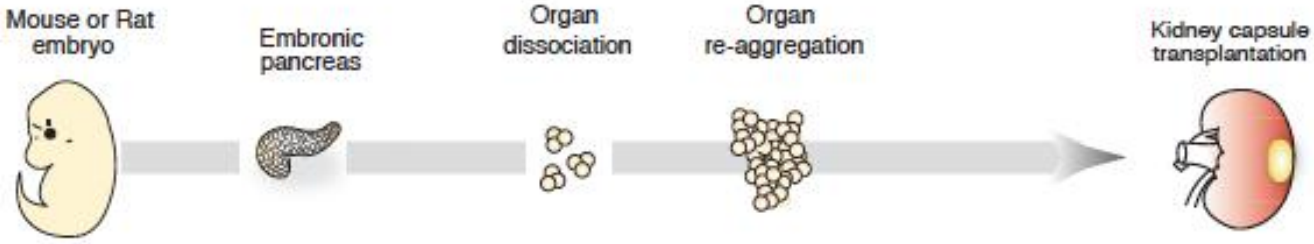
MARIE CURIE ACTIONS

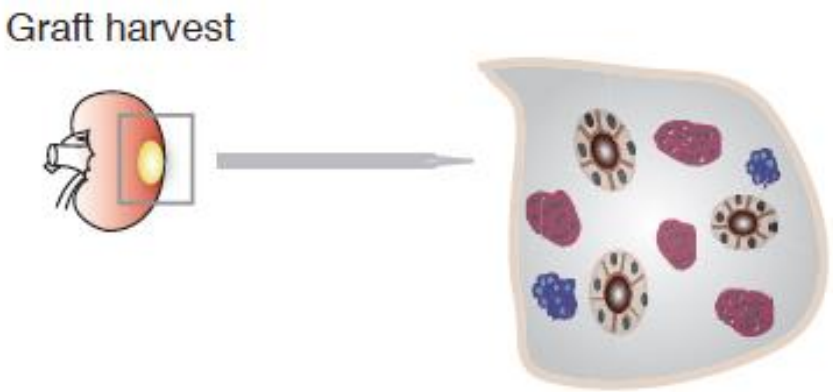
CANCER RESEARCH UK

CAMBRIDGE CENTRE

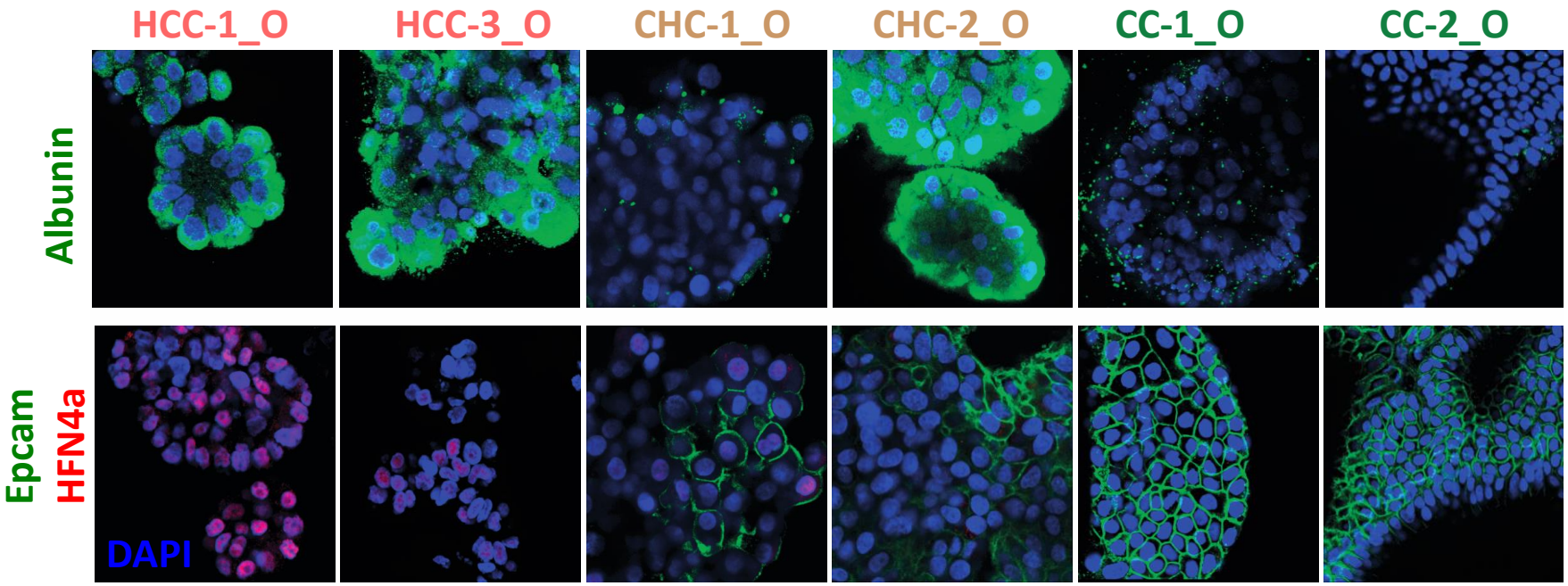
Pancreas Morphogenetic assay:
Embryonic pancreas fully maturates into adult pancreas lineages

Paola Bonfanti / Harry Heimberg

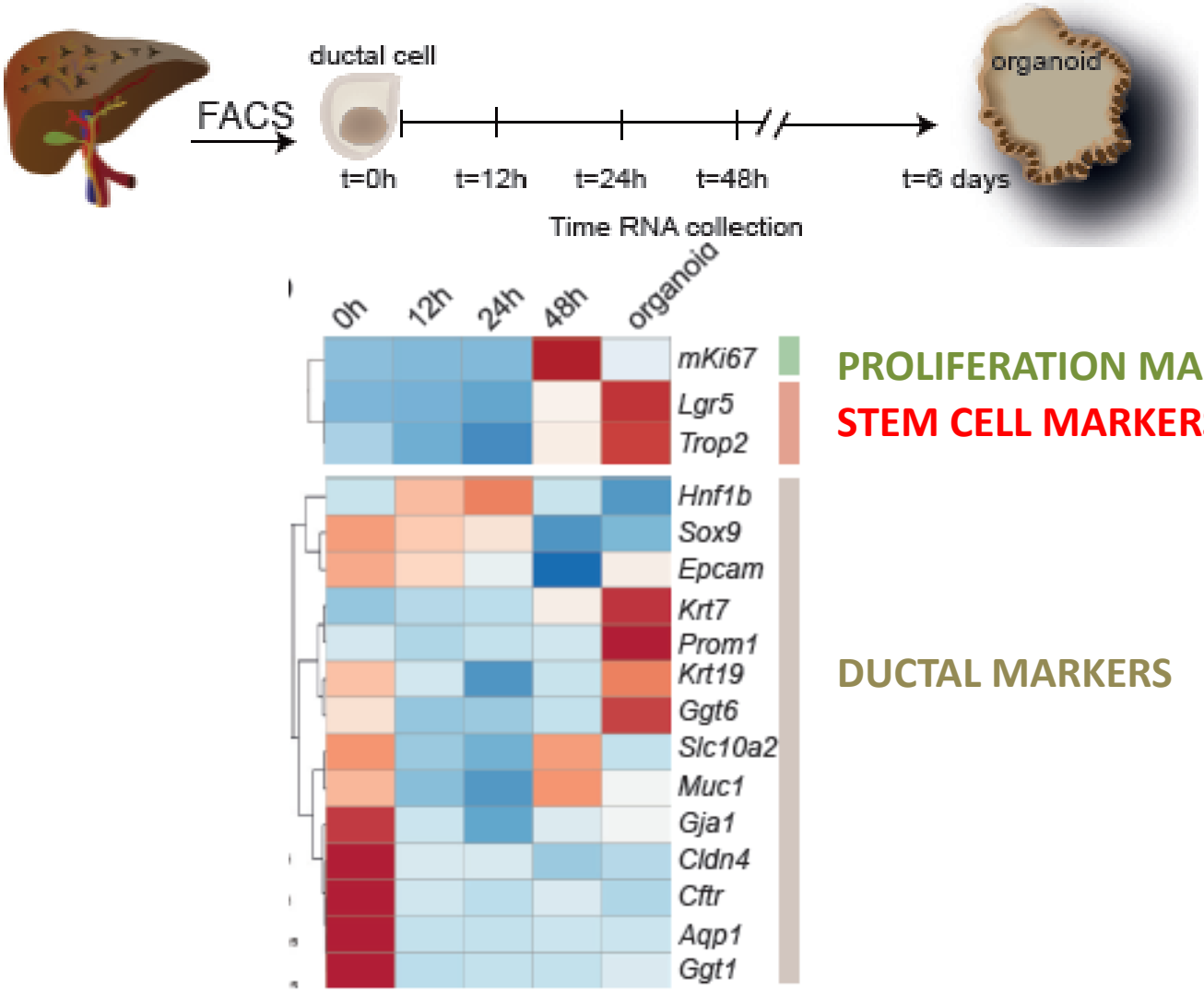




Tumoroids retain the **differentiation** state of the original biopsy after long-term expansion in culture

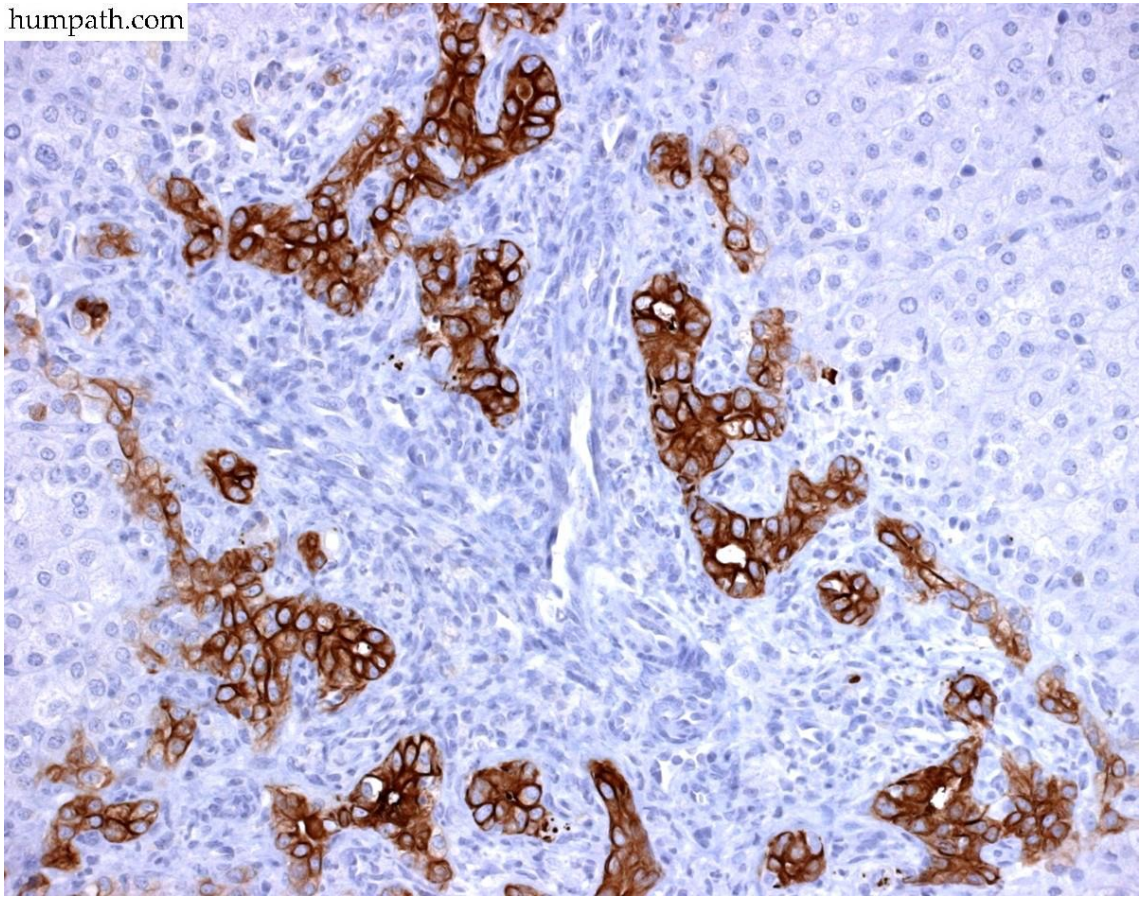


Ductal cells undergo a partial de-differentiation in their transition to a proliferative/progenitor state

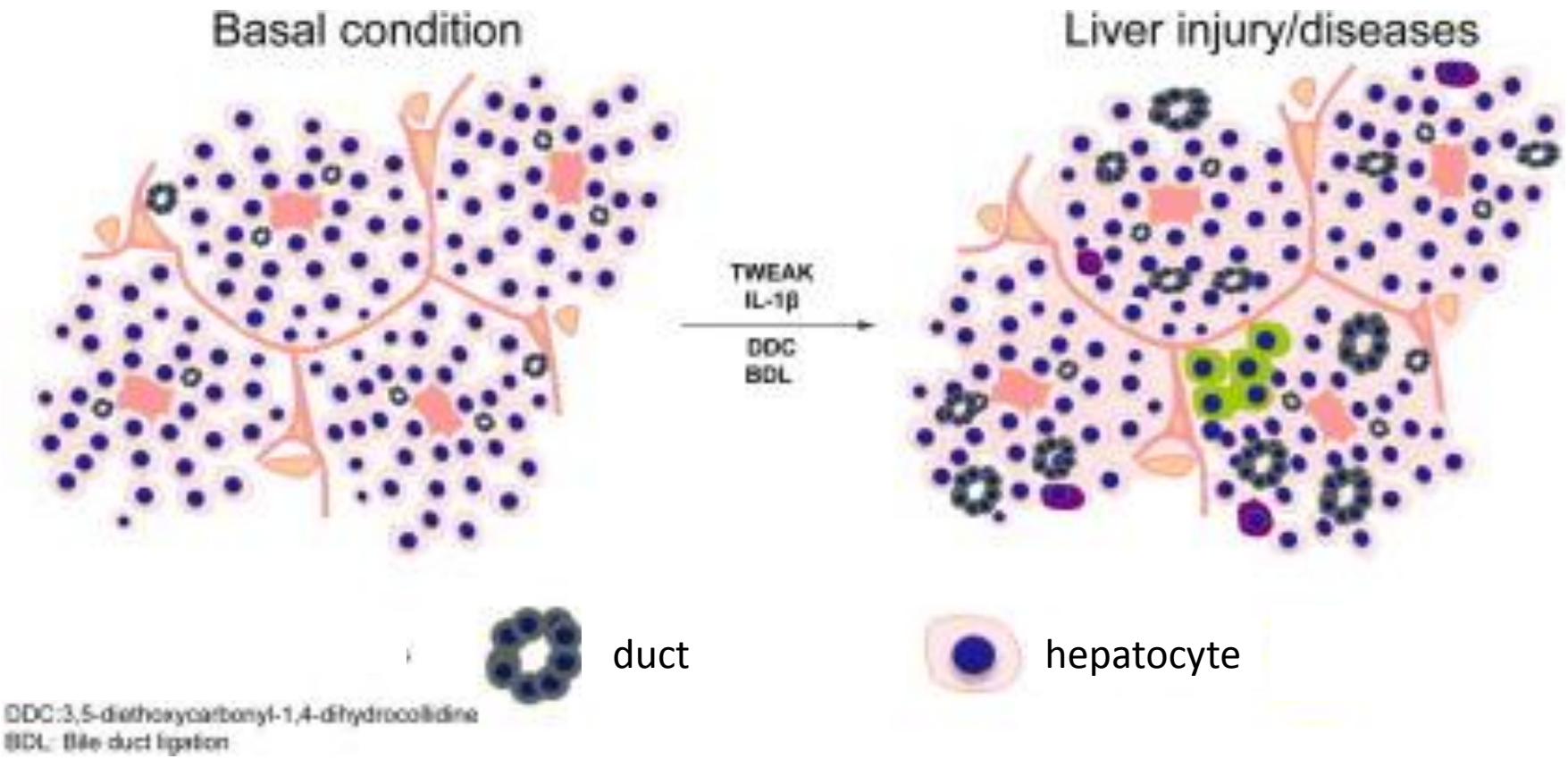


Human liver disease is marked by a prominent ductular reaction

Krt19

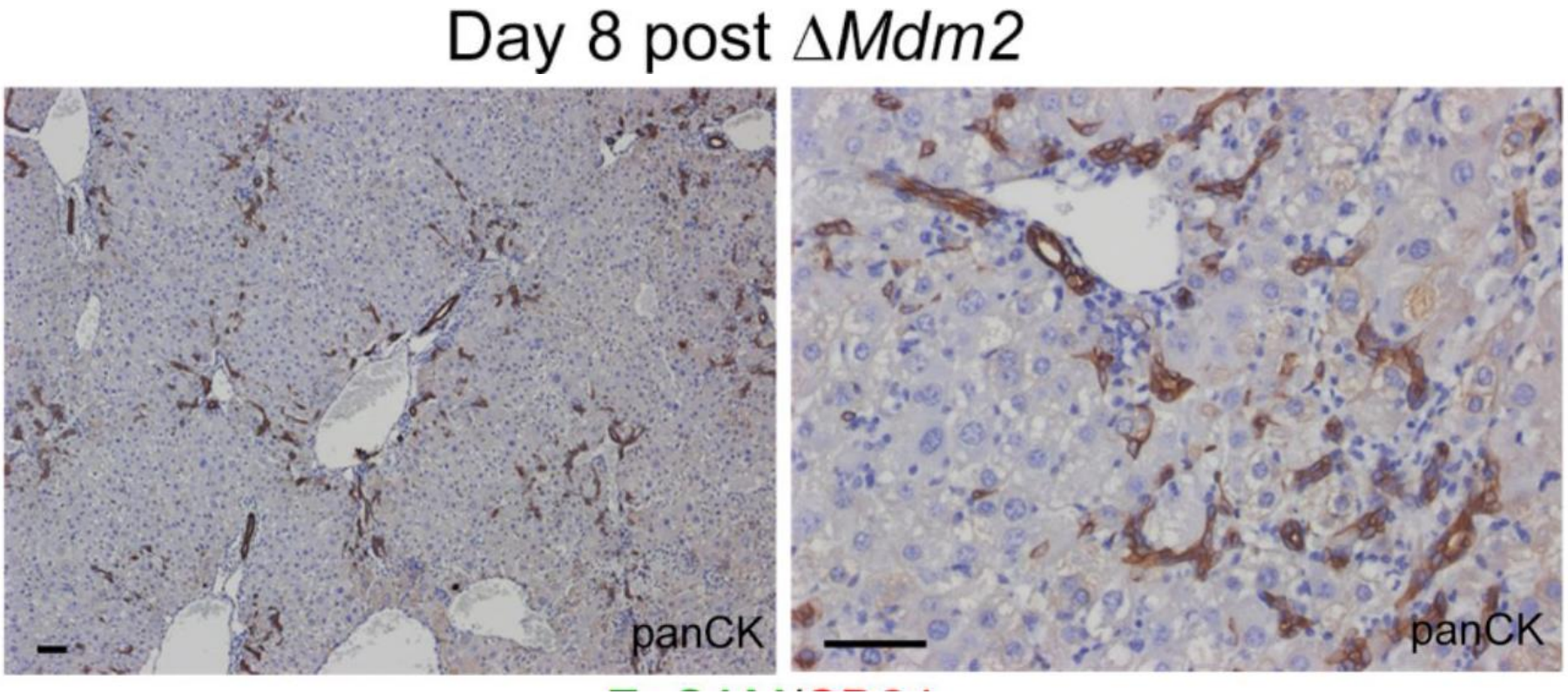


Etiology:
-acute or chronic liver damage
-massive hepatic necrosis
-hepatic fibrosis
-hepatic cirrhosis



Adapted from Guldiken et al., 2016

Mouse models with impaired hepatocyte regeneration show significant increase in ductular reaction



Forbes lab (Lu et al Nat Cell Biol 2015)

Methylcytosine is dynamically regulated during development