From Patients to Therapies

How could the BADIPS challenge progress towards improved in vitro models and novel patient therapies?

Aim of the BADIPS project

Studying bipolar affective disorder using skin-derived stem cells from patients

- Bipolar disorder represents a significant unmet medical need and a major burden to society and families.
- Since the disorder is poorly understood, very few medicines have been developed to tackle this unfortunate condition.
- The current animal models used to study bipolar disorder are not optimal and do not consistently predict which new treatments will work in patients.
- New methods for deriving brain cells from the skin or blood of patients can now be used to study neuropsychiatric disorders like bipolar disorder more directly and reliably.
- Janssen and Eli Lilly are supporting this challenge to develop tests for the treatment of bipolar affective disorder using **human** cell-based systems.
- These assays will be more relevant to the disease as it affects humans, reduce the dependence on animal models and should make some of the present animal testing obsolete.

BADIPS project

Overall objective

The development of relevant phenotypical high throughput screens for the discovery of new treatments for BAD.

Key deliverables

- Generate viable iPS cells from series of clearly defined BAD patients, ideally carrying polymorphisms in coding regions of risk genes or CNVs that will allow directed investigation of cellular properties as proof of concept
- Identify phenotypic characteristics of these cells (iPS or differentiated into neurons) that are specifically related to BAD
- Generate a robust and validated assay suitable for screening in an industrial setting.
- Searching for a central storage place for providing multiple cells to the research communities

3Rs benefits

- Current animal models used to study BAD include genetically altered mice and rodent models of schizophrenia or major depression.
- The latter involves the administration of drugs which cause psychosis in man, or subjecting animals to stress (e.g. maternal deprivation) and are therefore associated with significant welfare concerns.

Possible solution:

Using iPS cells from BAD patients as screening tools for the development of novel treatment options.

It will be possible to reduce the dependence on animal models, improve the predictive validity of the assays, and possibly even make some of the present *in vivo testing obsolete. Specifically this will include reducing the use of:*

- Standard rodent models for novel drug screening, which attempt to mimic some elements of BAD and rely on reference drugs to provide some predictive value. Typically dose-response curves are generated in these models using 7 to 15 animals per treatment concentration;
- Classical behavioural testing in transgenic animals where specific genetic factors derived from GWAS or disease pathway analysis are modified;
- Drug testing in transgenic models;
- *Ex vivo tissue from transgenic animals.*

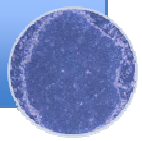
Critical Factors for Selecting Patients and Obtaining Samples for Stem Cell Based Phenotype Evaluation Studies

- Rigorous diagnosis with detail phenotype descriptions including comorbidities available for patient segmentation.
- It is best to have genetic information for selected patients and a particular variant of interest identified.
- Consistency in sample collection and handling procedures as well as availability of multiple tissues types.
- Consistency in tissue culture practices and characterization of primary cells for dedifferentiation.

High Level Pieces Involved in Application of Patient iPS to Drug Discovery

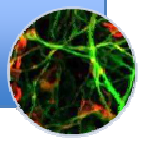
- Well defined patient phenotype and/or genotype with possible treatment stratification
- Population and Isogenic controls
- Multiple clones per patient
- Consistent process for generation of iPSC lines.
- Uniform process for scaling, banking, and quality control

iPSC Lines



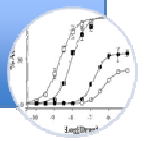
- Disease relevant cell types
- Pure and mixed cell populations
- Other cell types for co-morbidity studies
- Large cell numbers
- Reproducible batch to batch differentiation
- Uniform tissue culture practices

Differentiated Cell Types



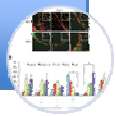
- Identify phenotypes in disease relevant cell types:
- Homogeneous population of cells
- Controlled co-culture conditions
- Evaluate co-morbidity phenotypes
- Provide POC of phenotype and connectivity to disease

ID Phenotypes and POC Assays



- Evaluate phenotype across dominant, recessive, and controls.
- Validate phenotype reproducibility by multiple labs.
- Validation of phenotype connection to gene and disease.

Phenotype Validation

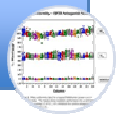


- Explore biological pathways involved in phenotype
- Validate pathways and modulate phenotype with targeted reagents
- Identify suitable approaches/targets for therapeutic intervention

Pathway and Target Identification

- Develop assays with sufficient throughput
- Transfer assays to screening sites if necessary
- Validate assays

Assay Development and Validation



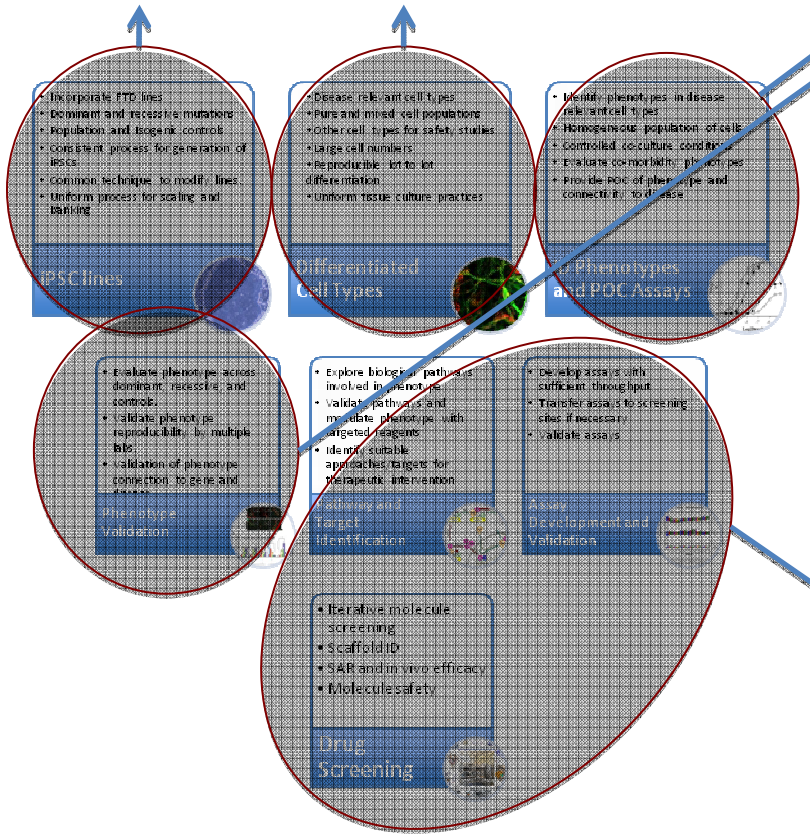
- Iterative molecule screening
- Scaffold ID
- SAR and in vivo efficacy
- Molecule safety

Drug Discovery

Opportunities to Speed Progress with **Well Coordinated** Academia and Industry Partnerships

Single Suppliers Create Reagents for all

Patient Selection and iPSC Lines	Differentiated Cell Types
Clinical expertise with large patient base	Core iPS facilities in academia or biotech companies
Well defined clinical diagnosis, phenotype, and genotype	Cellartis or Cellular Dynamics International



Focus Expertise of Academia on Breakthrough Science and New Technology
Consortia members evaluate in vitro phenotypes
Expanded access across industry and academia through for-profit suppliers of cells
Technology Industry/academia POC studies new tech development

Larger Network of Labs using same Cells

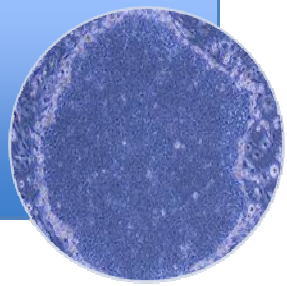
- Enable more rapid cross lab validation
- Opportunities for parallel advancement of phenotypes
- Faster uptake on opportunities for regenerative medicine by focused biotech companies.

Pharmaceutical Industry Focus
• Phenotype connected new target opportunities
• Robust assay development and validation
• Screening for new molecular entities

Key Factors of Challenge Proposals
iPS Cell Lines

- Well defined patient phenotype and/or genotype with possible treatment stratification
- Population and Isogenic controls
- Multiple clones per patient
- Consistent process for generation of iPSC lines.
- Uniform process for scaling, banking, and quality control

iPSC Lines

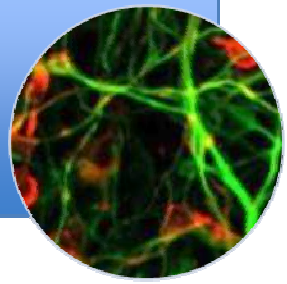


- Well defined strategy for Patient and Control identification criteria
- Accessibility of patient population
- Plan for consistent generation and evaluation of iPS lines
- Capabilities in scaling, banking, and distributing iPS lines

Key Factors of Challenge Proposals Differentiation

- Disease relevant cell types
- Pure and mixed cell populations
- Other cell types for co-morbidity studies
- Large cell numbers
- Reproducible batch to batch differentiation
- Uniform tissue culture practices

Differentiated Cell Types



- Definition of disease relevant cell types
- Availability of differentiation protocols for relevant cell types
- Plans to monitor and minimize variability during differentiation
- Plans to validate cell type vs primary cells.

Key Factors of Challenge Proposals Phenotype ID and POC

- Identify phenotypes in disease relevant cell types:
- Homogeneous population of cells
- Controlled co-culture conditions
- Evaluate co-morbidity phenotypes
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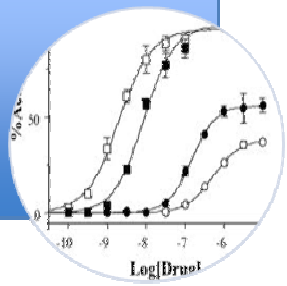
ID Phenotypes and POC Assays



- Connection of in vitro phenotype to patient phenotype
- Connection of in vitro phenotype to genotype
- Plans to modulate phenotype with target directed pharmacology
- Validation of phenotype through genetic modulation of controls lines
- Validate observed in vitro phenotype in patients.

Key Factors of Challenge Proposals Phenotype Validation

- Evaluate phenotype across dominant, recessive, and controls.
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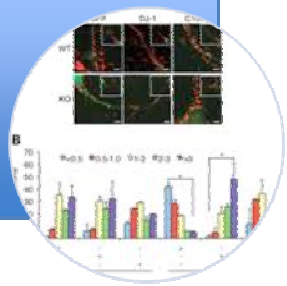
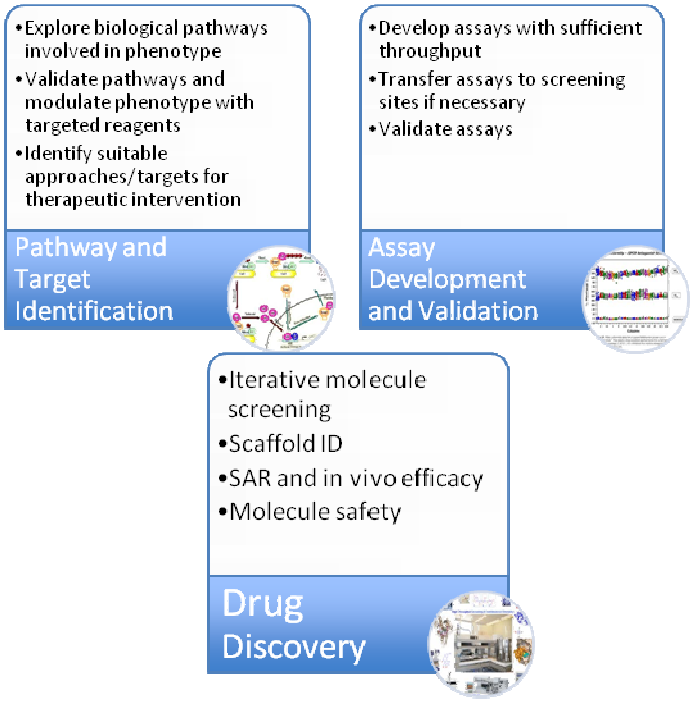
Phenotype Validation



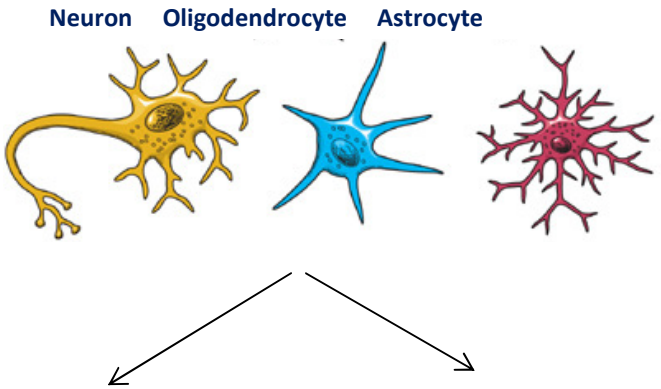
- Validation of in vitro phenotype and observations across labs
- Demonstration of phenotype prevalence in patient population

Pharmaceutical Industry Processes and Tools Exist to help with These Aspects



- Availability of 'omics tools
- Availability of well annotated selective tool compounds for pharmacology studies
- Rigorous Assay development and validation procedures
- Screening automation and technologies

Characterization hiPSC-derived neurons and glial cells



+ co-cultures

Morphological characterization

Immunocytochemistry

→ neuronal vs glial cell markers
→ neurotransmitter phenotypes (markers)
→ synaptic markers
→ neurite length (MIAS2)
→ # neurites, branches, synapses (MIAS2)
→ …

Functional characterization

Electrophysiology

→ spontaneous circuit activity (MEA)
→ spiking pattern & neuronal subtypes (patch clamp)
→ Glial cell differentiation by Ca^{2+} wave timelapse imaging
→ Glial ion channel expression (patch clamp)

Full 'profile' of iPSC-derived neurons and glial cells

Patients descriptions

The DSM-IV is the main classification system used in the US and some other regions as well. The main difficulty will be to define the types of bipolar patients you would like to include.

Bipolar I disorder requires a full manic episode whereas Bipolar II requires only hypomania (less severe). The diagnostic problem is that those with Bipolar II often shade into those with cluster B personality disorders (particularly in the US) which would affect signal detection. You may want to restrict entry to Bipolar I patients.

The types of scales used depends on the mood state being measured: YMRS Young Mania Rating Scale for mania and MADRS for depression are the most common scales used

There are many ways to define non-responders and it depends on which mood state you are measuring.
There are several good mood stabilizers for mania and maintenance : lithium, valproic acid, and second generation antipsychotics are probably the most commonly used. Antidepressants, some antipsychotics (quetiapine, olanzapine, and aripiprazole), and lamotrigine are often used for depression

Suggestion: contact genetists in the Wellcome Trust Case Control Consortium. Genetists use world-wide accepted standardized methods to collect family, personal, illness history and current state information for the diagnosis and other purpose.
They do have widely accepted way to make diagnosis too.

In-kind contributions

- This will include
- Gene expression profiling;
- High content characterization of iPS derived neurons: antibody labelling and imaging, *in vitro electrophysiological support;*
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Provision of shRNA or siRNA for knock-down of gene expression;
- Access to compound libraries and reference drugs for validation.
- Differentiation of the iPS cell lines into different types of neurons (e.g., GABA, glutamate, dopamine phenotypes);
- Genomic characterization (e.g., mRNA, miRNA, candidate gene expression);
- Functional characterization of the cells using biochemical, electrophysiological and imaging technologies with and without functional genomics and pharmacological tools/probes;
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Access to public domain compounds/reference drugs.

Specific attention points

- Well characterized patient descriptions
- Uniques storage / distribution capabilities
- Precompetitive approach