Next Generation of Electronic Translational Safety – NexGETS

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Objectives of the full project

- Development of an infrastructure for preclinical and clinical data sharing
- Accrual of large preclinical data sets into common a database, including CDISC SEND data.
- Exhaustive analysis of correlation and validity of animal data for human safety assessment
- Discovery of translational and reverse-translational biomarkers
- Development of predictive tools for both animal and human toxicities

Pre-competitive nature

- Based on the experience obtained in the eTOX project the climate and infrastructure for preclinical data sharing shall be expanded

- It is intended to develop guidelines or best-practice documents for data sharing among the partners

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Need for public-private collaboration

- Pharmaceutical companies providing large datasets on a diverse chemical and pharmaco-toxicological space
- Honest data broker allowing all participants to share data comfortably in a secure environment
- IT partners experienced in data analysis, data display and visualisation as well as interfacing with various types of pharmacological, preclinical and clinical databases.
- IT partners with expertise in the curation of clinical databases and exploitation of health records for research as well as for development of new predictive tools

Expected impact on the R&D process

- Re-use of existing data and in-depth data analysis will result in improved safety assessments of new drug candidates, reduced attrition in late stage development as well a diminished withdrawals
- Improved preclinical knowledge management will result in shorter cycle times
- Refined or reduced animal studies will result in contributions to 3R
- The NexGETS project should aim to set world standards and act as the central partner to go to in terms of preclinical data handling, analysis and use for predictive toxicology

Suggested architecture of the project

- The project will be led by an Executive Committee consisting of the leader of the EFPIA consortium and his deputy, the leader of the public consortium and the project manager
- The project shall be operatively managed by a professional project office (represented by the project manager in the ExCom)
- Leaders will be nominated for each work package, ideally with a leader from the public consortium and a deputy from EFPIA or vice versa
- Bi-annual consortium meeting will be held, with voting of the General Assembly if necessary.

Expected contributions of the applicants

- Act as a honest Broker for a large preclinical data repository
- Construct or provide a database that can be blinded to both the public and private participants and allows for a complex access and user administration
- Provide expertise and tools for data visualization and automated output formats (e.g. tabulated summaries, SEND)
- Provide statistical and bioinformatics expertise to enable appropriate design and analysis of the database
- Provide preclinical and clinical safety expertise to evaluate and interpret concordance of preclinical data with clinical outcome
- Construct in silico models based on complex data integration of preclinical in vivo studies and physicochemical properties (expertise in predictive algorithms integrating heterogeneous and complex data)

Expected (in kind) contributions of EFPIA members

- Provision of new preclinical data generated and structured under the SEND format
- Identify and extract legacy preclinical reports (endpoints to be significantly extended beyond systemic tox data, i.e. also covering safety pharmacology, DART, carcinogenicity etc.)
- Toxicological and clinical expertise
- Access to in house clinical data
- Input in project management
- Contribution to verification and validation processes

What's in it for you?

- Academic researchers:
  - Public funding
  - Access to large data sets not available in the public domain
  - Close interaction with experts in industry
- SMEs
  - Public funding
  - Contribution to a database, which will set standards in preclinical assessment for both industry and regulators
  - Insider knowledge of potential customer needs
  - Marketing opportunities for data base, visualisation tools, data converters (SEND), database interfaces and predictive tools

Key deliverables of the full project (I)

- Guidance or best-practice documents on safe data sharing
- An extended preclinical database, able to incorporate individual animal data in SEND format together with structural and pharmacological information
- Easy and automated extraction tools of study reports including expert conclusions
- Interfaces to clinical databases
- Extended search & datamining tools, allowing for complex multi-parametric search and concomitant searches in clinical databases
- Advanced tools for data display and visualisation, cross-study and compound analysis and reporting

Key deliverables of the full project (II)

- Advanced tools for similarity searches based on both the chemical structure, the pharmacology (target) and the toxicology and corresponding graphical display solutions of the various similarity metrics
- Reliable in silico predictive tools for drug toxicity which incorporate innovative read-across approaches and multi-level, multi-scale modelling methods (multi-level methods: the system should be able to incorporate individual experimental in vitro data to refine predictions; multi-scale methods: the system should be able to provide quantitative predictions with respect to the extent of toxicity expected for various doses)
- Tools for correlation analysis of preclinical to clinical safety prediction, including identification of biomarkers

Current EFPIA companies engaged in NexGETS

- Abbvie
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Johnson & Johnson
- Merck Darmstadt
- Novartis
- Roche
- Sanofi
- Servier
- Takeda

Still Pending:

- Astellas
- GSK
- Pfizer
- Dai-Nippon Sumitomo

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In summary

Three objectives:

- exhaustive analysis of correspondence and validity of animal data for human safety
- discovery of translational and reverse-translational biomarkers
- predict animal toxicities

Four deliverables:

- preclinical data base with retrospective and prospective data (SEND) from multiple companies
- mining and visualisation tools for cross-analysis with human data
- in silico predictive platform (algorithms)
- new translation and reverse-translation biomarkers

Impacts

- preclinical studies adapted to human outcome = increased safety, reduced attrition
- 3Rs
- preclinical knowledge management

- Industry: Data
- Industry + Public: Data base, mining, algorithms, people
- Public: Visualisation and analysis tools

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Questions?

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Overview on Work Packages (I)

1. Work package: *Scientific Coordination*
   - Project management (budget, timing, milestones, etc...)
   - Coordination and synergies with other initiatives
2. Work package: *Overarching Policies*
   - Establishment of general rules for sensitive data management and sharing
   - Proposal of guidelines – OECD-like
   - Interface with health authorities
3. Work package: *Historical data & DB*
   - Historical Data gathering as per eTOX
4. Work package: *SEND format & DB*
   - SEND format and SEND data gathering/handling
   - Open source platform for facilitating SEND management (free access)
   - eTOX db formatting and migration into full SEND compatible format
5. Work package: *Ontologies*
   - Maintenance of existing eTOX ontologies, completion of unfinished ones
   - Preclinical and clinical ontologies interfaces
   - Grouping and normalising disparate preclinical data sets

Overview on Work Packages (II)

6. Work package: *Translational Data analysis*
   - Establishment of cross-databases analysis tools, based on above ontologies (needs hyper-specialists)
   - Inter-operability for data mining tools (preclinical, clinical, chemical, environmental, cosmetic)
7. Work package: *Safety Biomarkers*
   - Translational and reverse translational search for safety biomarkers
   - Connection with IMI1 SAFE-T consortium and further qualification of biomarker candidates
   - Potentially run pre-clinical studies to generate new samples and qualification of candidate biomarkers
8. Work package: *In silico*
   - Development of predictive tools for toxicity and side effects (Translational)
9. Work package: *Platform*
   - User data access
   - Visualisation platform for large data & enabling tools for data harmonisation and sharing
10. Work Package: *Sustainability*
    - Business plan, dissemination to stake-holders, communication