Human CryoHeps - Suspension

Acute Cytotoxicity Assessment

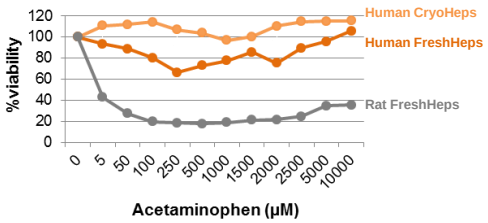
Cytotoxicity profiles and **IC50 determinations** using **Suspensions** of human CryoHeps (4h treatment) are equivalent to plated human hepatocytes (1-3d treatment)

Acute Cytotoxicity Ranking – Human

IC 50 (µM)	Acute (day 1-3)	suspension 4h
Amiodarone	40-100	40
Chlorpromazine	15-25	20
Cyclosporin A	25-50	>50
Fenofibrate	>5000	>5000
Ibuprofen	>2000	2000
Metformin	2000	2000
Paracetamol	>5000	>5000
Rosiglitazone	175-300	>300
Troglitazone	22-30	>100
Valproic acid	>1000	>1000

Alexandre et al., HUV-HUF 2010

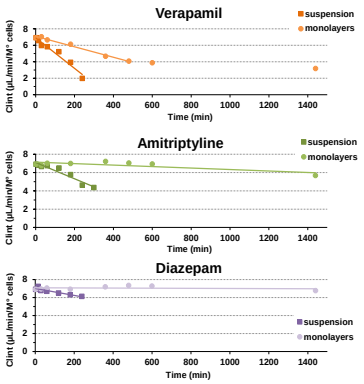
Acute Cytotoxicity – Various species



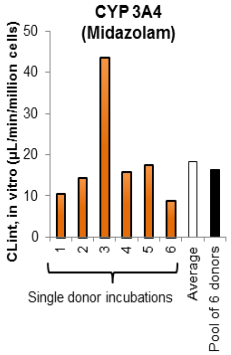
Alexandre et al., ISSX 2010

Prediction of Hepatic Clearance

Suspensions of human CryoHeps allow **intrinsic clearance** (CL_{int}) measurement for **low metabolic compounds**, can be used as **single or pools** of donors, and give better **prediction of hepatic clearance** (CL_H) than microsomes



Desbans et al. , submitted

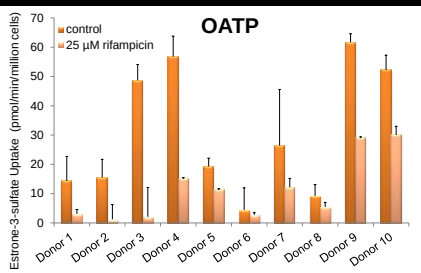


Pekthong et al. In preparation

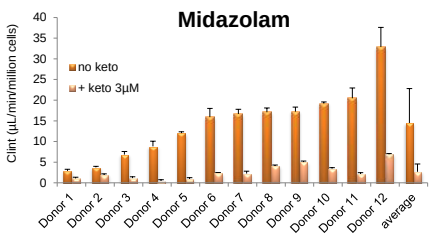
CYP	Substrate	CL_H (mL/min/kg) Predicted with CryoHeps	Predicted with microsomes	Observed *in vivo*
2B6	bupropion	**8.7 – 13.7**	0.3 – 9.3	**13.4**
2C8	paclitaxel	**1.9 – 6.3**	0.0 – 0.2	**4.0 – 10.9**
2C9	diclofenac	**1.9 – 16.5**	1.4 – 15.2	**3.4 - 7.5**
3A4	midazolam	**0.3 – 17.1**	9.6 – 17.9	**4.6 - 12.0**
2D6	bufuralol	**3.8 – 17.4**	1.8 – 12.3	**6.0 – 8.8**

Pekthong et al. In preparation

Prediction of Drug-Drug Interactions through Inhibition



Alexandre et al., HUV-HUF 2010



Suspensions of human CryoHeps allow evaluation of donor-dependent **uptake transporter inhibition** and **CYP inhibition**

Prediction of **fraction metabolized** (*fm*) close to observed *in vivo*

	Midazolam	Loratadine	Methylprednisolone	Tacrolimus	Amitriptyline
in vitro $fm_{CYP3A4/5}$ prediction (CV%)	79% (17%)	40% (59%)	60% (48%)	62% (31%)	40% (60%)
in vivo $fm_{CYP3A4/5}$	89%	NA	60%	24%	21%

NA: Not available

Desbans et al., 2012 submitted

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