



Innovative Medicines Initiative

Improved early prediction of Drug Induced Liver Injury (DILI)

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efpia

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Pre-competitive nature



- DILI is a leading cause of withdrawal, cautionary labelling and restricted usage of licensed drugs, and is an important cause of attrition of candidate drugs during development, in all pharmas.
- Numerous scientific advances have been made which have improved our understanding of DILI, and have the potential to provide useful new predictive approaches.
- Effective evaluation of these approaches, and development of “best practice” guidelines, will require close interaction between pharmas and academic scientists and can best be tackled pre-competitively.

Need for public-private collaboration



- Academic groups have been limited by lack of access to compounds terminated due to DILI observed in drug development, in animals and/or in clinical trials.
- Pharmaceutical companies have been hampered by the complexity of the science, uncertainty about which model systems justify investment, and lack of clarity on the most effective DILI prediction strategy.
- Only a coordinated and collaborative approach that links activities involving multiple institutions will permit significant new progress towards tackling DILI.

Objectives of the full project



The primary goal of this project is to identify new assays and models, which can be used during drug discovery and early non-clinical development to support design, ranking and selection of drugable candidates that have low propensity to cause DILI in man.

The successful proposal will have as objectives:

1. To identify and validate an improved panel of *in vitro* “best practice assays” for predicting DILI in the human population (***major objective***)

Objectives of the full project



2. To explore and understand the relationship between *in vitro* assay signals and DILI *in vivo*, in preclinical test species and in man (**supportive**)
 3. To develop and validate novel Systems Modelling approaches that integrate multiple preclinical data types to improve prediction of DILI in man (**supportive**)
 4. To enhance shared understanding, between academia, pharma and regulatory agencies, of the value and limitations of new and existing approaches for DILI hazard identification and risk assessment (**supportive**)
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Key deliverables of full project



- A panel of improved and/or novel *in vitro* assays which enhance prediction of DILI in man
 - Novel *in vivo* preclinical models that improve DILI hazard identification and risk assessment
 - Industrial and regulatory acceptance of the new approaches.
 - Understanding the most appropriate use of new preclinical approaches for replacement, refinement and reduction of animals usage.
 - New data and knowledge, resulting in best practice guidance and computational DILI systems models and requiring widespread data dissemination.
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Expected contributions of the applicants



The applicants will be expected to evaluate, and where necessary build, suitable in vitro and in vivo assays and models which provide useful prediction of DILI.

- In view of the nature of the challenge, a multi-disciplinary approach will be required.
- The work will require close collaboration with pharmas and is expected to include relevant SME technology service providers (e.g. for cell supply, mathematical modelling).
- Engagement with regulatory bodies will be needed, since regulatory acceptance is a long term goal.

Suggested architecture of the project



The following distinct but inter-related workpackages are proposed:

- Evidence-based selection of models to evaluate
- Evaluation of currently available *in vitro* assays
- Development of new *in vitro* assays
- Evaluation of *in vivo* models
- Immunologic assays and models
- Data correlation & statistical analysis, Systems modelling
- Communication and publication
- Project management

Expected (in kind) contributions of EFPIA members



- Provision of legacy data that aids in selection of the most promising assays and models for evaluation.
 - Supply of reference hepatotoxic compounds (which have caused DILI in preclinical species and in man), plus non-hepatotoxic compounds.
 - Intellectual support to experimental design and data analysis (informatics, statistics, computational modelling).
 - Complex instrumentation and technology (e.g. robotics, high content biology, omic profiling).
 - Design and execution of live phase evaluation of promising new *in vivo* models.
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Additional DILI Background - 1



- Many different classes of therapeutic medicines licensed for clinical use are known to cause DILI in man.
- Some drugs cause dose-dependent, reproducible “Type A” DILI (e.g. paracetamol). This can be replicated readily in various animal species and therefore is evident during pre-clinical safety testing.
- However, by far the most common pattern of DILI observed in man is idiosyncratic. This occurs only in certain susceptible patients and is not overtly dose dependent.

Additional DILI Background - 2



- The incidence of idiosyncratic DILI caused by some drugs can be high as 1 in 100 patients (e.g. chlorpromazine), but more typically is less than 1 in 10,000 patients (e.g. halothane).
- Idiosyncratic DILI is of major concern because it is not predictable from pre-clinical safety assessment studies and typically is not evident until late clinical trials or after regulatory approval.
- Many different drugs have been reported to cause idiosyncratic DILI. Therefore the cumulative DILI burden on professional health services, coupled with patient well-being and/or mortality, is high.

Additional DILI Background - 3



- Prior to licensing, DILI observed during clinical trials or preclinical safety evaluation in *in vivo* animal species may lead to serious delays in drug development, and termination of entire project portfolios.
- In addition, DILI is an important and leading cause of withdrawal, cautionary labelling and restricted usage of licensed drugs.
- It is clear that the preclinical approaches available today to the pharma industry are insufficient to enable adequate assessment of the risk that DILI may arise in man.

Additional DILI Background - 4



- Numerous promising new technologies and approaches have been described or are being developed which replicate many of the key biological processes implicated in both Type A and idiosyncratic DILI.
- These range from simple cell systems to complex *in vivo* models, and may have the potential to enhance prediction and risk assessment of DILI in man if used during drug discovery and/or pre-clinical development.

Expected impact on the R&D process



- Improved preclinical prediction of DILI will enable pharmas to select compounds that have reduced likelihood to cause DILI *in vivo*, in preclinical species and in man.
- This can be expected to reduce the incidence of compound attrition and project delay caused by DILI, and so to improve the efficiency of drug discovery and drug development.
- This will benefit pharmas (which will be able to develop drugs more effectively) and the European population (who ultimately may have access to an increased number of efficacious and safe drugs).

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