PRO-EURO DILI NETWORK

Prospective European Drug-induced Liver Injury Network

Outreaching biotechnological enterprises in DILI

Andreas Benesic

PRO-EURO DILI NETWORK Meeting Malaga

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Tesla driver killed while using autopilot was watching Harry Potter, witness says

Driver in first known fatal self-driving car crash was also driving so fast that 'he went so fast through my trailer I didn't see him', the truck driver involved said

Did this incident **stop the development** of self-driving cars**?**

Most popular

Weinstein ex-aide breaks confidentiality agreement over alleged harassment

Singapore: no more cars allowed on the road, government says

Drug-induced liver injury (DILI)…

…is the major cause for acute liver failure leading to death or requiring liver transplantation[1,2]

…has been the **most frequent single cause** of safety-related drug marketing withdrawals **for the past 50 years, continuing to the present**.” (FDA Guidance to industry)

DILI is an unforeseeable adverse side effect with major consequences

Drug development process	Preclinical	Phase I-III	Phase IV postmarketing
Cumulative Investments	0.8 billion	2.3 billion	2.5 billion
Attrition by DILI	20%	38%	42%

„**Intrinsic**“ (drug properties):
-**dose dependent**
-**predictable**

„**Idiosyncratic**“ (individual patient susceptibility):
-**rare**
-**unpredictable**

The case of Ximelagatran:
How Dll ruined a potential blockbuster drug

Direct oral Thrombin-Inhibitor

Evaluated Indications:

Atrial fibrillation/Stroke
Venous thrombosis
Pulmonary embolism
Thrombosis prophylaxis

No liver issues detected in preclinical development

Clinical development:

Study	participants
SPORTIF II	254
SPORTIF III	3.407
SPORTIF IV	167
SPORTIF V	3.922
METHRO I	135
METHRO II	1.916
METHRO III	2.788
EXPRESS	2.885
EXULT A	2.301
EXULT B	2.303
TOTAL patients in clincial trials	**20.078**

Severe Liver Issues:
in 0,5%
(~100 cases)

Ho S-J, and Brighton TA. Vasc Health Risk Man. 2006;2(1):49-58.
Dt. Ärzteblatt, 15. Februar 2006

The case of Ximelagatran:
Nine unproven DILI cases - no FDA approval

Severe Liver Issues: FDA review for NDA 21-686 (08/2004)

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.08% (5/6230) of patients exposed to comparators. Nine ximelagatran-treated patients (24.3%, 9/37) died with concomitant ALAT >3xULN and bilirubin >2xULN. Among these, 3 died from heart failure; 3 died from carcinomas with hepatic metastases; 2 (ID# 7259, and 7859) died from GI bleeding with coagulopathy (1 with biopsy documented hepatic necrosis) and 1 (ID# 5442) died from hepatitis B. Liver failure/toxicity by ximelagatran might have caused or at least contributed to these deaths. Only one autopsy was done in these 9 deaths and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis.

http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069B1_03_FDA-Backgrounder-Execsummaryredacted.pdf
(page 12, 2nd paragraph)

Σ: 37 cases, 9 dead

USA: NOT APPROVED

The case of Ximelagatran:
One suspected case – EU withdrawal

Melagatran AstraZeneca 3 mg/0,3 ml Injektionslösung/
Exanta® 24 mg Filmtabletten

Marktrücknahme

14. Februar 2006

Sehr geehrte Damen, sehr geehrte Herren,

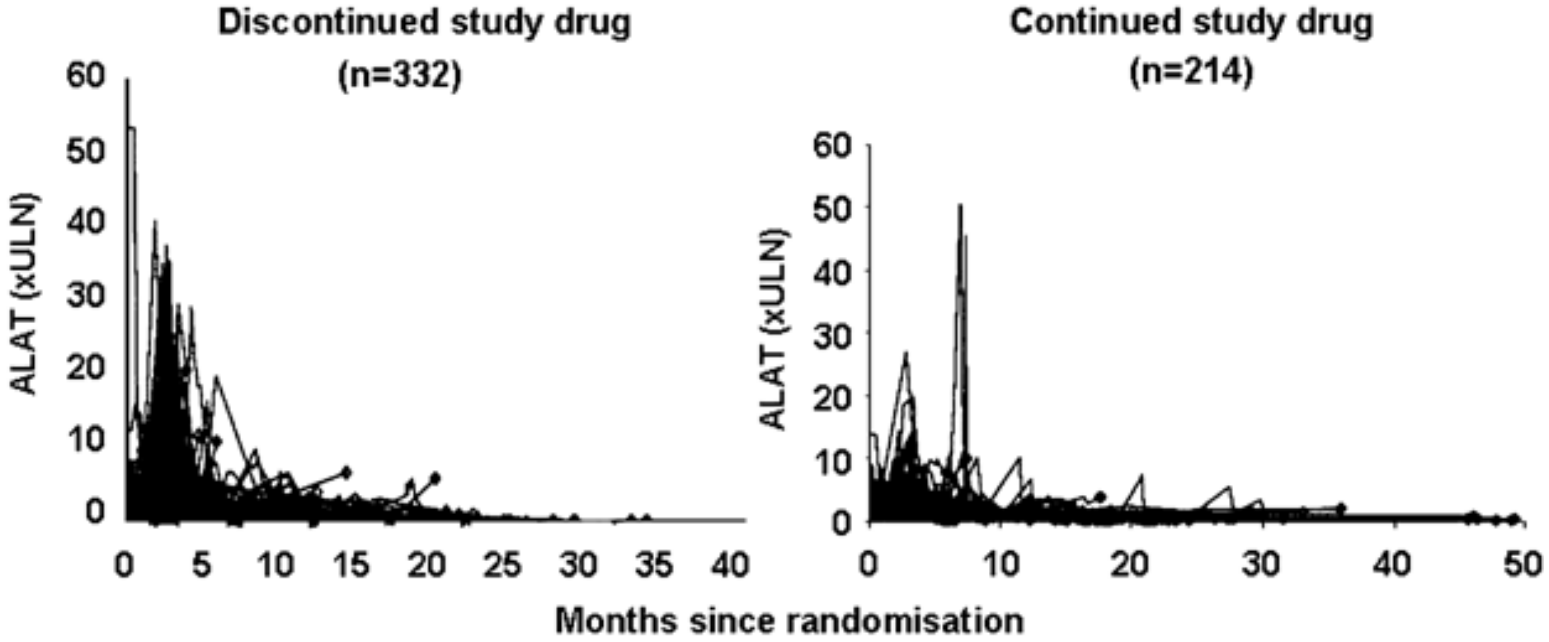
AstraZeneca hat sich, nachdem die zuständigen Behörden informiert wurden, dazu entschlossen, die Antikoagulanzien Melagatran AstraZeneca 3 mg/0,3 ml Injektionslösung und Exanta® 24 mg Filmtabletten (Melagatran/Ximelagatran) vom Markt zu nehmen.

AstraZeneca hat kürzlich eine Nebenwirkungsmeldung über einen ernsten Leberschaden bei einem Patienten erhalten. Dieser nahm an einer klinischen Studie teil, bei der eine verlängerte VTE-Prophylaxe in der orthopädischen Chirurgie mit Exanta® (von bis zu 35 Tagen) untersucht wurde. Der hier vorliegende Fall beschreibt erstmals eine schwerwiegende Hepatitis

Σ: 1 case, 0 dead

EUROPE: WITHDRAWN

The case of Ximelagatran:
Liver enzyme patterns during therapy



ALAT elevations≥3xULN in patients treated with ximelagatran with and without discontinuation of study drug. Data from 546 out of 6948 patients randomized to ximelagatran long-term (in studies SH-TPA-0002, SH-TPA-0003, SH-TPA-0004, SH-TPA-0005, SH-TPV-0003, SH-TPV-0002, SH-TPV-0005, SH-TPC-0001, see the AstraZeneca Clinical trials registry at http://www.astrazenecaclinicaltrials.com/).

Kindmark A et al; *The Pharmacogenomics Journal* (2008) **8,** 186–195
http://www.nature.com/tpj/journal/v8/n3/full/6500458a.html

The case of Ximelagatran: EXGEN-Study – rescue by biomarker?

Study	Subjects	No. of subjects with genotypes			Frequency of DRB1*07 (%)	Sensitivity of DRB1*07 (%)	Specificity of DRB1*07 (%)
		DRX,X	DRX,7	DR7,7			
EXGEN	Cases	39[b]	32[a]	3[a]	26	47	83
	Controls	108[c]	22[d]	0[d]	8.5		
Replication	Cases	5	5	0	25		
	Controls	16	0	0	0		

Table 2. Individuals carrying HLA DRB1*07 genotypes in EXGEN and in the replication data set

DR7 refers to DRB1*07. DRX refers to all alleles of *DRB1* apart from DRB1*07. For the biomarker analysis, a=true positives, b=false negatives, c=true negatives and d=false positives. Sensitivity is calculated as $a/(a+b)$, and specificity is calculated as $c/(c+d)$.

Kindmark A et al; *The Pharmacogenomics Journal* (2008) **8,** 186–195
http://www.nature.com/tpj/journal/v8/n3/full/6500458a.html

Summary

- DILI risk could not be identified by preclinical testing
- Rare severe liver issues more likely to occur with increased patient exposure
- Genetic association shown, but PPV low
- Diagnosis/Causality not always unequivocal

December 2017

https://www.fiercepharma.com/pharma/ema-investigates-allergan-blockbuster-hopeful-esmya-reports-liver-damage

Pharma

EMA investigates Allergan blockbuster hopeful Esmya on reports of liver damage

by *Carly Helfand* | Dec 4, 2017 12:04pm

February 2018

http://www.spiegel.de/gesundheit/diagnose/iberogast-streit-um-nebenwirkungen-des-magen-darm-mittels-a-1195411.html

February 2019

https://www.fiercebiotech.com/biotech/liver-toxicity-concerns-spike-motif-bio-s-iclaprim-filing

FierceBiotech

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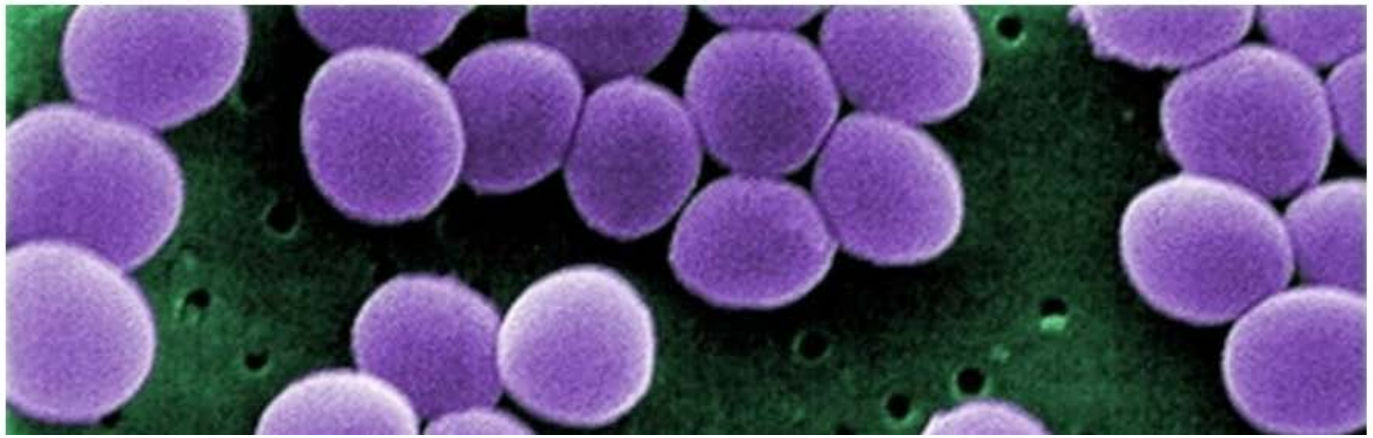
Biotech

Liver toxicity concerns spike Motif Bio's iclaprim filing

by Phil Taylor | Feb 14, 2019 10:30am



About the Author

Phil Taylor

Examples of Drugs affected by DILI

2016:	2017:	2018:	2019:
Pexidartinib **solithromycin** **vadastuximab talirine**	**Telapristone** **Daclizumab** **Ulipristal**	**Iberogast®** **Flupirtine** **MDG009**	**Iclaprim** **….**

~3 Drugs with regulatory actions due to DILI per year

~1 market withdrawal per year due to DILI

Historic data from 1950s-2013: **~1 withdrawal due to DILI per year**…

Onakpoya et al.; BMC Med. 2016; 14: 10.

DILI Stakeholders

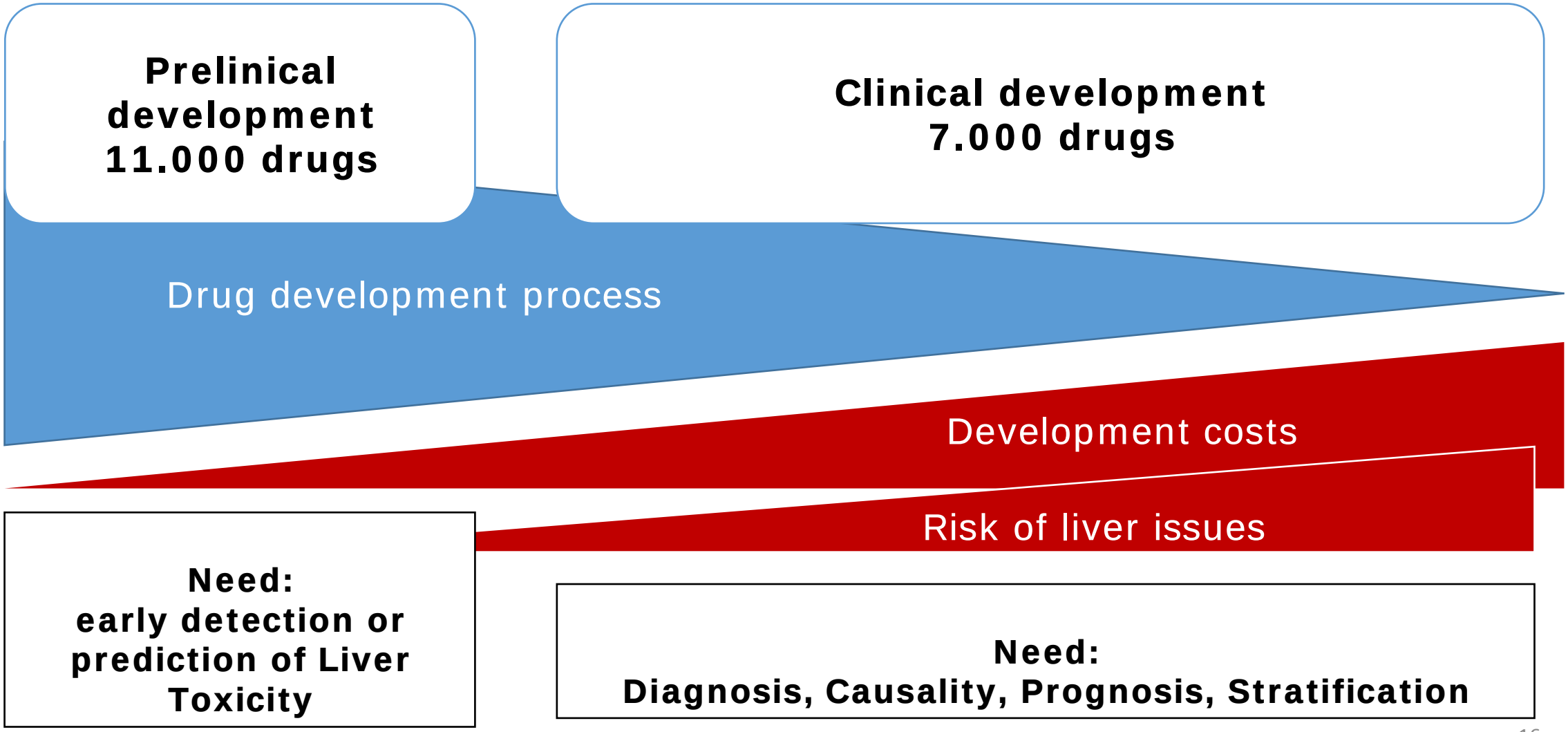
Drug Developers

Drug development process

Patients

Regulators

DILI in Drug-Development

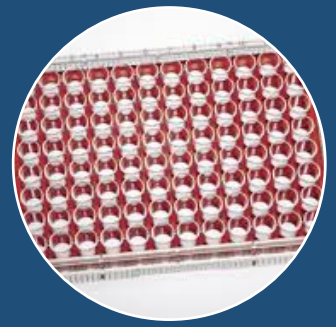


DILI - unmet needs

Preclinical identification of risky drugs	**Clinical** tools for iDILI
Aim: avoid bringing forward *molecules that are potentially hepatotoxic* by - improved selection of candidates - improved drug design	**Aim: reducing the risk of severe *hepatotoxicity in the population*** by - improved risk/benefit assessment - safety biomarkers enabling personalized therapies
Methods: - in silico models - structural alerts - in vitro/animal models	**Methods:** - Diagnostic algorithms - Diagnostic tests - Biomarkers

Ref.:
1) Lewis JH Clin Gastroenterol Hepatol. 2015 Nov;13(12):2173-2189.e8

Mind the gap: Preclinical to clinic



Ppreclinical liver safety testing validated with:

- **Diclofenac**
- **Amiodarone**
- **Tamoxifene**
- Etc…

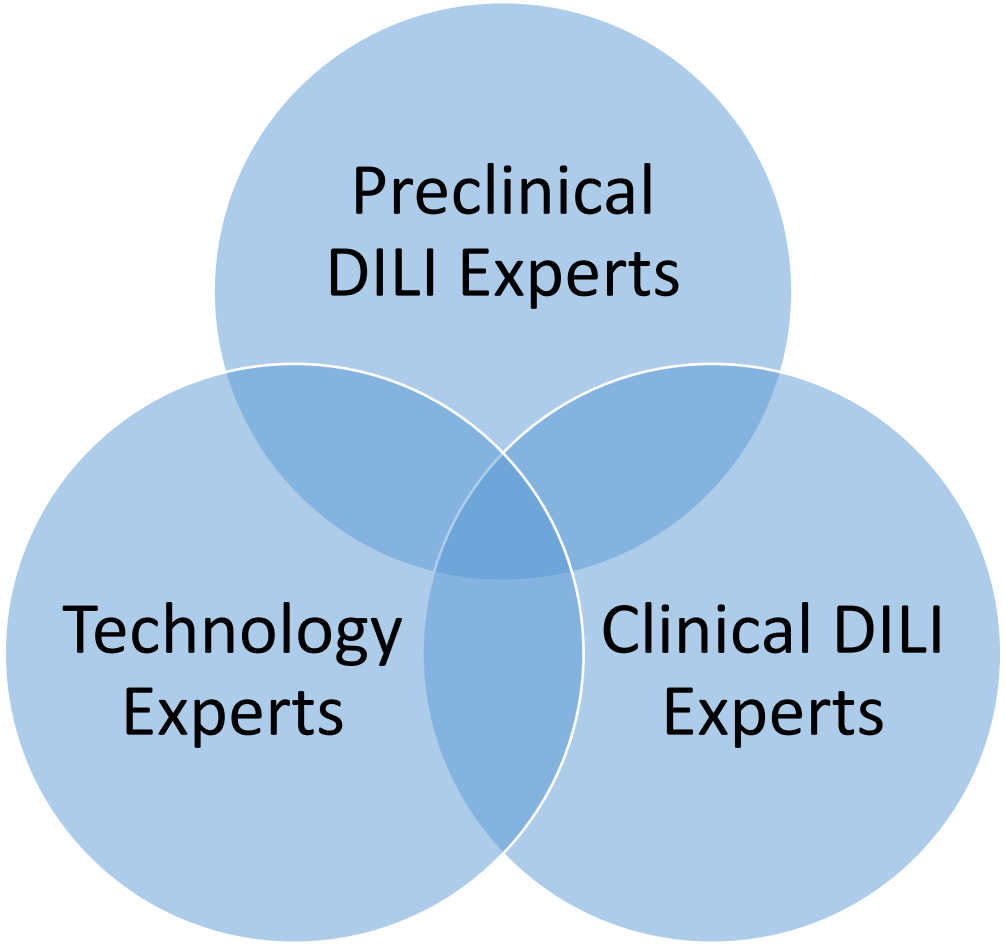
Only few cases **in clinical trials and post-marketing,**

- **worldwide most commonly used NSAID**
- **30% Market share in antiarrhythmics**
- **world's largest selling hormonal drug for the treatment of breast cancer**

Bridging the Gap

PRO-EURO DILI NETWORK

Prospective European Drug-induced Liver Injury Network



Biotech Companies in PRO-EURO DILI

Cherry Biotech	France	High-end 3D cell culture technologies
VLVbio	Sweden	Cell death ELISA for clinical applications
C4X DISCOVERY	UK	Provider of a unique software platform
MetaHeps®	Germany	Blood Test for DILI causality in patients

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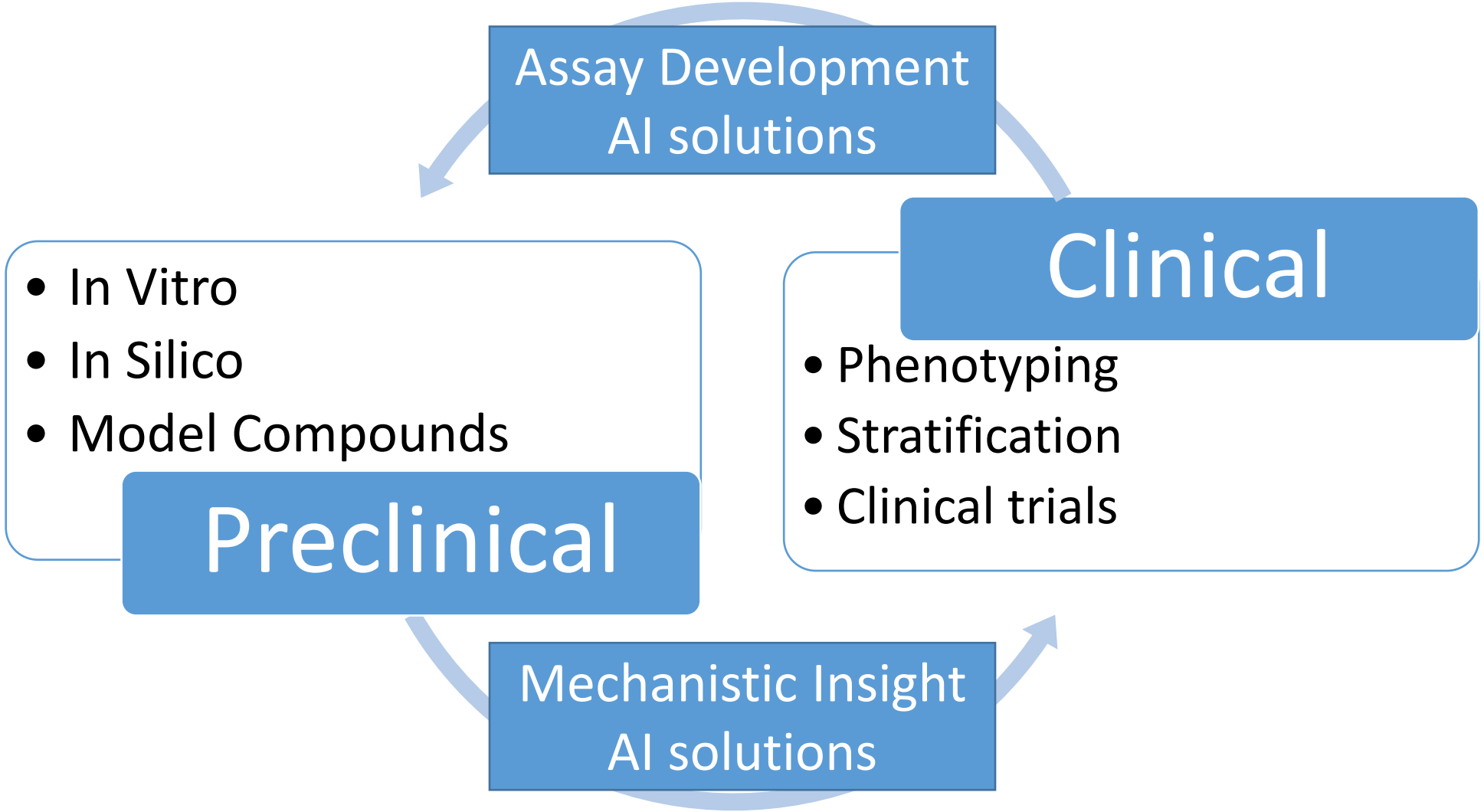

Summary

Collaboration is mandatory to get the full picture in the complexities of DILI

Clinical and preclinical approaches can inform each other in both ways

Biotech can create innovative DILI approaches and realize their valorization