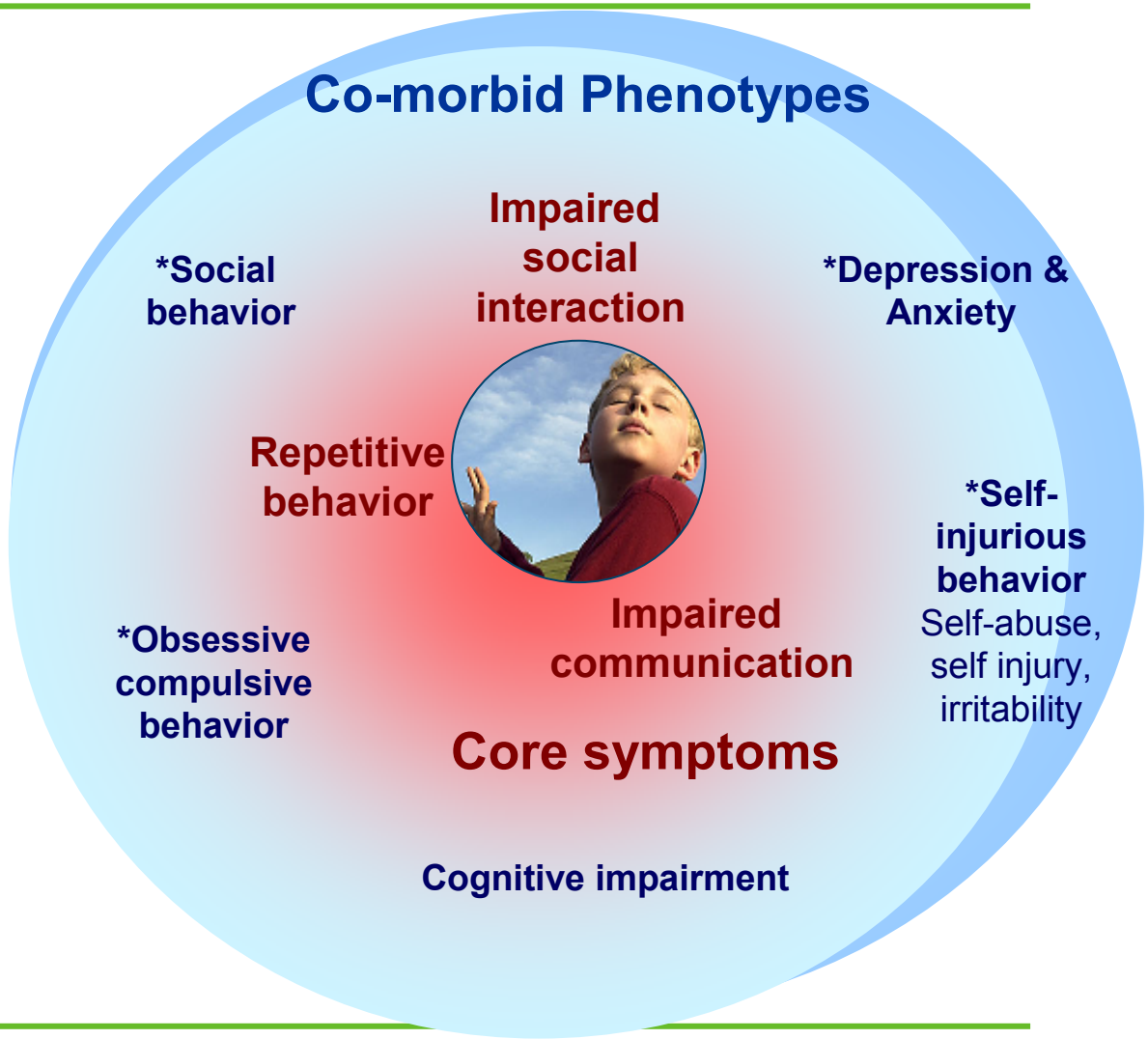
Innovative Medicines Initiative

Translational endpoints in Autism

Will Spooren
Project Coordinator

Autism - General Introduction

- ±1% of all children is diagnosed with autism representing nearly 5.5 million patients in the EU.
- The prevalence rate of autism is increasing 10-17 percent annually for which there is no obvious explanation.
- Treatment based on drugs developed for other indications that ameliorate behavioural symptoms with a high impact on individual functioning.
- No medication is available that can change the core symptoms of autistic disorders or improve the long-term outcome.
- ASD is characterized by a lack of evidence based therapy.

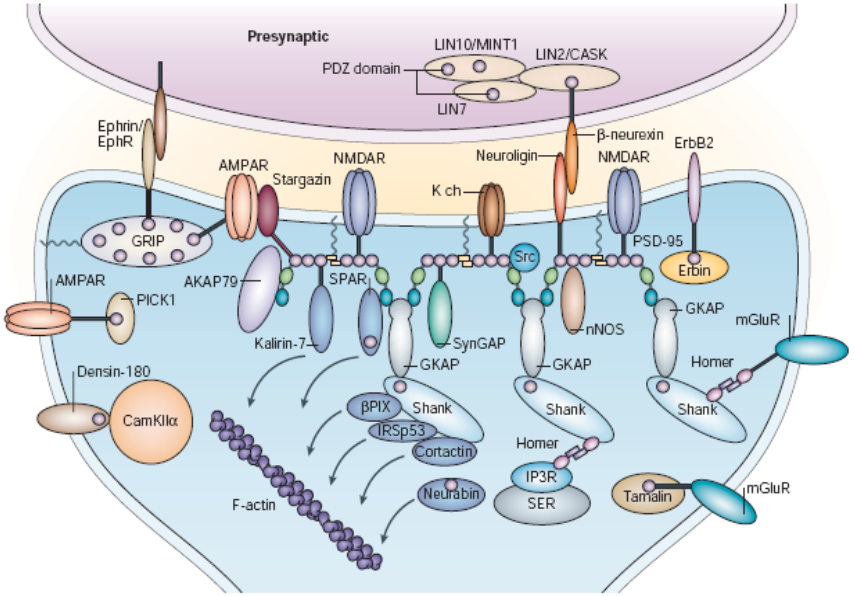


Key New Developments (1)

ASD and synaptic function

- Recent genetic studies have identified multiple candidate genes that may confer susceptibility to ASD.
- Several of these genes are linked to **synaptic function**.
- Mouse models recapitulating these mutations exhibit defects in behaviour and in synaptic physiology supporting the importance of corresponding proteins in ASD.
- Furthermore, common biological pathways for brain development and plasticity across ASD are starting to be identified.

- **These findings point to a core deficit in synaptic function in many of the genetic forms of ASD.**

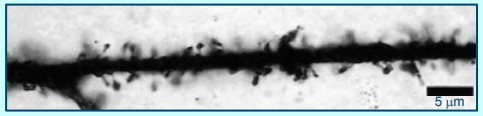


Key New Developments (2)

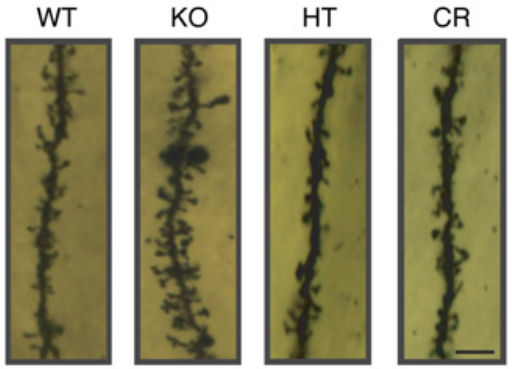
Recent pre-clinical developments have brought major excitement:

- Using animal models of monogenetic diseases leading to ASD, key behavioural and neuroanatomical phenotypes have shown to be responsive to drug intervention:
  - mGlu5 receptor antagonists for Fragile X
  - Sirolimus for Tuberous Sclerosis
  - Statins for neurofibromatosis Type 1
  - Insulin-like Growth Factor-1 (IGF-1) for RETT syndrome.
- These approaches are currently in translation to the clinic, offering novel perspectives for the control of ASD even in adolescence or adulthood, a concept that was not generally believed only a few years ago.

Healthy subject



Fragile X patient

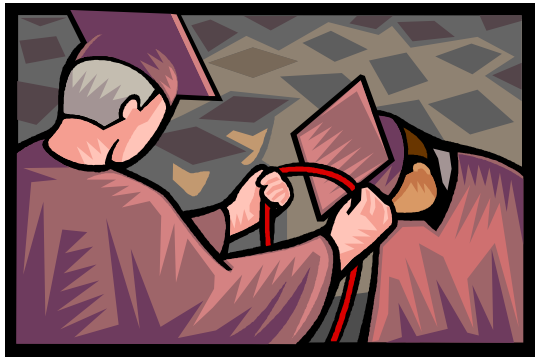


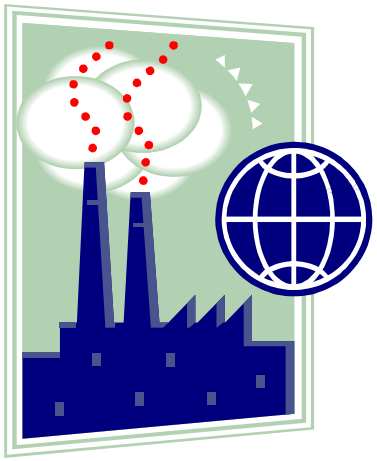
Need for public-private collaboration

There are major advances in the understanding of underlying neurobiology of ASD, and there is emerging awareness that it is a viable treatable condition: this needs now to translate into registered drugs.

- An integrated clinical and pre-clinical ASD research approach, built on academia and industry strengths is missing in Europe

To produce a real impact on this field, a united effort of a variety of stakeholders including **academia, industry, regulators, foundations and patients groups** is urgently needed.





Objectives of the full project

This topic offers a unique opportunity to create a European wide strategy for ASD treatment integrating public and private strengths.

Key objectives:

- Set new standards in Research and Clinical Development to aid the drug discovery process.
- Develop and validate translational approaches for the advancement of novel therapies to treat ASD.
- Identify, standardize and develop expert clinical sites across Europe to run clinical studies and trials and so create an interactive platform for ASD professionals and patients.
- Evidence based treatment of ASD patients
  - Diagnosis, clinical assessment, outcome measures

Pre-competitive nature

- Connecting critical mass to exploit innovative advances in Autism
- Standardization between public and private organizations
- Rapid sharing of information to ensure progress
- Alignment across the whole value chain: research, clinical development, regulators and patients

Expected impact on the R&D process

- Identification of reliable and predictable assays
  - Cellular
  - Animal
  - Translational
- Standardization in research and clinical praxis
- Alignment of the field including regulatory praxis

- Europe as an area of preference to run well designed and controlled clinical studies with NME for Pharma and Academia.







Suggested architecture of the project

Work Package 1: In vitro systems development.

This work package will take advantage of emerging advances in the field of autism genetics and aim to develop in vitro model systems for drug characterization & evaluation.

- **New assay development**

  Examples:

  - **Primary embryonic neuronal cultures**
  - **In vitro slice preparations**
  - **Embryonic and induced pluri-potent stem (iPS) cells**
- **Define phenotypes at synaptic, cellular and circuitry level**
- **Determine reliability and reproducibility of assays**
- **Use promising assays to asses pharmacological tool compounds**
- **Translation of assay endpoints to animal models and man**

Suggested architecture of the project

Work Package 2: Animal model development.

This work package should deliver recommendations on the most appropriate animal behavioural endpoints for use in genetic and/or environmental disease models relevant to ASD.

- **Define translational measures of i.e. cognitive, affective and social behaviour in ASD animal models**
- **Develop and standardize outcome measures of ASD animal models**
- **Assess reliability and reproducibility across collaborating labs**
- **Assess and validate most promising models for pharmacological testing**
- **Use promising models to asses efficacy of pharmacological tool compounds**
- **Other relevant endpoints and recommendations**

Suggested architecture of the project

Work Package 3: Translational research development.

This work package should develop objective biomarkers linked to ASD to translate electrophysiological, imaging and pharmacological outcome measures from animal to man and back to animal.

- **Identify translational objective markers of neuro-anatomical changes in animal models i.e. fMRI, PET**
- **Define phenotypes in models using markers to define shared common signatures among different ASD genes**
- **Use promising models to asses efficacy of pharmacological tool compounds**
- **Translate end-points from animal studies to ASD patients and back**
- **Establish the susceptibility for pharmacological challenges to any of the measures above**

Suggested architecture of the project

Work Package 4: Clinical research development.

This work package should facilitate and enhance scientific collaboration and exchange across Europe for ASD professionals – clinicians and researchers from both private and public sectors - and to significantly promote research and development of drugs for ASD.

- **Assess Standards of care of ASD patients in Europe.**
- **Facilitate the implementation of Clinical Research to assess interventional pharmacological studies with Pharma and Academic sites.**
- **Validate diagnostic, biochemical, electrophysiological and imaging markers that will help to identify the disease at an early stage and improve detection of treatment outcome**
- **Initiate pharmacogenomic assessment ("bio banking") from ongoing trials possibly linking to other libraries i.e. AGRE.**
- **Develop standardized assessments (outcome measures, treatment and long term follow up criteria across Europe)**
- **Develop an educational program together with key stakeholders to increase awareness/make the knowledge in ASD accessible to a wider public (establish symposia/ training courses for scientists/physicians, patients and their families).**

Suggested architecture of the project

Work Package 5: Data handling, management and integration.

The work package should provide the strategy and implementation for efficient handling, management and integration of all data produced by the project activities.

- **Develop methods for rapid sharing and handling of data across work packages.**

Work Package 6: Project management and communication.

The work package should cover all aspects of project management and coordination, including dissemination and communication strategy.

- **Professional project management**

Expected contributions of the applicants

The Applicant Consortium is expected to provide both **pre-clinical** and **clinical** expertise and ability for interdisciplinary and inter-sectorial work to cover the following critical fields:

- Preferably scientific and clinical expertise and leadership in ASD including a broad multidisciplinary dimension **such as**,
  - Innovative project design and science
  - Clinical trial expertise
  - Regulatory expertise
  - Data management and integration expertise
  - Involvement of Patient organisations
  - Educational program to create awareness
  - Professional Project management (specialized SME's welcome)

Expected (in kind) contributions of EFPIA members

- **WP 1: Lead: Pfizer - Participants: Roche, Novartis, Johnson&Johnson, Eli Lilly**
  - In vitro technologies expertise and experiments
  - Neuro-anatomical and electrophysiological expertise and experiments
- **WP2: Lead: Johnson&Johnson - participants: Roche, Eli Lilly, Pfizer, Sigma Tau**
  - Behavioural models and generation of transgenic animals
  - Methods, expertise and experiments
  - Supplies of pharmacological tools
- **WP3: Lead: Roche - Participants: Eli Lilly, Johnson&Johnson, Novartis, Pfizer**
  - Biofluid biomarker development and experiments
  - Imaging expertise, methods and experiments
  - Translational behavioural procedures and experiments
- **WP4: Lead: Novartis - Participant: Roche, Eli Lilly, Pfizer**
  - Clinical and neuropsychological expertise and experiments
  - Imaging and electrophysiological expertise and experiments
  - Experience, expertise and data from relevant clinical trials - past and present
  - Clinical trials supplies and logistics
  - Regulatory approach

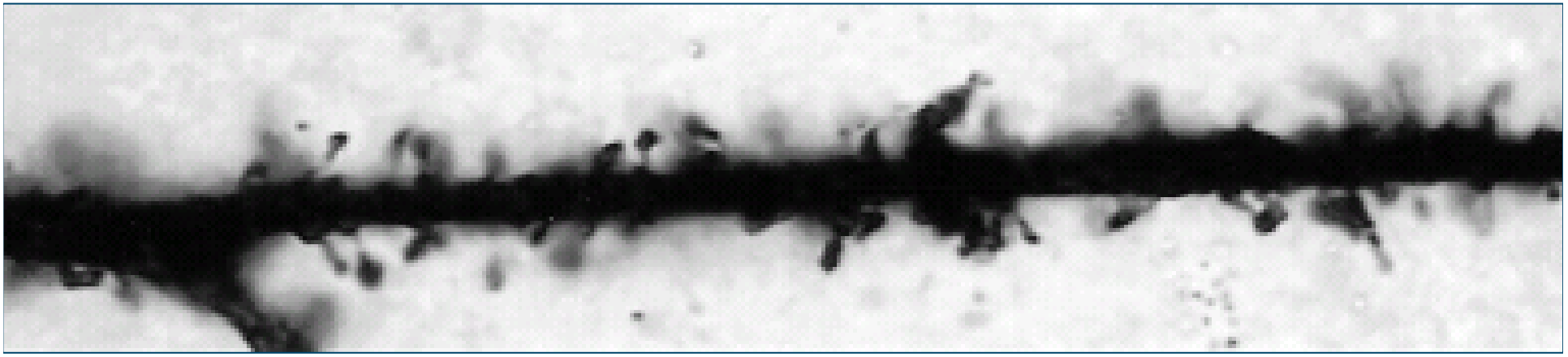
Key deliverables of full project

The establishment of an integrated approach using cellular assays, animal models and translational biomarkers to enable drug discovery and development in ASD.

- The development of cellular/animal models with a close link to the neurobiology of ASD and that supports translation from animals to patients.
- The validation of biomarkers that aid the drug discovery process to predict pharmacodynamic responses to drugs, to allow patient stratification and support regulatory submissions.
- An integrated clinical and preclinical research approach for ASD built on academia and industry strengths across Europe.
- The promotion of an educational program to increase awareness/ make the knowledge on all aspects of ASD accessible to a wider public, involving patient organizations.

EFPIA Consortium

Thank you for your attention!



contacts

All questions should go through the IMI Executive office

infodesk@imi.europa.eu

www.imi.europa.eu