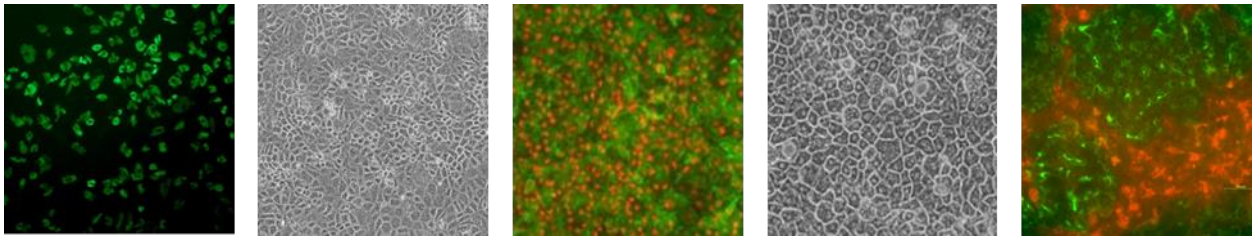
TaKaRa

Clontech TaKaRa cellartis



肝脏细胞模型专题（二）
Takara 人iPS细胞来源肝脏细胞

宝日医生物技术（北京）有限公司

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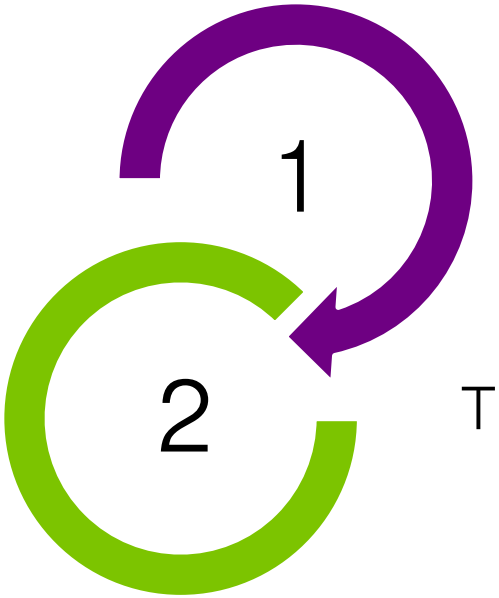
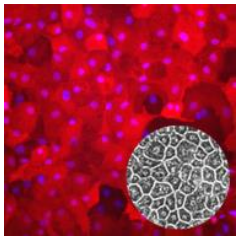


Takara :即用的人iPS细胞来源肝脏细胞



- 高度同质化，批次间差异小，拥有14天的实验窗口
- 肝脏细胞($1.2x10^7$ cells/管)+包被剂+解冻铺板液+培养液

- 具备成体肝脏细胞功能特征，应用于肝脏代谢疾病模型和ADME-Tox研究

表达标志蛋白质，分泌Alb，具备CYP活性，调控胰岛素和葡萄糖，调控脂质代谢
表达药物代谢机制相关的Ⅰ相酶、Ⅱ相酶、转运蛋白等，对毒性药物呈现预期反应

产品货号	产品名称	规格
Y10133	Cellartis® Enhanced hiPS-HEP (from ChiPSC12) v2 Kit	1 Kit
Y10134	Cellartis® Enhanced hiPS-HEP (from ChiPSC18) v2 Kit	1 Kit
Y10135	Cellartis® Enhanced hiPS-HEP (from ChiPSC22) v2 Kit	1 Kit

人iPS细胞来源肝脏细胞

All-in-one型

肝脏细胞
C12/C18/C22

+

25 ml解冻液

+

20 ml接种液

+

6 ml包被剂

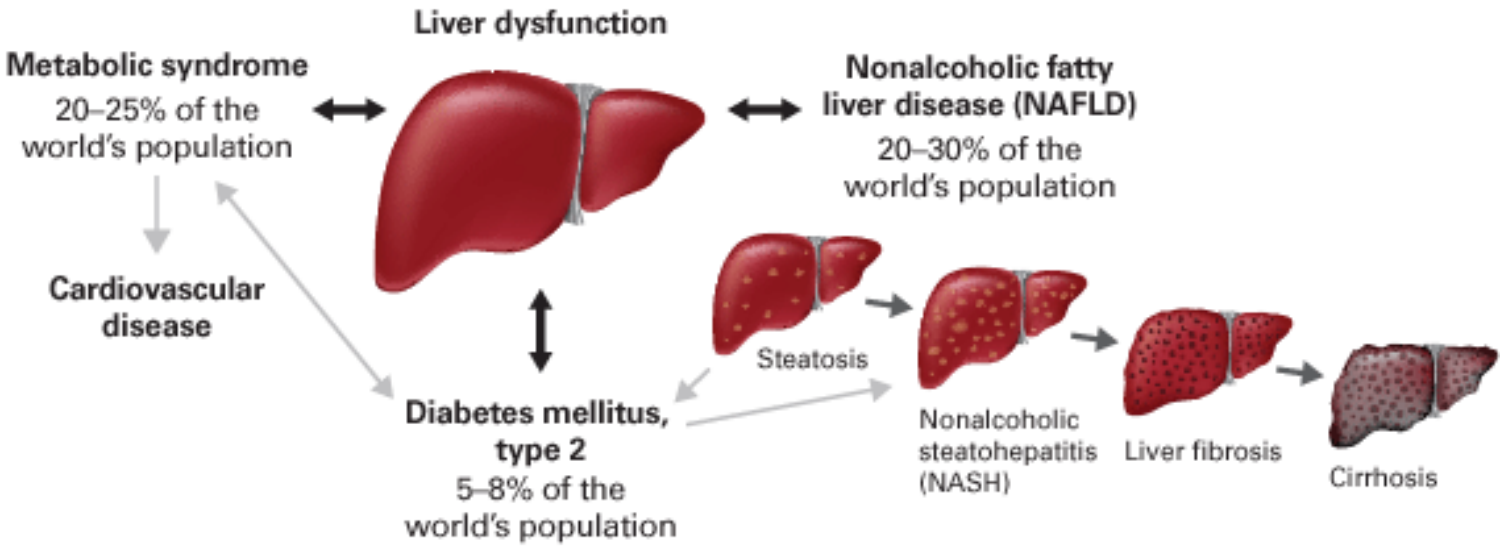
+

35 ml清洗液

+

200 ml培养液

应用一：肝脏代谢疾病研究



肝脏：

① 通过储存或释放糖原，对血糖变化作出反应。
② 与胰腺相似，肝脏也对胰岛素有所反应。
③ 脂肪酸、胆固醇和脂蛋白输送至肝脏并输出。
（当肝脏开始积累这些脂类物质，会导致NAFLD，最终会导致脂肪变性–肝炎–肝硬化）

技术数据：应用于代谢疾病模型

TECH NOTE

Next-generation human iPS cell-derived hepatocytes for metabolic disease modeling

Improved hepatocytes for modeling metabolic disorders
Cells express expected markers and display functional characteristics of mature hepatocytes >>

Functional glucose regulation
Cells demonstrate normal insulin response and functional glucose regulation >>

Functional lipid metabolism
Cells demonstrate important features of lipid metabolism >>

An appropriate model for progressing NAFLD
Upon induction of steatosis, cells show elevated triglycerides and TNFα >>

全文链接：
https://www.takarabio.com/learning-centers/stem-cell-research/stem-cell-technical-notes/hepatocytes-for-disease-modeling

人iPS细胞来源肝脏细胞：新型的代谢疾病模型

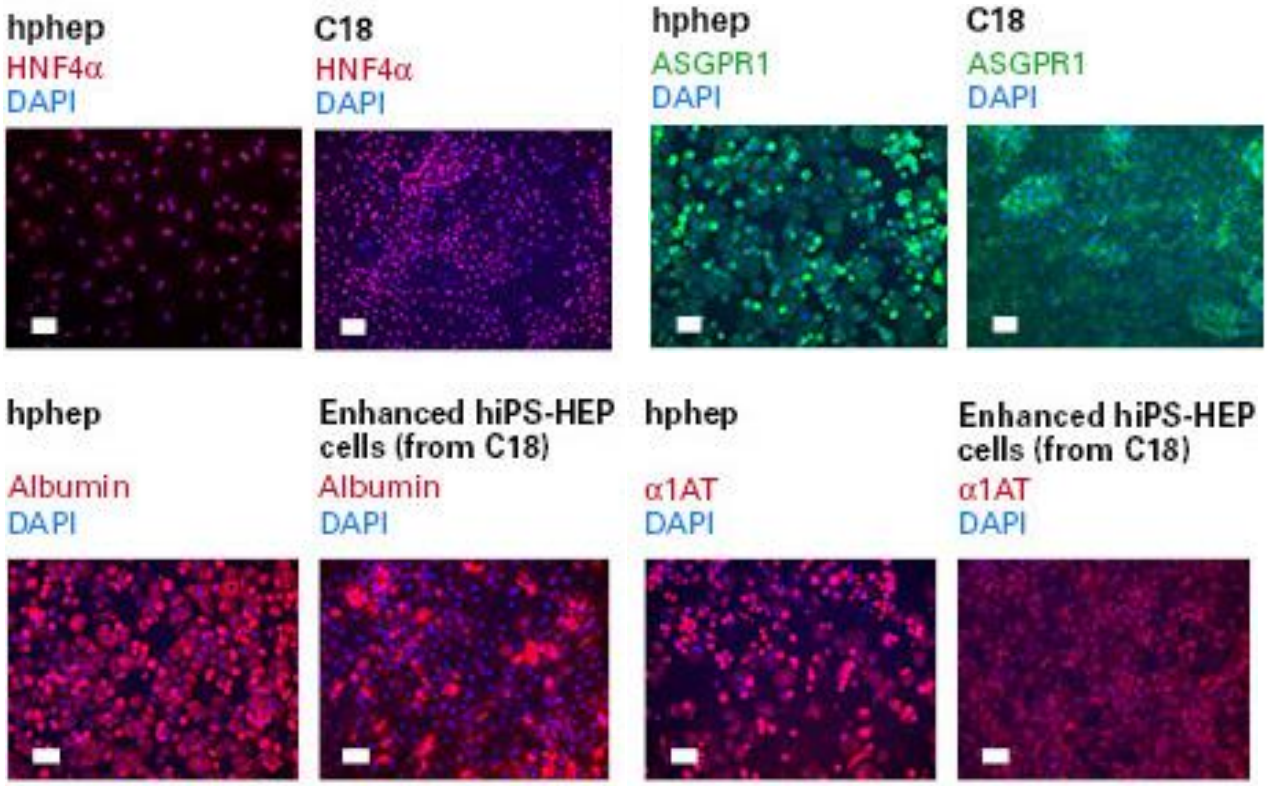
Enhanced hiPS-HEP：

表达预期的标志物和呈现成熟肝脏细胞的功能特征>>
显示功能性的葡萄糖调节>>
显示功能性的脂质代谢>>
作为NAFLD模型>>

人iPS细胞来源肝脏细胞：代谢疾病模型

成熟肝脏细胞特征

Enhanced hiPS-HEP表达多种肝脏细胞特异性标志物（HNF4α；ASGPR1；Alb；α1AT）



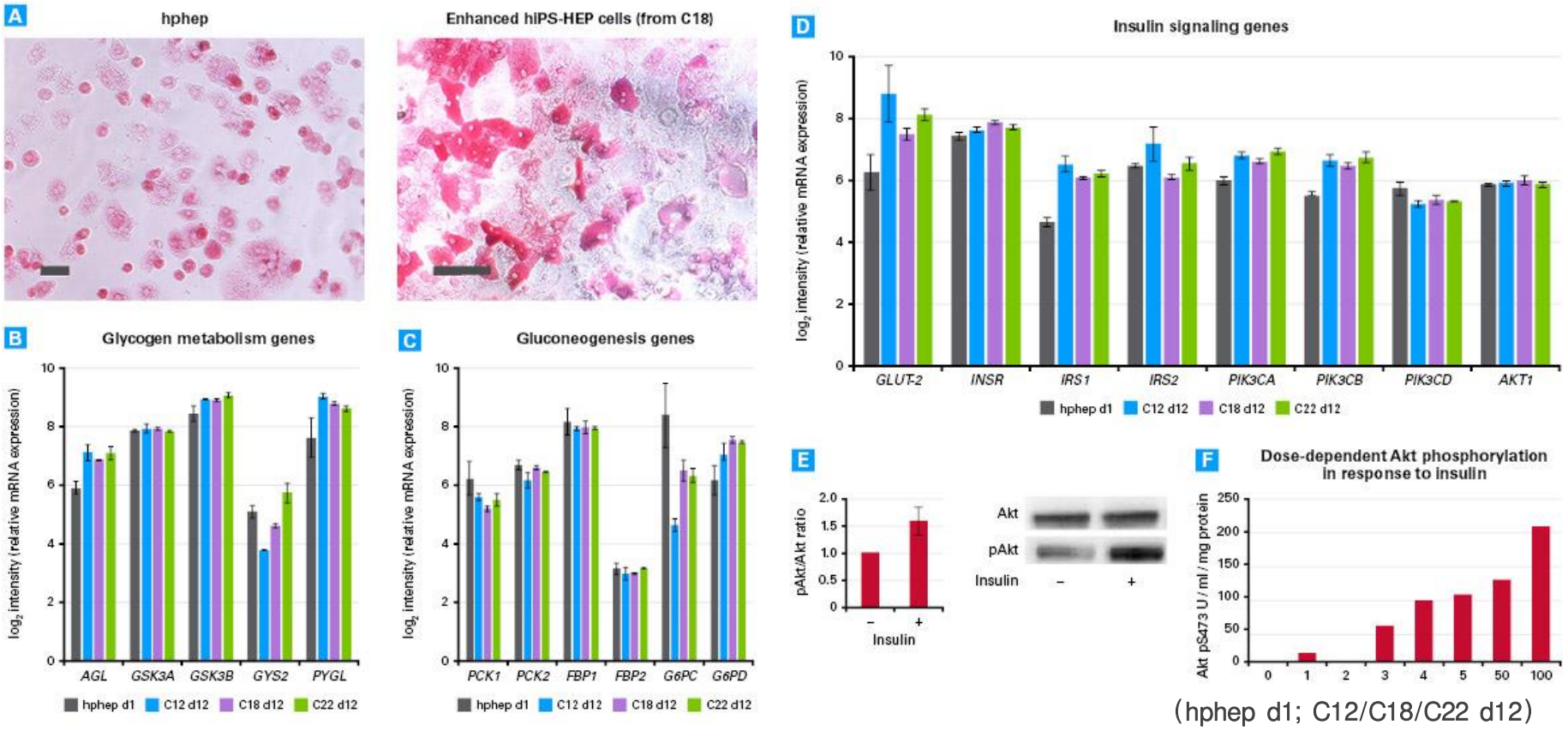
（hphep d1；C18 d12）

hphep：human primary hepatocytes (BioreclamationIVT)
C12/C18/C22：Enhanced hiPS-HEP cells from C12, C18, C22(Takara)

人iPS细胞来源肝脏细胞：代谢疾病模型

功能性葡萄糖调节

Enhanced hiPS-HEP可以储存糖原，表达涉及糖原代谢、糖异生、胰岛素信号的基因，通过磷酸化Akt对胰岛素反应

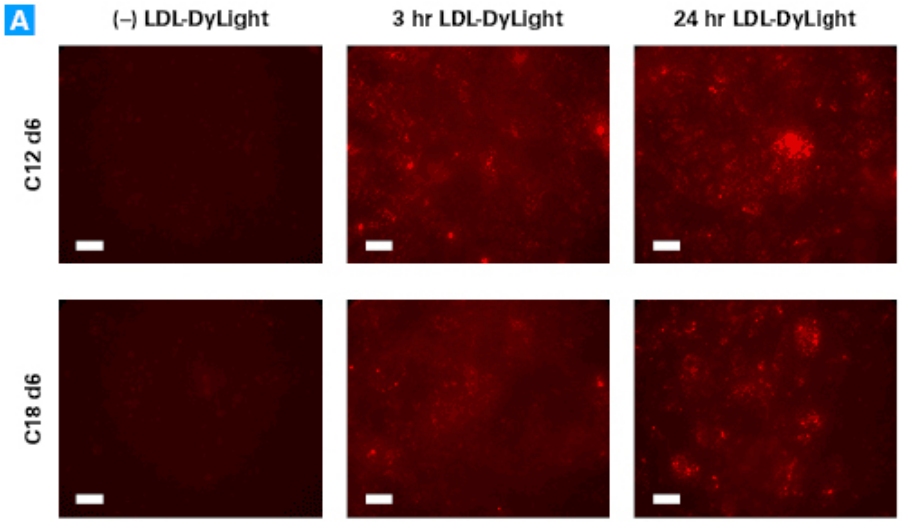


(hphep d1; C12/C18/C22 d12)

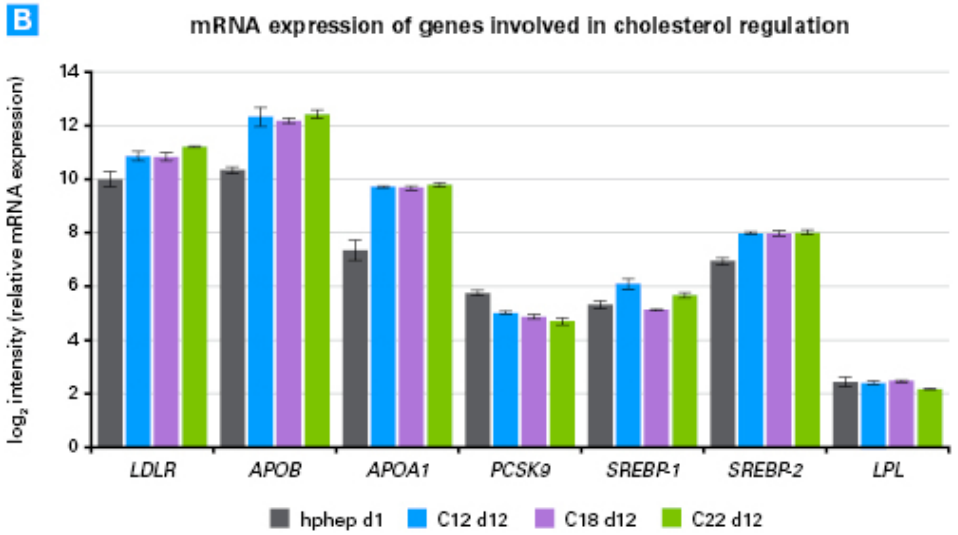
人iPS细胞来源肝脏细胞：代谢疾病模型

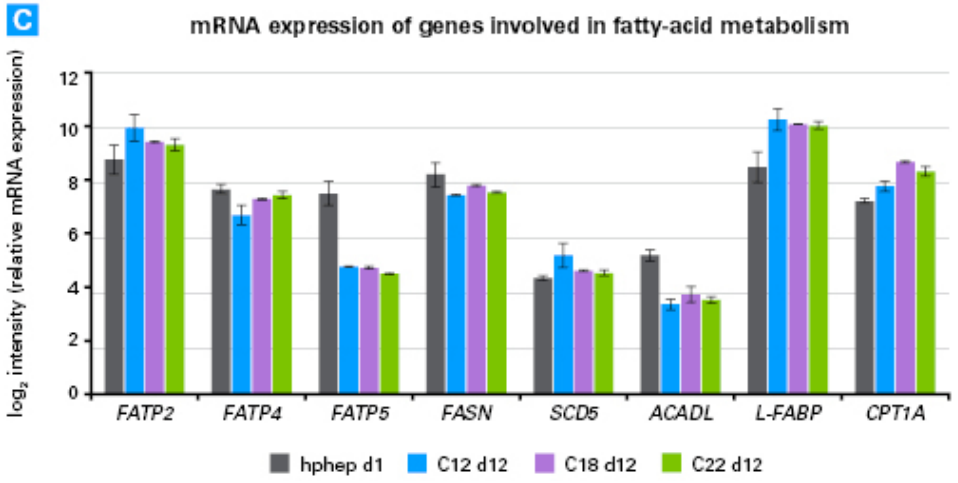
功能性的脂质代谢

Enhanced hiPS-HEP可以摄取LDL，表达胆固醇、脂肪酸代谢调节相关的基因



（hphep d1; C12/C18/C22 d12）

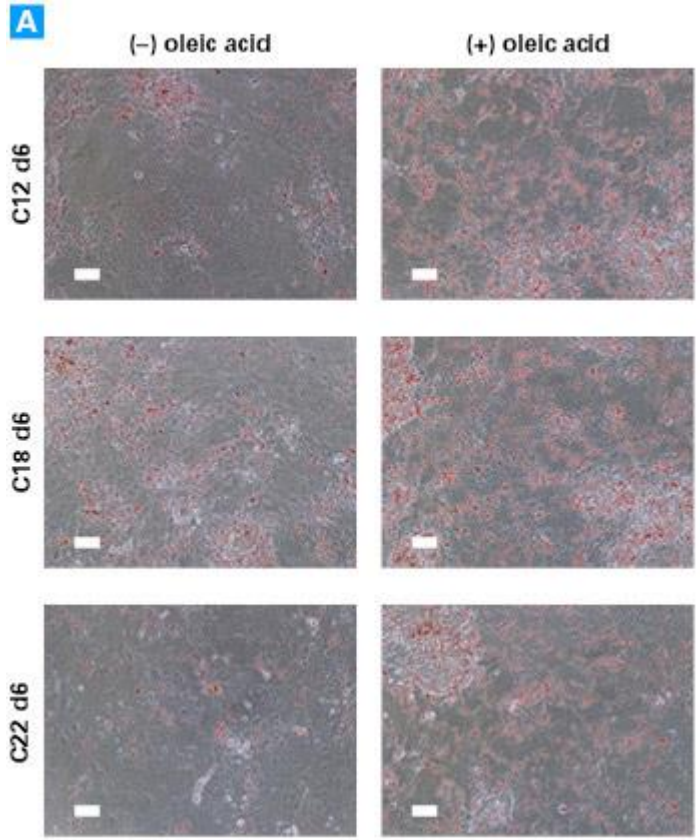


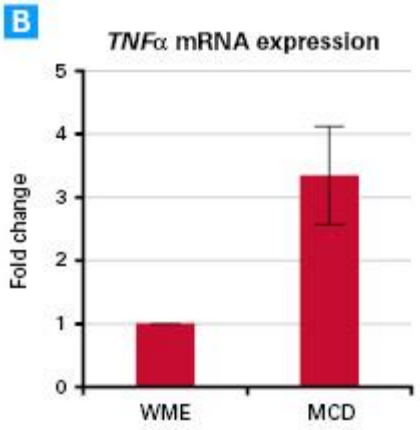


人iPS细胞来源肝脏细胞：代谢疾病模型

NAFLD模型

Enhanced hiPS-HEP在高油酸处理后，类似如NAFLD，积累了甘油三酯；
在MCD培养基处理后，如预期显示炎症因子TNFα的表达升高，模拟NAFLD中脂肪变性的进程

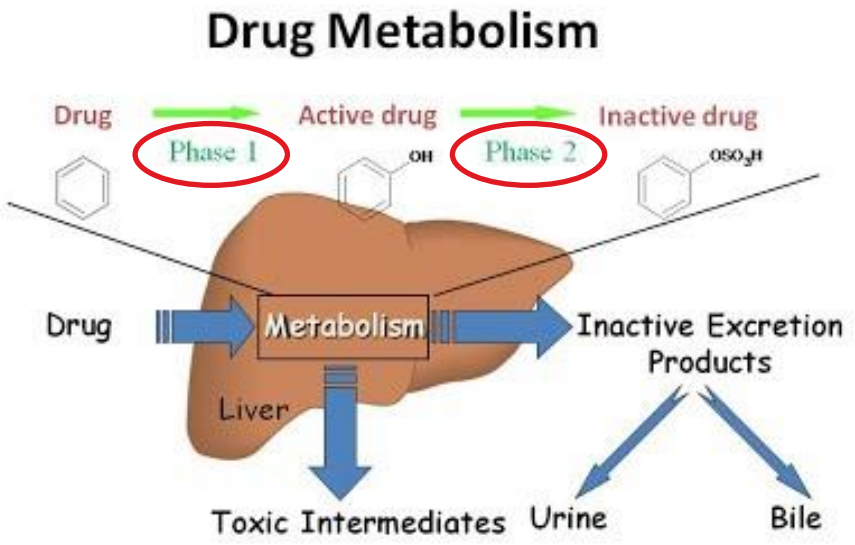




WME: Williams medium E
MCD: Methionine-&choline-deficient WME
蛋氨酸胆碱缺乏培养基，可诱导TNFα表达，类似脂肪变性进程
(Sahai et al. 2006)

(–) oleic acid: BSA
(+) oleic acid: oleic acid coupled to BSA

应用二：药物ADME-Tox研究



药物在肝脏内的代谢阶段：

Phase Ⅰ:

氧化、还原、水解等反应直接改变物质的基团或使之分解，激发活性或毒性

Phase Ⅰ Enzyme:

CYP450 enzymes(细胞色素P450酶）

Phase Ⅱ:

药物进一步与内源性结合剂的结合反应，使药物毒性或活性降低和极性增加，进而经由尿液或胆汁排出体外

Phase Ⅱ Enzyme:

SULT（磺基转移酶）

UGT （尿苷二磷酸葡萄糖醛酸转移酶）

技术数据：应用于药物代谢研究

TECH NOTE

Next-generation human iPS cell-derived hepatocytes for long-term drug metabolism studies

Long-term expression of drug-metabolizing machinery
Cellartis enhanced hiPS-HEP cells express hepatic uptake and efflux transporters, phase II enzymes, and cytochrome P450 (CYP) enzymes until Day 20 post-thawing.

High batch-to-batch consistency
Cellartis enhanced hiPS-HEP cells display consistent CYP activity levels and high homogeneity between batches.

Interindividual variation in CYP activities due to availability of three donor lines
Cellartis enhanced hiPS-HEP cells derived from different hiPSC lines display different CYP activity profiles, as expected.

全文链接：
https://www.takarabio.com/learning-centers/stem-cell-research/stem-cell-technical-notes/hepatocytes-for-drug-metabolism-studies

人iPS细胞来源肝脏细胞：长时间的药物代谢研究

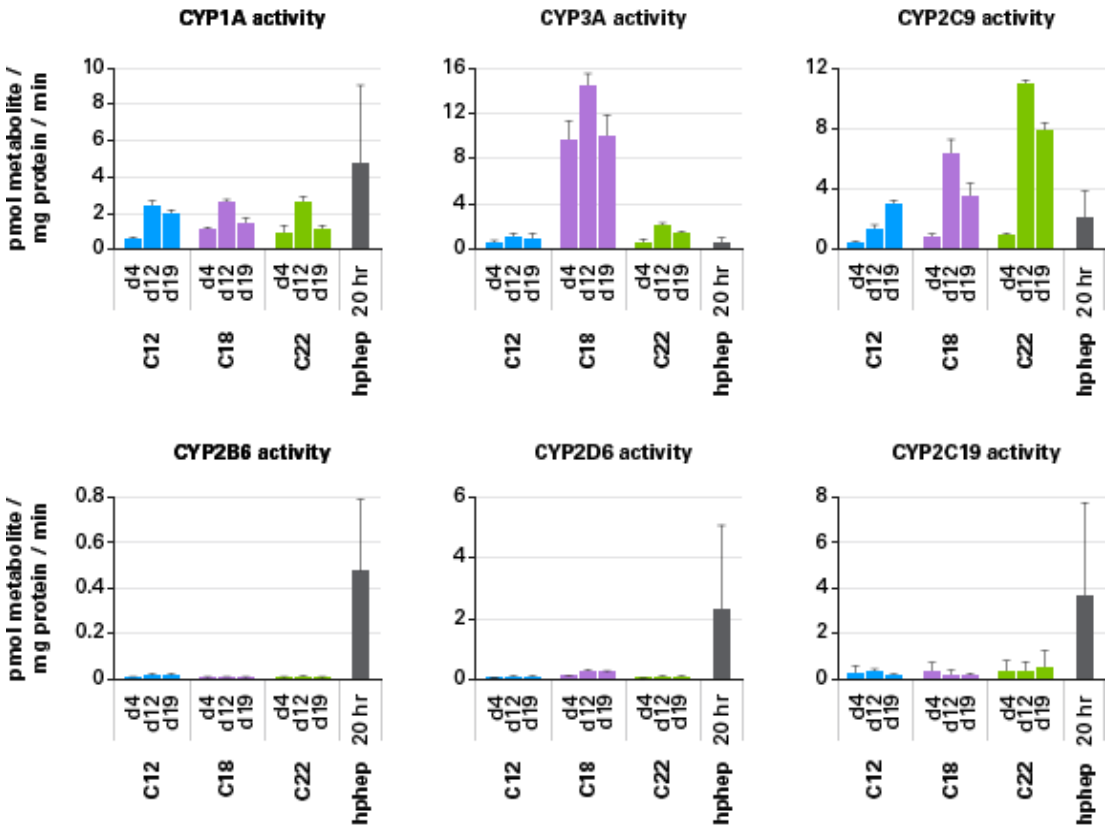
Enhanced hiPS-HEP：

长时间表达药物代谢机制（CYP酶、II相酶、转运蛋白等）>>
不同批次间差异小，CYP活性水平一致>>
三种供体来源细胞如预期显示不同的CYP活性谱>>

人iPS细胞来源肝脏细胞：药物代谢模型

CYP酶

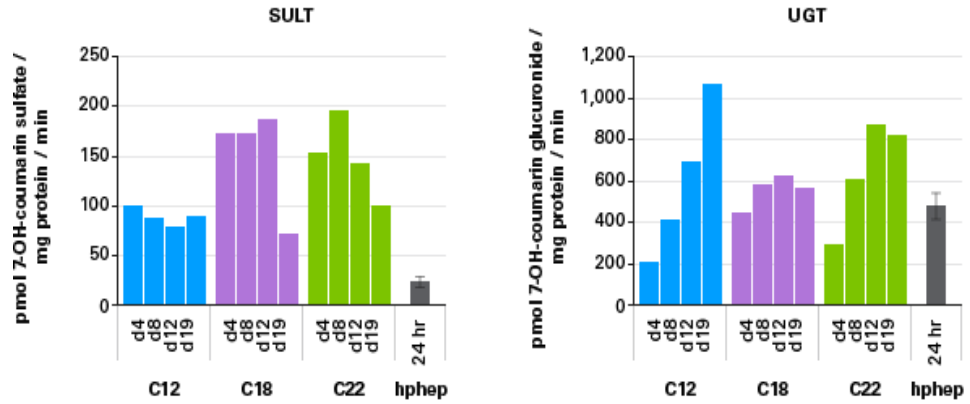
Enhanced hiPS-HEP长时间具备CYP酶活性，同一供体批次间差异小，CYP酶活性稳定
三种供体来源Enhanced hiPS-HEP具备不同的CYP活性谱，反映了个体之间的CYP差异



人iPS细胞来源肝脏细胞：药物代谢模型

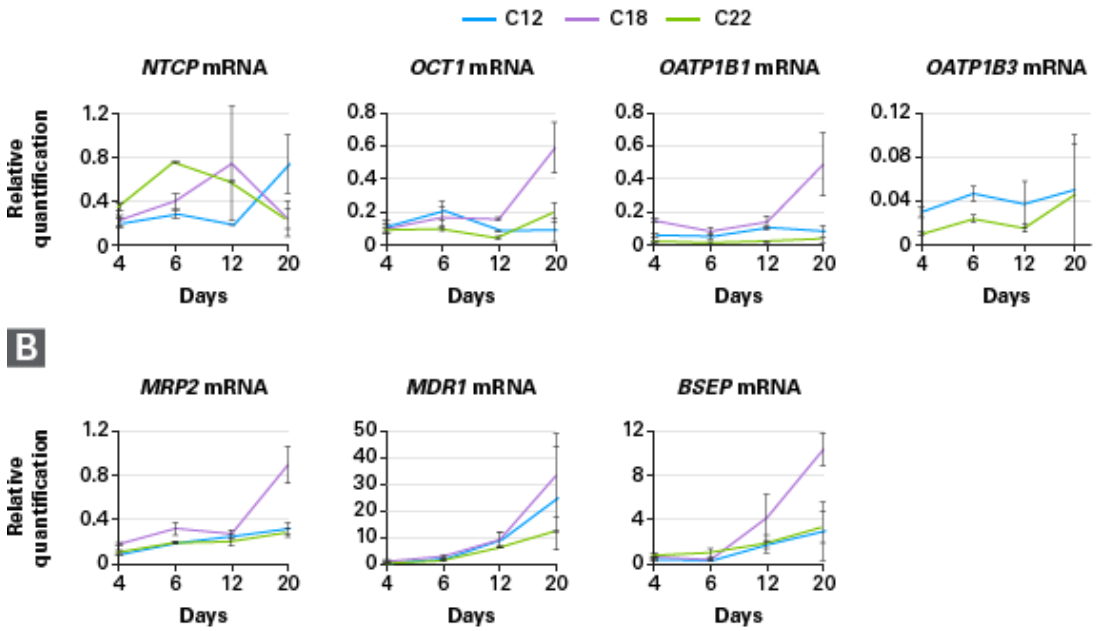
II相酶

Enhanced hiPS-HEP
长时间维持II相酶活性



转运蛋白

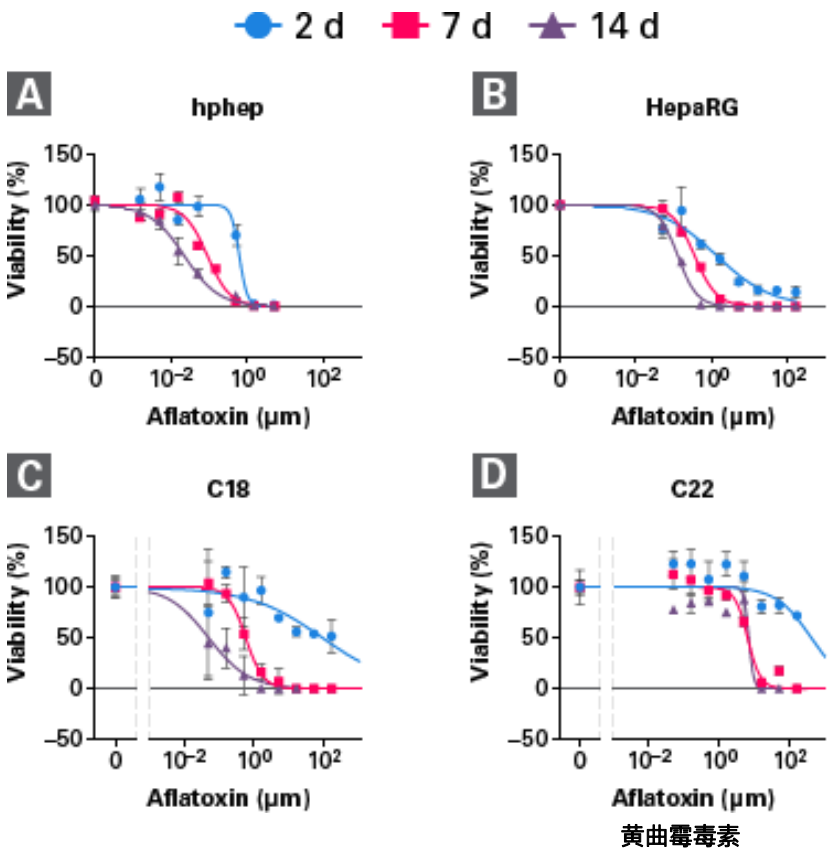
Enhanced hiPS-HEP长时间表达摄取转运蛋白（上）、外排转运蛋白（下）

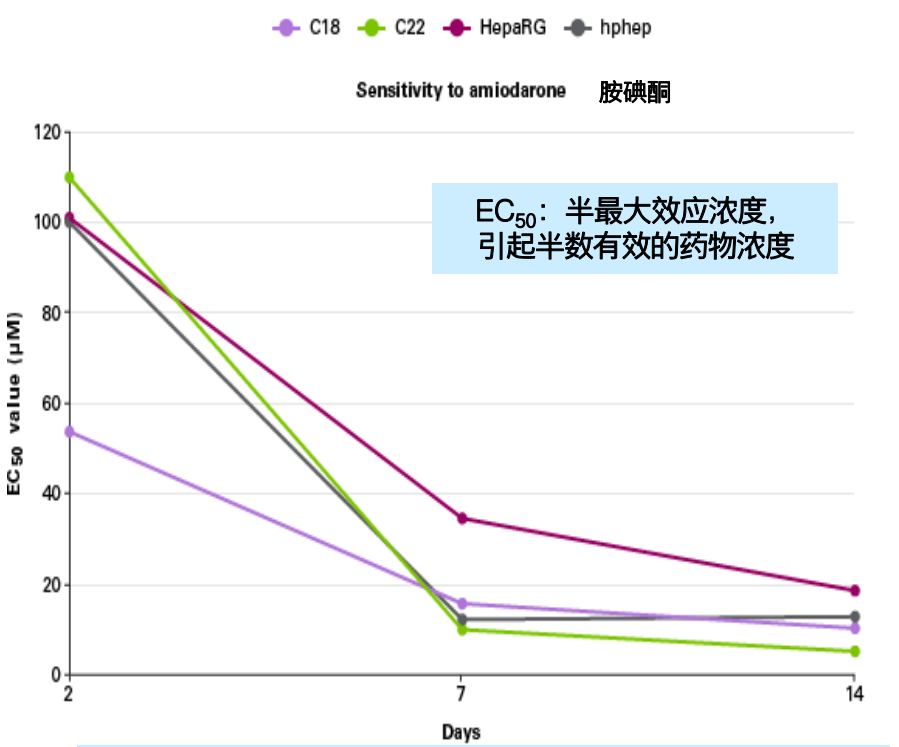


人iPS细胞来源肝脏细胞：药物代谢模型

慢性毒性研究

Enhanced hiPS-HEP对已知的肝毒性药物呈现正确反应，即延长重复给药时间后，灵敏度增加



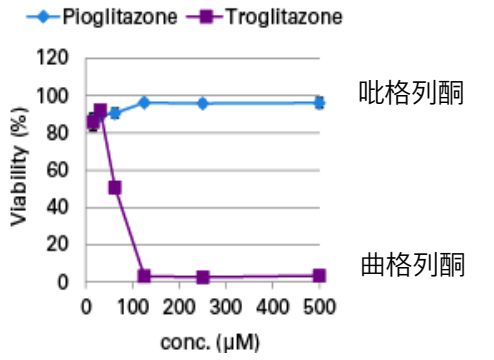


Hphep (BioreclamationIVT), 3D spheroids
HepaRG (Thermo Fisher Scientific), 2D conditions
Cellartis Enhanced hiPS HEP, 2D conditions

人iPS细胞来源肝脏细胞：毒性评价模型

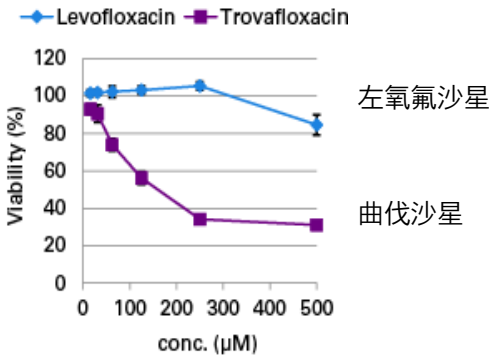
对已知的肝脏毒性药物呈现高特异性和高敏感性

可区分有毒和无毒的结构类似物



吡格列酮

曲格列酮

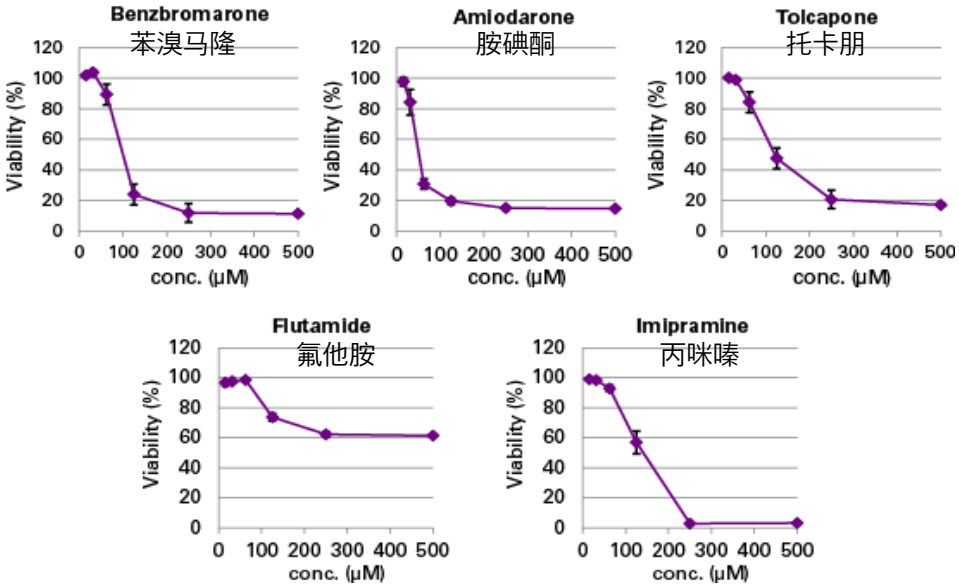


左氧氟沙星

曲伐沙星

获得的体外毒性检测数据与临床反应相关

对引起临床肝脏受损的化合物呈现预期反应



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7. Holmgren, G. *et al*. Long-term chronic toxicity testing using human pluripotent stem cell-derived hepatocytes. *Drug. Metab. Dispos.* **42**, 1401–1406 (2014).

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