European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS)

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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

Sleep-deficits
Social Communication Deficits
Language Disability
Seizures
Gi disorders
Immune Dysfunction
Sleep-medication
Sleep deficits
Mood
Attention
Stimulants
Hyper-reactivity
Aggression
Tantrums
Self Injury
Repetitive Behaviours
Anxiety
Anti-depressants

Intellectual Disability

Anti-convulsants

Courtesy: Autism Speaks – Rob Ring

IMI Stakeholder Forum - 13 May 2013 - Brussels
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 translational 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
Neurodevelopmental disorders: from sin to synapse

Synaptic dysfunction: development, maturation and stabilization of synapses.

Translational models
Molecular pathophysiology and target id.
Mechanistic therapeutics
Genetics of mendelian forms
Clinical outcomes and diagnostic BM
Target selection
Translation to drug

Fragile X syndrome
Unaffected brain
Excitatory synapse

Dendritic spine
Neck
Head
Inhibitory synapse

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EU-AIMS

Unprecedented public-private consortium

Launched April 2012

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Headline achievements

12 publications in 1st year of the project

Animal Study Offers Prospect Of Autism Treatment
Roche, in collaboration with Seaside Therapeutics, is testing treatments for autism spectrum disorders, targeting the mGlu receptors.

Roche: New Findings From A Preclinical Study Of Autism
“The pharmaceutical company Roche along with the Biozentrum has discovered new insights to the study of autism.”

The Emerging Biology of Autism Spectrum Disorders
“Synaptic connections in the brain of an autistic mouse”

New Scientific Research Attacks Behaviors In Autism
“According to Swiss drug maker, Roche Holding, Changes in the brain caused by autism can be reversed in mice, a new preclinical study showed, opening a potential path to develop a treatment for the incurable.”

Including toplines journals:

Mean Impact factor: 13.8
Age father is a risk factor for child to have deleterious mutation leading to autism
Headline achievements

Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism

Stéphane J. Baudouin, Julien Gaudias, Stefan Gerharz, Laetitia Hatstatt, Kuikui Zhou, Pradeep Punnakkal, Kenji F. Tanaka, Will Spooren, Rene Hen, Chris I. De Zeeuw, Kaspar Vogt, Peter Scheiffele

Divergent genetic pathways

- single variants/gene(s)
  - <5%
    - Neuroligin 3
    - Shank 3

- Comorbid Phenotype
  - ~10%
    - Fragile-X
    - Rett Syndrome
    - Tuberous Sclerosis

- Chromosome abnormalities
  - ~10%
    - Trisomy Chr. 21
    - Chromosome 15
    - Chromosome 22

- CNV/gene(s)
  - ~65-70%
    - Chr 2q, 5p, 7q
    - Chr 9p, 11p, 15q
    - Chr. 17q, 19q, 22q

Group I mglu receptors

Convergent pathway

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Headline achievements

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
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

Follow-up after 2-3 year

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
Remaining challenges

• Heterogeneity in patients
  – Stratification and relevant biomarker
• Evidence based therapy
• Clinical endpoints
• General awareness of ASD across Europe
EU-AIMS: a boost to autism research

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Thank you

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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.