



Innovative Medicines Initiative

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

**Will Spooren
F. Hoffmann-La Roche**

Autism spectrum disorders (ASD): Current situation



Sleep-medication

- Core clinical features
- Associated neurological symptoms
- Associated physical symptoms

Anti-convulsants

Anti-depressants

Stimulants

Incidence

- 1 in 88 births

Males vs females

- 4x frequent in males

Strong Genetic link

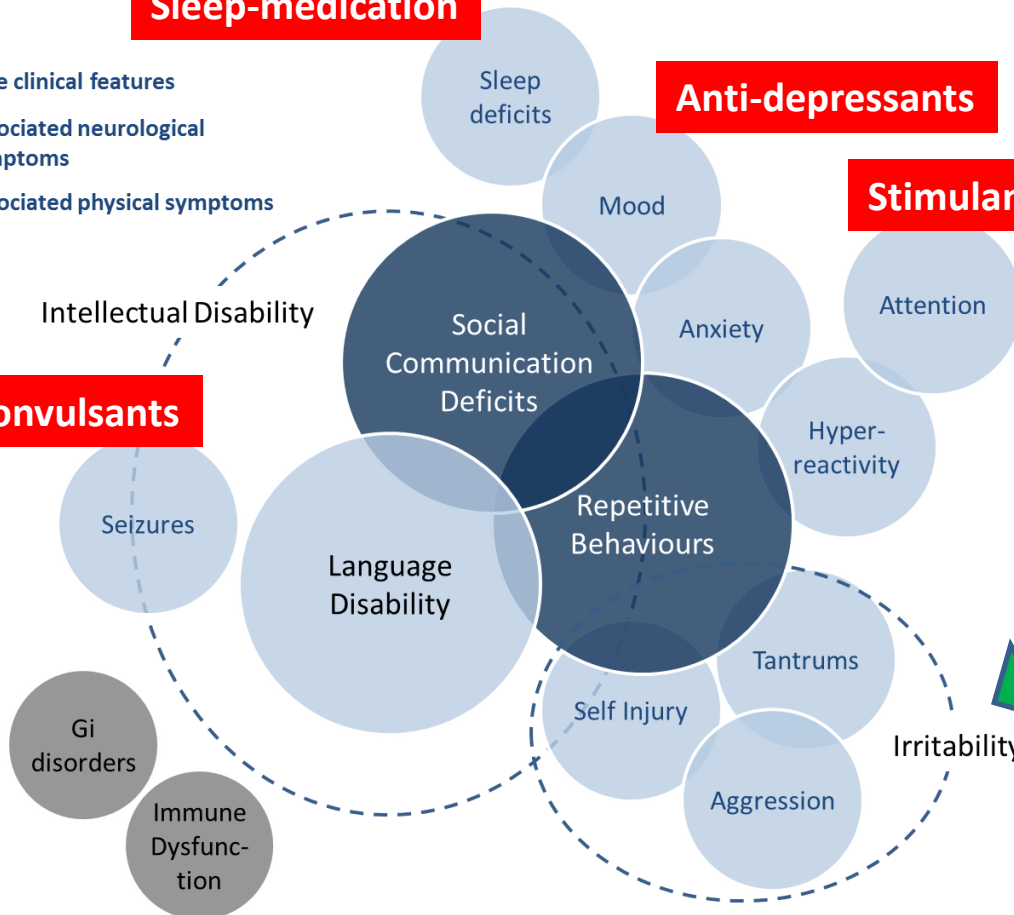
- 10-40% defined genetic alterations, High penetrance

Treatment

- No treatment for core symptoms
- Risperdal and Abilify for irritability

Synapse disorder

- Various targets



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

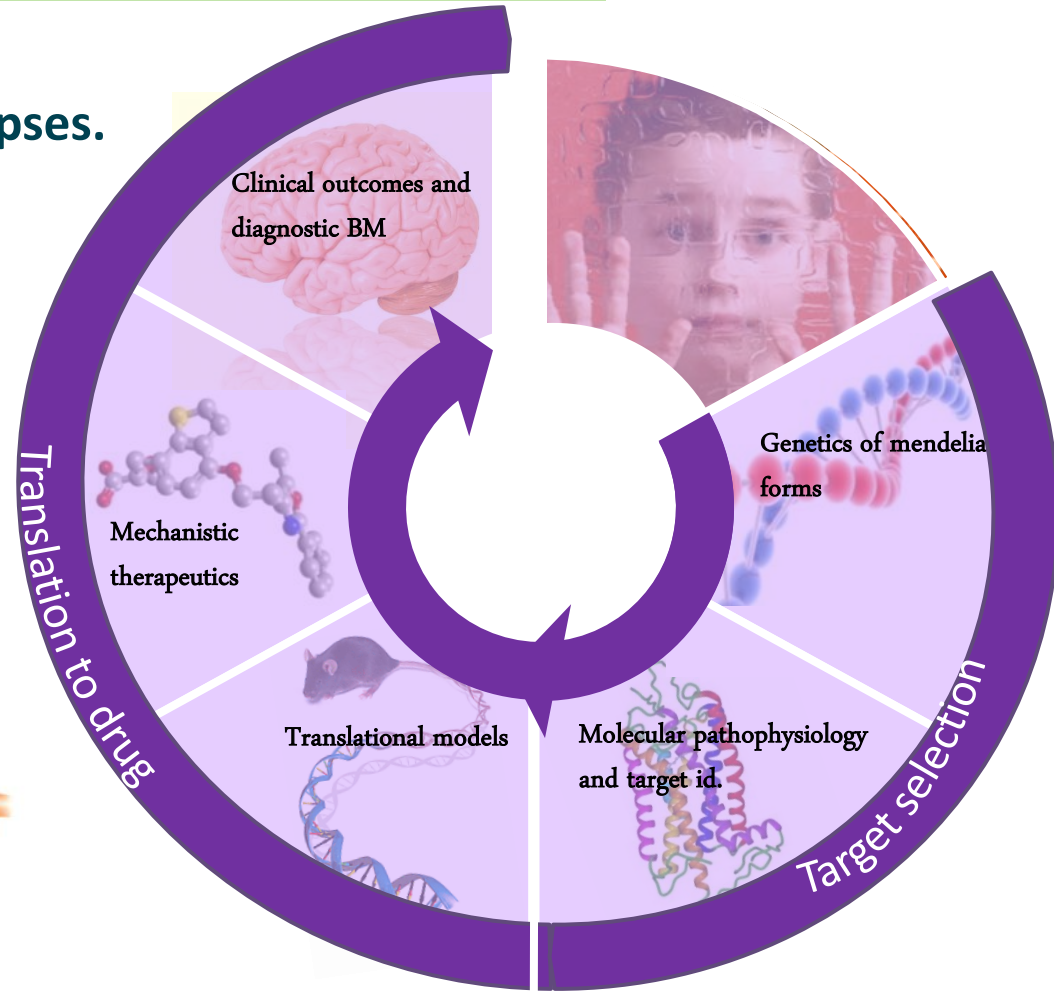
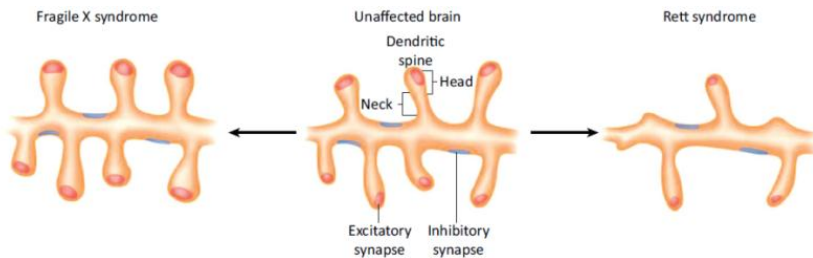
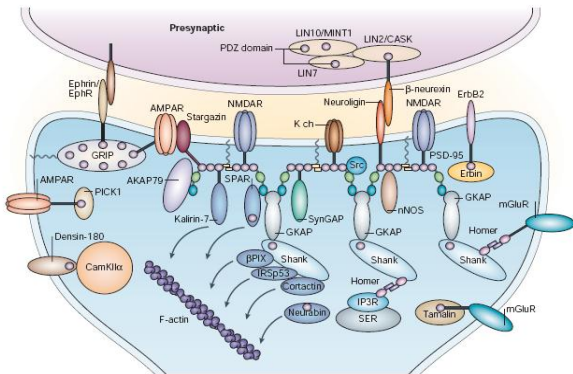
a concerted effort of key stakeholders is needed
Private Public Partnership



Neurodevelopmental disorders: from sin to synapse



Synaptic dysfunction: development, maturation and stabilization of synapses.



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



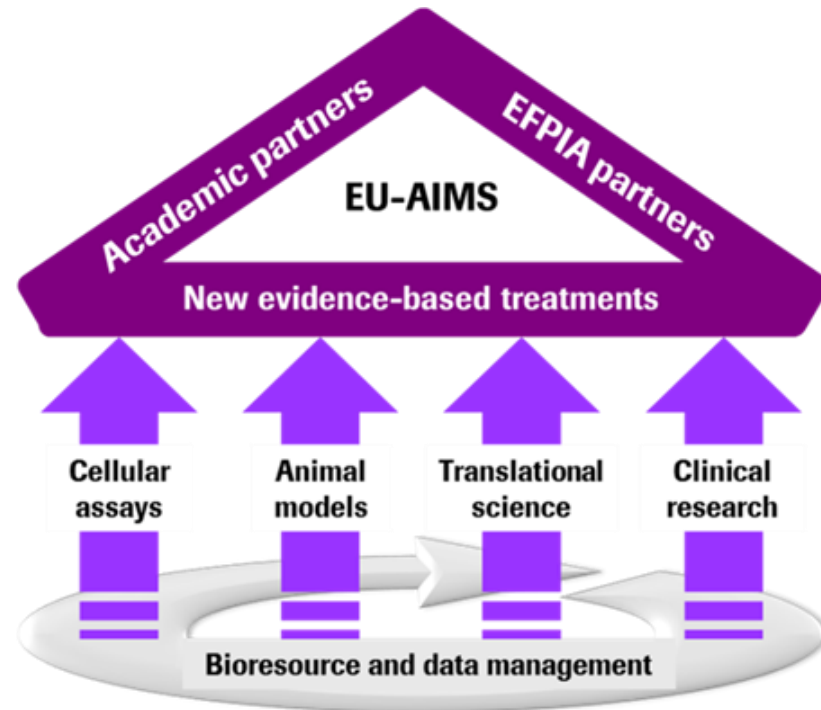
Identification and development of expert clinical sites across Europe to run clinical studies and trials, and the creation of an interactive platform for ASD professionals and patients.



EU-AIMS



Unprecedented public-private consortium **EU-AIMS**



Launched April 2012



Headline achievements



12 publications in 1st year of the project

DOWJONES WALL STREET JOURNAL

Animal Study Offers Prospect Of Autism Treatment

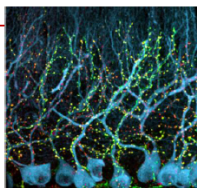
Roche, in collaboration with Seaside Therapeutics, is testing treatments for autism spectrum disorders, targeting the mGlu receptors.

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."



Science
NAAAS

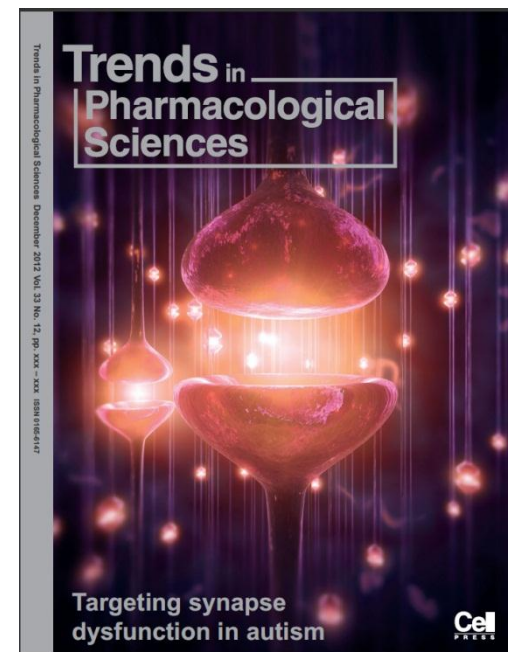


The Emerging Biology of Autism Spectrum Disorders

"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"



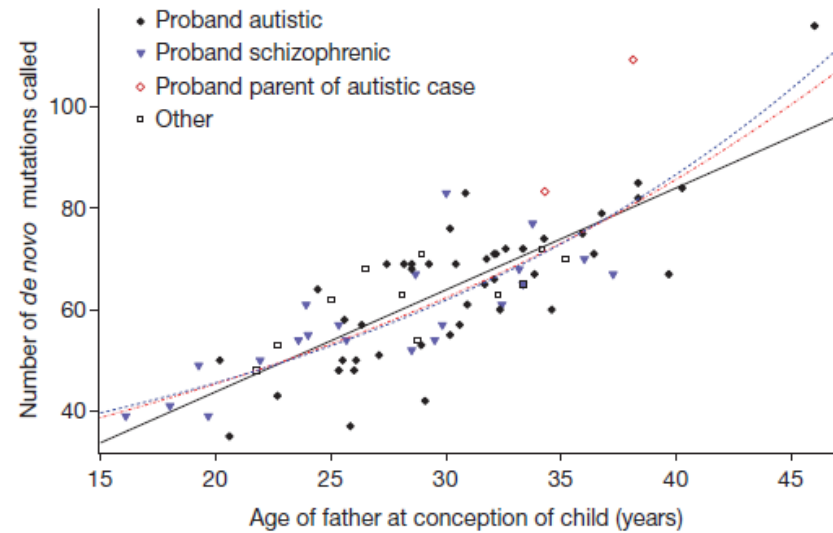
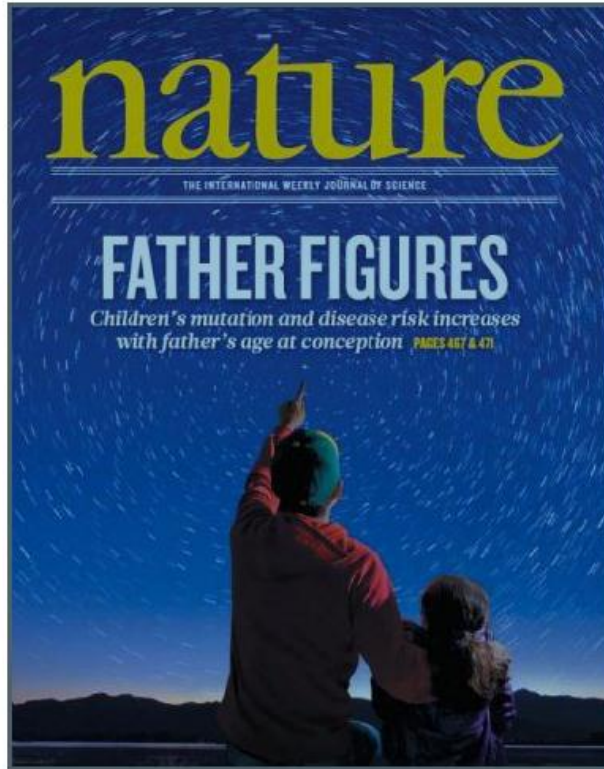
Including topline journals:

Nature, Nature – Drug Discovery, Science, PNAS, Molecular Psychiatry, JAMA, TiPS

Mean Impact factor: 13.8



Headline achievements



Age father is a risk factor for child to have deleterious mutation leading to autism

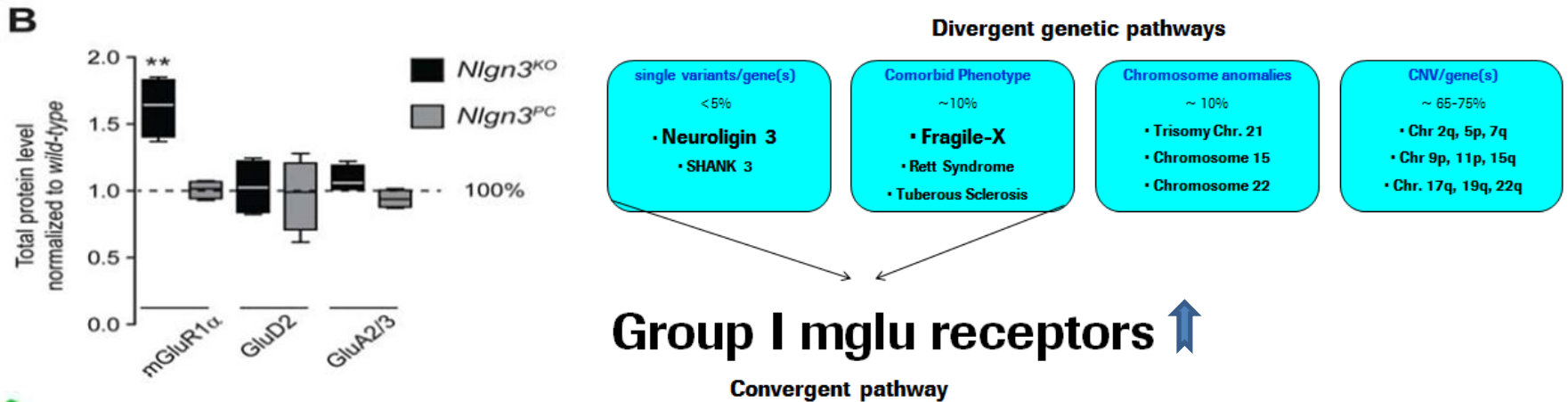


Headline achievements



Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism

Stéphane J. Baudouin,¹ Julien Gaudias,¹ Stefan Gerharz,^{1*} Laetitia Hatstatt,¹ Kuikui Zhou,² Pradeep Punnakkal,¹ Kenji F. Tanaka,^{3,4} Will Spooren,⁵ Rene Hen,³ Chris I. De Zeeuw,^{2,6} Kaspar Vogt,¹ Peter Scheiffele^{1†}



Headline achievements



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- 1 21 March 2013
- 2 EMA/CHMP/40896/2013
- 3 Committee for Medicinal Products for Human Use (CHMP)

- 4 Concept paper on the development of Medicinal
- 5 products for the treatment of Autism Spectrum
- 6 Disorder

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Agreed by CNS Working Party	February 2013
Adopted by CHMP for release for consultation	21 March 2013
Start of public consultation	4 April 2013
End of consultation (deadline for comments)	4 July 2013

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Comments should be provided using this [template](#). The completed comments form should be sent to CNSWPSecretariat@ema.europa.eu

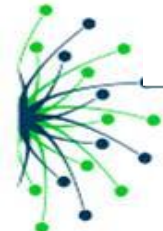
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Keywords	Autism, Paediatric population, Asperger's Disorder, Rett's disorder, Childhood disintegrative disorder and Pervasive Developmental Disorder – not otherwise specified
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**Regulatory
guidance 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





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:

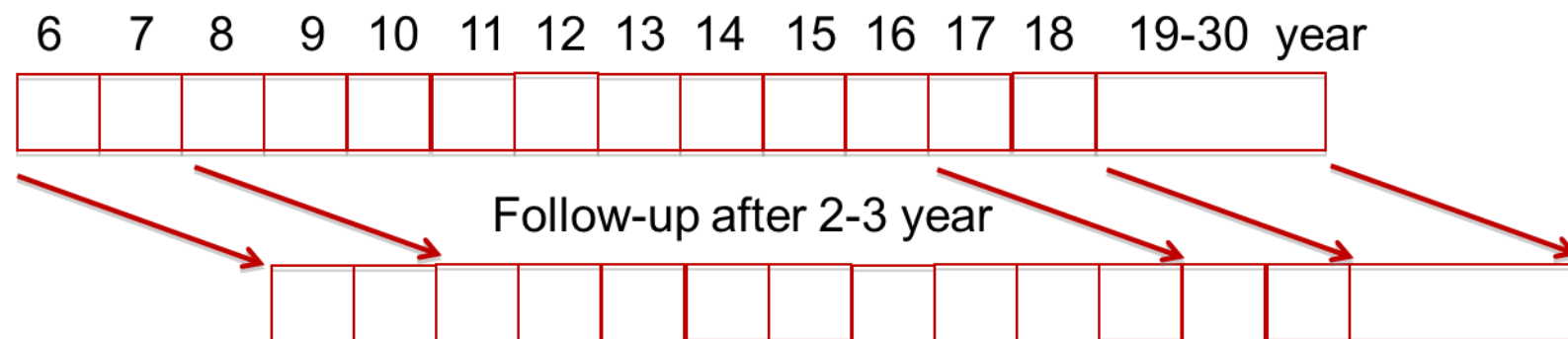
A: HFA adolescents/adults (100 + 100)

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



 May indicate multiple sites in the same city

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



EU-AIMS – Full details



EU-AIMS: a boost to autism research

Declan Murphy, Will Spooren

**Nature Reviews Drug Discovery
11, 815-816, 2012**



Thank you



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