Creating new models for R&D in areas of unmet medical need: Autism Spectrum Disorders

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Autism spectrum disorders (ASD): Current situation

Incidence
• 1 in 88 births

Males vs females
• 4x frequent in males

Strong Genetic link
• 10-40% defined genetic alterations, High penetrance

Treatment
• No treatment for core symptoms
• Risperdal and Abilify for irritability

Synapse disorder
• Various targets

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Courtesy: Autism Speaks – Rob Ring
Autism spectrum disorders (ASD): European Situation 2012

- No major strategy defined within Europe
- No major or concerted efforts in drug discovery
- No pre-clinical network
- No clinical trial network
- No regulatory strategy
- Late diagnosis and poor awareness (adults)
- Poor knowledge of patients needs across life-course (teens into adulthood)
- Wide range in treatment strategy with no evidence of efficacy

A concerted effort of key stakeholders is needed
Private Public Partnership

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Neurodevelopmental disorders: from sin to synapse

Synaptic dysfunction: development, maturation and stabilization of synapses.

- Clinical outcomes and diagnostic BM
- Genetics of mendelian forms
- Mechanistic therapeutics
- Translational models
- Molecular pathophysiology and target id.

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Major goals for Europe

Development and validation of translational approaches for the advancement of novel therapies to treat ASD

Setting new standards in research and clinical development to aid the drug discovery process

Identification and development of expert clinical sites across Europe to run clinical studies and trials, and the creation of an interactive platform for ASD professionals and patients.
EU-AIMS

Launched April 2012

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Headline achievements

12 publications in 1st year of the project

Including toplines journals:

Mean Impact factor: 13.8
Age father is a risk factor for child to have deleterious mutation leading to autism
Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism

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Divergent genetic pathways

- Single variants/gene(s): <5%
  - Neurologin 3
  - Shank 3
- Comorbid Phenotype: ~10%
  - Fragile-X
  - Rett Syndrome
  - Tuberous Sclerosis
- Chromosome anomalies: ~10%
  - Trisomy Chr. 21
  - Chromosome 15
  - Chromosome 22
- CNV/gene(s): ~65-76%
  - Chr 2q, 5p, 7q
  - Chr 9p, 11p, 15q
  - Chr. 17q, 19q, 22q

Group 1 mglu receptors
Convergent pathway

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Regulatory guidance document initiated in March 2013

Concept paper expected in 2014
Headline achievements

• **WP1 Cellular Assays**
  – Robust methods to reprogram keratynocytes into iPSc from autism patients and controls
  – Shank3 iPSc and control lines delivered to EU-AIMS partners

• **WP2 Animal models**
  – Central Animal (TG) repository established (Harlan, Italy)
  – A multi-site study for standardization and cross-site comparison completed (Oxytocin)
    • First results indicate excellent correlation between sites across Europe
  – Genetic rescue of NRL3 KO phenotype
  – New target identified for the treatment of autism (mGlu1)
    • Pharmacological intervention studies initiated
    • Findings are being translated to man including potential PET study (new being negotiated)
  – Agreement with Sage labs for (50%) discount for TG autism rats
  – First TG rats at various behaviour groups of EU-AIMS – testing initiated
Headline achievements

- **WP3 Translational Sciences**
  - **New data**: evidence that brain functional abnormalities can be reversed – and in adults with ASD – by modulating brain 5HT. Currently tested as an *outcome predictor* for clinical trials.
  - **New data**: ASD patients have significant differences in GABAalpha5 binding.

- **WP4 Clinical Sciences**
  - **New data**: individuals with ASD have significant differences in cortico-cortical anatomical connectivity. This is now being tested as an outcome predictor for clinical trials.
  - **New data**: infants at risk for autism have significant differences in brain functional response to emotional sounds. This is now being investigated as a risk predictor
  - **New data**: Published first study of EU wide prescribing in ASD - demonstrated; 1) very low prescription rates for associated symptoms, and 2) very wide variation across countries (NL highest).
  - **Regulatory succes**: Worked with EMA to launch concept paper for regulatory guidance (2014).

- **WP5 Biorepository and data base**
  - Biorepository ready to receive samples
  - Data base nearly functional

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What next?
Identify biomarkers of ASD which precede onset of clinical symptoms – High-risk sibling study

- **OBJECTIVE:** To investigate patterns of brain development that may be associated with early detection of ASD
- **white matter development**
- **infant brain processing of human voice sounds** (+ emotions).

- Participants: n=300 HR infants, n = 100 LR infants
- **infants between 3 and 7 months**
Validate biomarkers of ASD in children and adults – Accelerated Longitudinal Study

Large scale multi site clinical study

Total 480/450 **ASD**, 320/330 **HC**

Four schemes:
- A: HFA adolescents/adults (100 + 100)
- B: HFA children (100)
- C: LFA adolescents / adults (100)
- D: MZ and DZ twins (50 + 30)

Follow-up 18 months

knowledge of patients needs across life-course
Build clinical trial network

- Contacted **existing partners**
  European networks; ECNP, ESSEA
  COST Action, & other **major clinical research centres** across Europe

- 48 invitation letters sent to 41 sites

- **Response**
  - 34 sites from 15 countries showed willingness (83% of sites contacted)
  - Second wave of letters focus on Eastern Europe and scandinavia

EU-AIMS is now being contacted by centers that want to participate!
Develop inventory and data mining of clinical databases

Develop European inventory of ASD patients & measures

- Potential sites will complete a brief online survey in early summer 2013
- Focus on patient numbers, characteristics, & routine assessments
- Help data compatibility

Coordinate large clinical databases

- Collect historical anonymised data from clinical research network
- Analyse datasets to answer informative questions
- Help identify potential outcome measures

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EU-AIMS – Full details

EU-AIMS: a boost to autism research

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Nature Reviews Drug Discovery
11, 815-816, 2012
Thank you

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