Innovative Medicines Initiative

Understanding and Optimising Binding Kinetics in Drug Discovery

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The Problem

- Compounds can be clinically differentiated by their binding kinetics
- Compounds with optimum kinetics will suffer reduced attrition in development
- Currently, such compounds are found by chance and realised late

Objectives of the full project

- Understanding binding kinetics at a molecular level
  - Molecular interactions and conformational changes
  - Relationship between thermodynamics and kinetics
  - X-ray, NMR, SPR etc.
  - Computational modelling
  - **Ability to design appropriate kinetic behavior rationally**
- Assay technologies
  - Evaluation and standardisation of existing technology
  - Generation of new higher throughput methodology
  - Applicability to membrane proteins
  - **Information feedback in a DMTA cycle timeframe**
- Understanding in vivo translation
  - In vivo models
  - PKPD modelling
  - Scaling to man
  - **Confidence that in vitro effects will lead to clinical differentiation**

Expected impact on the R&D process

- Compounds with optimised kinetic profiles will be more likely to succeed in development and hence attrition will be reduced
- Ability to bring this about by design will lead to more compounds with appropriate kinetics being progressed

Need for public-private collaboration

- Previous work has been sporadic and knowledge kept within individual projects
- Pooled expertise and complete, consistent datasets
- Structural, biophysical, pharmacological (both *in vitro and in vivo*) and chemical experts
- Tool compounds, assay reagents and *in vivo* models
- Of interest to potential academic collaborators

Pre-competitive nature

- Systems will be provided that EFPIA members are willing to share freely
- Data made available to all
- Deliverables should have general relevance and not be specific to individual targets

Suggested architecture of the project

- All aspects of the proposal to be addressed through collaboration
- Other innovative proposals welcomed
- Workpackage1 – **Molecular understanding**
- Work package 2 - **Assay technology**
- Work package 3 – **Link to in vivo**

Expected contributions of the applicants

- Proposals targeted at any of the three areas outlined
- Consortium will coordinate studies and ensure knowledge is shared
- **Molecular understanding**
- Determination individual contributions to on and off rates to allow the analysis which could lead to general considerations for optimization of these parameters
- Prediction of protein conformational changes which may be tested with the proposed systems to assess their future predictive value
- **Assay technology**
- New methodologies that address the identified short comings of current technology
- Development of methods that are applicable to membrane proteins
- **Link to in vivo**
- Study of binding events in open systems such as cells, isolated tissues and ultimately *in vivo* models
- Understanding additional phenomena governing receptor occupancy in these more complex systems
- Comparing systems which translate from isolated enzyme and those that do not

Expected (in kind) contributions of EFPIA members

- Entirely in kind.
- FTEs for coordination of the consortium, intellectual input and experimental work (~1 to 2 FTEs / company)
- Appropriate targets / systems and selected tool compounds
- In vivo probe compounds / models
- Computational support (molecular modelling & dynamics, systems biology)
- Coordination, active participation and input
- Hosting post doctoral workers and students in industrial laboratories to provide access to technology and assays

What's in it for you?

- Academics
  - Fundamental science (understanding molecular interactions) with direct societal and economic impact
  - Opportunity for collaborative research not possible individually
- SMEs
  - Marketable technology platforms
- Patient groups
  - More efficacious, safer medicines
  - More stable, secure pharmaceutical industry

Key deliverables of full project

- Guidelines for understanding the molecular phenomena that allow manipulation of kinetics by design
- Technology evaluation using agreed benchmark tool compounds and molecular systems
- Improved methods and recommendations for obtaining high(er) throughput kinetic measurements
- Robust, predictive PKPD kinetic modeling paradigms
- Enhanced data-sharing within the network of drug binding and kinetics
- **Reduced attrition in drug development**

Questions?

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