Innovative Medicines Initiative

hiPS cells for Drug Discovery and Safety Assessment

Laura Suter-Dick

On behalf of the EFPIA Consortium: Roche, Astra Zeneca, Novo Nordisk, Orion, Sanofi-Aventis, Merck-Serono, Lilly, Pfizer, Boehringer Ingelheim & Janssen

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Need for public-private collaboration

The main objectives are ideally tackled by public/private partnerships, for example

- Establish a biobank for iPS cell lines
  - Requires strong links with hospitals, patient organizations, and pharmaceutical industry with access to human samples
- Establish and make accessible a collection of IRB-approved iPS cell-lines
  - Generate (or acquire) cell lines from different patient and healthy populations
  - Include well-characterized responses to drug treatment and side effects
- Establish standardized biological assays
  - Access to stem cell differentiation protocols
  - Address disease biology, response to treatment and safety assessment
- Communication with other consortia

Pharmaceutical industry and academia drive the scientific effort, but the inclusion of patient groups, of SMEs (possibly providing existing iPS cell lines), hospitals, and of regulators are vital

Objectives of the full project

- Access to well characterized, genetically diverse iPS-derived cell types in large scale for Pharma and Academia in Europe (Biobank)
- Optimized assays predictive for liabilities concerning preclinical or clinical toxicity
- Optimized assays for *in vitro* disease modelling and compound efficacy (e.g. sensory neurons for pain, cardiomyocytes for heart failure)
- Implementation of a central test facility (beyond the funded period)
  - Accessible to Academia and EFPIA
  - Development and Maintenance of a Biobank
  - Pre-competitive assessment of small molecules
- Optimize protocols for the appropriate maintenance of stem cell derived cell-types, in particular complex cell culture systems such as 3D-cultures, co-cultures, specific matrices

Pre-competitive nature

- Availability of more relevant *in vitro* tools for academia and Pharma in Europe will
  - Improve research in the discovery process
  - Provide a suitable degree of standardization of cell-based assays with iPS
  - Provide acceptable standards for iPS quality assessment
  - Provide platform for exchange of technologies and knowledge, between stake holders and between this an other consortia
  - Provide adequate forum for discussion with external scientific experts and health authorities that will benefit all

- Advances in basic research in this area will benefit
  - Pharmaceutical industry
  - Academic research
  - SMEs
  - Patient organizations

Expected impact on the R&D process

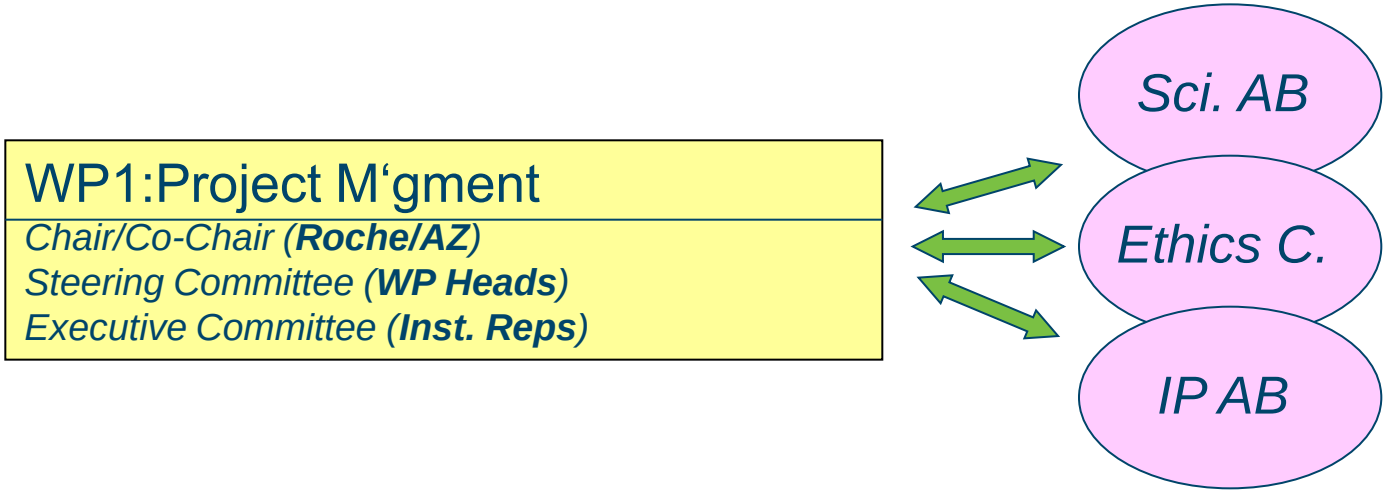
- Improved, patient-relevant *in vitro* biological systems will have major impact on
  - Understanding of disease biology
  - Elucidating drugable pathways for pharmacological intervention
  - Facilitating the evaluation of efficacy on modulating disease-relevant pathways in specific cell types and patient populations
  - Evaluating the likelihood of unwanted side effect in specific cell types and in healthy and susceptible patient populations
  - Accelerating drug discovery process leading to benefits to the patients and to the pharmaceutical industry
  - Contributing to 3R (Reduce, Refine & Replace animal experimentation)

Suggested architecture of the project

Preliminary structure: program is divided in 9 WPs, envisaged co-governance of each WP by EFPIA/Academic member to optimize integration of both EFPIA and Applicant consortia and scientific co-ownership of the project

- **WP1: Project management**
  - Governance: Chair/Co-chair, Executive Committee (institute representatives) & Steering Committee (WP-heads)
  - Advisory boards: Scientific Advisory Board; Ethical Committee; IP-Advisory Board
  - Progress will be monitored in regular project meetings
- **WP2: Sample collection/patient selection**
- **WP3: Establishment & assessment of viability of a biobank**
- **WP4: Data management**
- **WP5: Communication with other consortia**
- **WP 6-8: Application of iPS for the study of Diabetes (WP6), CNS and neurodysfunction (WP7) and toxicology (WP8)**
  - These three work packages will address the scientific core of the proposed research plan. They may be organized on sub-packages as needed
- **WP 9: Assay development, validation and scaling**

Consortium Architecture



WP2	WP3	WP4	WP5	WP9
Sample collection	*Biobank*	*Data M‘gment*	*Conmmunication*	*Assay develop.*

WP6	WP7	WP8
Diabetes	*CNS*	*Toxicology*

Joint EFPIA & Academic WP Leadership will be strongly encouraged

Areas of scientific focus

WP6 *Diabetes*	WP7 *CNS*	WP8 *Toxicology*
Several cell types Beta cells Kidney (nephropathy) Skeletal Muscle Adipocytes Sensory Neurons Liver Entero-endocrine cells	**Several diseases** Parkinson Schizophrenia Autism Depression Alzheimer‘s Disease Pain	**Several Organs** Liver Kidney Heart Vascular
Diabetic patients	**Neurons**	**Healthy (& susceptible)**

Expectations from the Applicant consortium (1)

- Clinical expertise
  - Selection of patient populations
  - Access to patient tissues
  - Access to patient records
- Standardized production of iPS lines
- Quality control of cell lines
  - Genetic characterization: Karyotyping, genotyping, CNV, pluripotency markers
  - Functional characterization:
    - iPS: differentiation into 3 germ layers, teratoma formation
    - iPS-derived mature cells: appropriate cellular markers
- Biobanking of cell lines under standardized conditions

Expectations from the Applicant consortium (2)

- Expertise in data analysis and databases (DB)
  - Storage, analysis and querying
- Experience in cell culture systems
  - Differentiation inducing biomolecules
  - Extracellular matrices
  - Complex co-culture systems
  - 3-dimensional organotypic bioreactors
- Cellular assay development and validation
  - Scaling of differentiation process
  - High throughput methodologies, e.g. High Content Imaging (HCI)
- Knowledge of specific disease- and/or toxicity-related pathways

Expected (in kind) contributions of EFPIA members

- **WP1**: Project management, inclusive fees and grants for external support
- **WP2** (Sample collection): Clinical expertise for the selection of patient populations and access to samples from selected clinical trials if appropriate
- **WP3** (Biobank): Scientific guidance, business and legal advice on feasibility and sustainability
- **WP4** (Data M'gment): Generation of data sets in an appropriate format and statistical evaluation of predictive models
- **WP5** (Communication): Crucial point of contact for initiatives involving EFPIA-sponsorship. Active participation in training exchanges either as hosts or guests from the institutions of the applicant consortium
- **WP6-WP8** (Application of iPS-derived cells): EFPIA contribution: Clinical expertise to guide the research. Experimental support for the characterization of cell types with assays that require complex technologies (e.g. genotyping, HCI, gene expression analysis, etc). Possibly fees and grants for purchasing of cell lines
- **WP9** (Assay development): Compound supply (commercially available or proprietary compounds) to serve the validation of the assays. Experimental support in automation and throughput as necessary

What's in it for you?

- Pharmaceutical industry
  - Better scientific knowledge will improve the available tools to generate safe & efficacious medicines for the patients
- Academic research
  - Better understanding of the needs of Pharma would allow to direct and focus research in academia. It will also facilitate access of academic partners to knowledge from Pharma
- SMEs
  - SMEs can benefit by generating tailored-made, commercially attractive technologies to address the needs of academia and Pharma
- Patient organizations
  - Patient organizations will profit from the opportunity of discussing main areas of interest and thus influencing medical research

Key deliverables of full project

- **Definition and selection of suitable patient populations**
  - For specified diseases (Diabetes, CNS, Toxicology) specific patient sources and patient populations will be defined and recruited
- **Bio-bank and Central test facility**
  - Bio-bank for patient derived iPS cells (independent, applicant consortium or existing bio-bank)
  - For each iPS cell, documentation of its characterization (phenotype, genotype, score card)
  - Provision of a large scale source of 20-100 human cell lines (iPS) per disease and cell type
  - Adapt validated assays to suitably available commercial HTS platforms and milieu
  - A central resource for assay performance should be established
- **Drug efficacy**
  - Preliminary panel of assays to be defined (year 1). Additional assays and endpoints may be developed throughout the project period
  - Validation of panel of defined panel of assays
  - Miniaturization and HTS approaches will be undertaken in year 5
  - Assay outcome of different donor phenotypes will be assessed in year 5
- **Safety assessment**
  - Preliminary panel of assays to be defined (year 1) and continuously updated. In the 2nd and 3rd years, some of these assays will be validated using model compounds with known toxic liabilities
  - Assays will be performed in cells derived from specific patient populations in the 2nd and 3rd years. The results will be used to correlate donor phenotype with outcome
- **Scalability and improved culture conditions (year 5 and beyond)**
  - Improved 3D-protocols in terms of scalability, longevity of the cultures, multicellular culture systems
  - Improved biomaterials for scalability, longevity of the cultures, multicellular culture systems
  - Comparison of performance of “simple” and complex culture conditions for assay performance

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infodesk@imi.europa.eu

www.imi.europa.eu