Precision Medicine Approaches in Autism Spectrum Disorders

Will Spooren

Webinar call 10 • Brussels

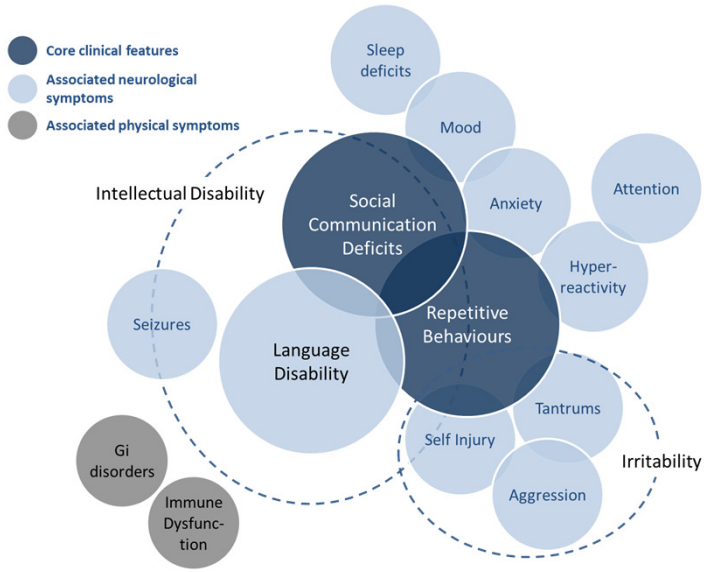
Autism Spectrum Disorders

Incidence
- 1 in 88 births

Gender differences
- 4x more frequent in males **versus females**

Strong Genetic link
- 10-40% defined genetic alterations; high penetrance

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



High medical need with no therapy available and no research and clinical development infrastructure

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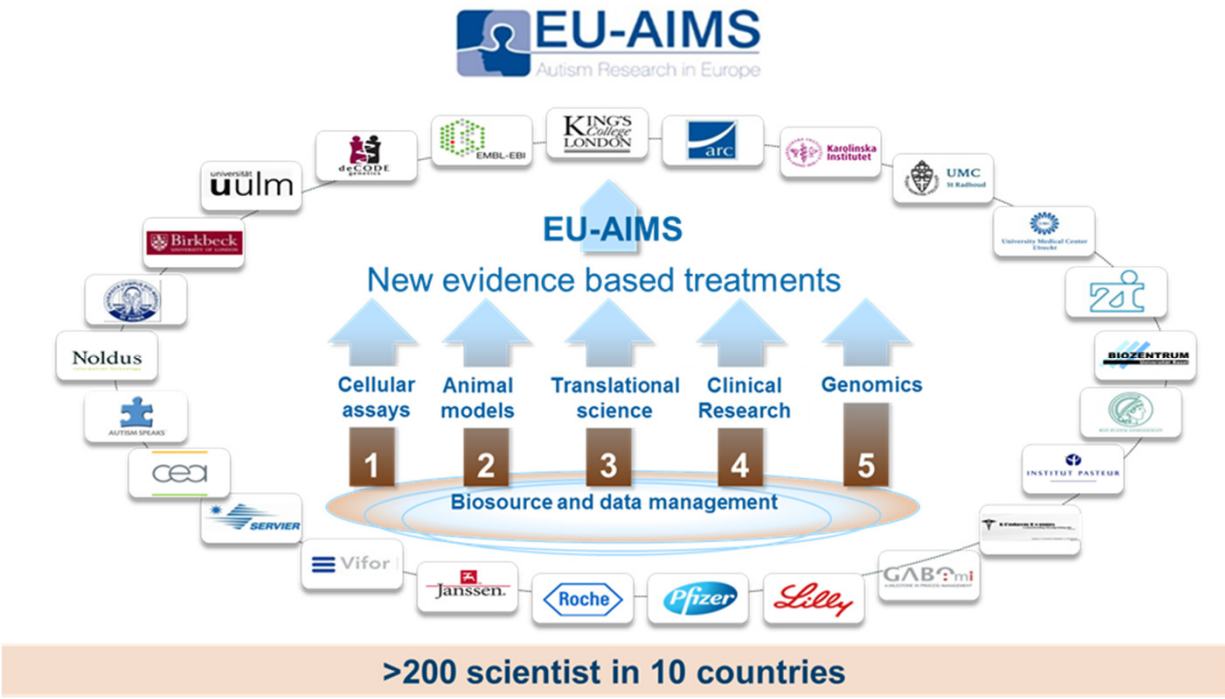

High medical need with no therapy available and no research and clinical development infrastructure

(I) Deep phenotyping and biomarkers

Extend baby sib and LEAP study

Identification of early predictive/diagnostic biomarkers for ASD

- Prospective study of infants with older sibling with ASD
- Cognition, Behaviour, Neuroimaging and Neurophysiology
- Relation to symptoms/diagnosis of ASD at outcome
- Subjects: **405** N = 305 (High-Risk infants; 4 – 36 months)
  N = 100 (Low-Risk infants; 4 – 36 months)
- Time points: 5, 10, 14, 24 and 36 months

Clinical sites: London, Cambridge, Stockholm, Nijmegen, Ghent

Risk factors and early diagnosis

Deep phenotypic longitudinal characterization of children/adults

- Subjects: **605** Total : N= 370 ASD individuals (6 – 30 y), 235 controls

Clinical sites: London, Cambridge, Stockholm, Utrecht, Nijmegen

Clinical endpoints and biomarkers

(II) Build clinical capability

- **Building on key pre-existing assets:** Clinical Trial Network

- **> 90 sites in 37 countries**
- Build and Implement:
  - GCP stardization
  - Fast fail/trial ready cohorts
  - EMA Regulatory framework
  - Drug study – repurposed
  - Big data/mining
  - Alignement with US efforts

Largest multi-national, autism network in the world

Key deliverables

- **Validation of stratifications markers in infants, children and adults including regulatory aspects**
  - Fluid biomarkers; imaging and EEG/EMG; Clinical endpoints; Genomics/proteomics
  - Develop and implement smart Phone based clinical assesments
- **Clinical network development**
  - GCP standardization and training; Study ready and Fast-fail cohorts
- **Clinical Trials**
  - Efficacy studies with re-purposed clinical assets in patients using stratified medicines approaches
- **Stakeholder engagement**
  - EU policy; Payer/reimbursement; Educational program across Europe; Regulatory alignment
  - Alignement with US Based eforts
- **Knowledge Management**
  - Tissue and data repositories; Registries / Patients big-data international networks

Consortium Composition

Confirmed participation:

EFPIA:

F. Hoffmann-La Roche Ltd

UCB Biopharma

Janssen

Novartis

Associated Partners:

National Institute of Mental Health (NIMH)

Simon Foundation Autism Research Initiative (SFARI)

Autism Speaks

Thank You

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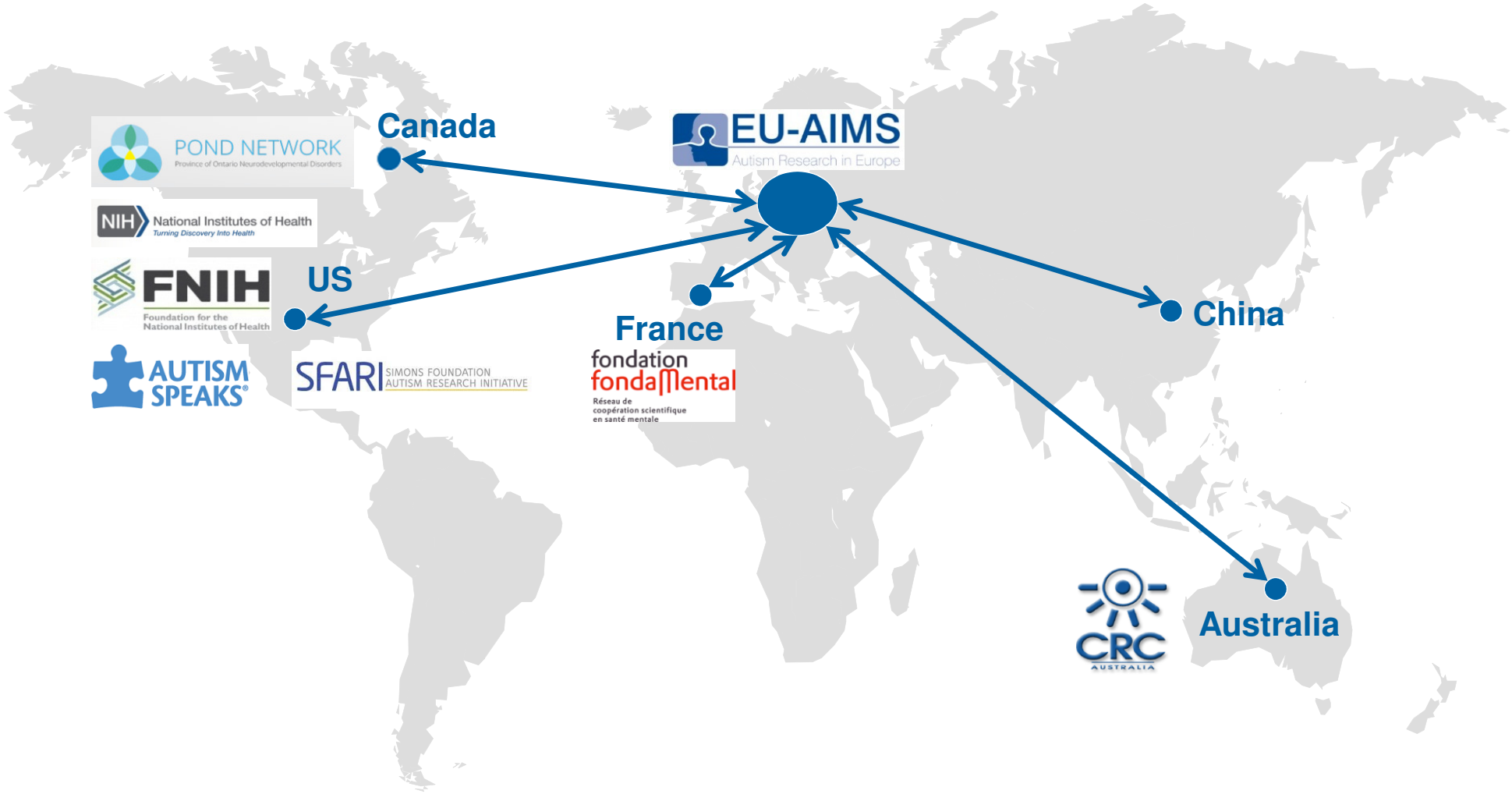
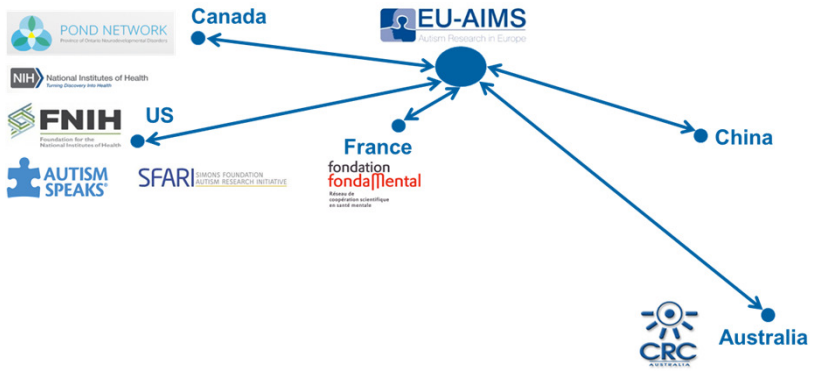
Data sharing and alignment



A global approach for success (I)

- **Increased probability of success (POS) in establishing stratification biomarkers of ASD that:**
  - Apply to patients in need in terms of diagnosis and treatment in the EU
  - Catalyse development of novel treatments with more rapid access to patients

- **Increased alignment of biomarker data acquisition and analysis**
  - Coordination of biomarker qualification through EU and US regulatory agencies via an integrated EU / US biomarker approach for ASD



A global approach for success (II)

- **Biomarker validation requires large sample sizes (e.g. genetics), complete harmonization / refinement of methodologies, data analytic strategies and replication**
  - Precise protocol details across groups can only be implemented with shared oversight of study design
  - Quality control of all elements of studies is optimal when ongoing experience is brought to the attention of a central group with oversight of projects
  - Rapid replication of results from POC fast fail in idiopathic cases into more targeted subgroups from deep phenotyped samples
  - Rapid transfer of POC from ‘fast fail’ work to clinical trials in humans
- **Sharing of data in real-time to focus ongoing research efforts**
  - Only possible with active team participation of NIMH (NDAR) and with SFARI / Autism Speaks for genetics and outcome measures

The key deliverables (1/2)

GP1

Roche

Personalised medicine through more biologically homogeneous subgroups and objective outcome markers.

- Validated risk factors, biomarkers and stratification markers in across age and severity spectrum in ASD

  Fluid biomarkers, imaging, EEG/EMG, clinical endpoints, genomics/proteomics

- Initiate international 'big data' networks, linked to U.S. efforts) around

  Genetics/omics, other biomarkers (i.e., brain tissue banks)

- Biological understanding of risk vs protective factors for common co-morbidities.

  Intellectual dysfunction, epilepsy, ADHD…

  Leads to…

  Identification of other novel molecular / systems and symptom approaches (cross-diagnostic

Folie 12

GP1 Edited
Pandina, Gahan [JRDUS]; 24.02.2016

The key deliverables (2/2)

Improving research translation from bench to bedside.

- Align international efforts on ‘first in human’ proof of concept for compounds impacting on neural systems implicated in ASD.

Share risk target validation, ‘fast fail’ novel / repurposed compounds and speed to PoC new compounds (link to NIH ‘fast fail’ network)

- Conduct large scale trials with objective stratification, outcome tools

e.g. international collaborations with SFARI

Essential steps for successful trials

- EU wide clinical trials network trained to GCP standards

Study ready and fast fail cohorts

- EU registry of ‘deeply phenotyped’ clinical trials population for ASD
- Develop novel objective trial methodologies

- Select / replace treatment arms
- Reduce placebo response rates.

- **Run Europe’s first GCP standard large scale multi center drug study in ASD.**

Folie 13

GP2 Reworked

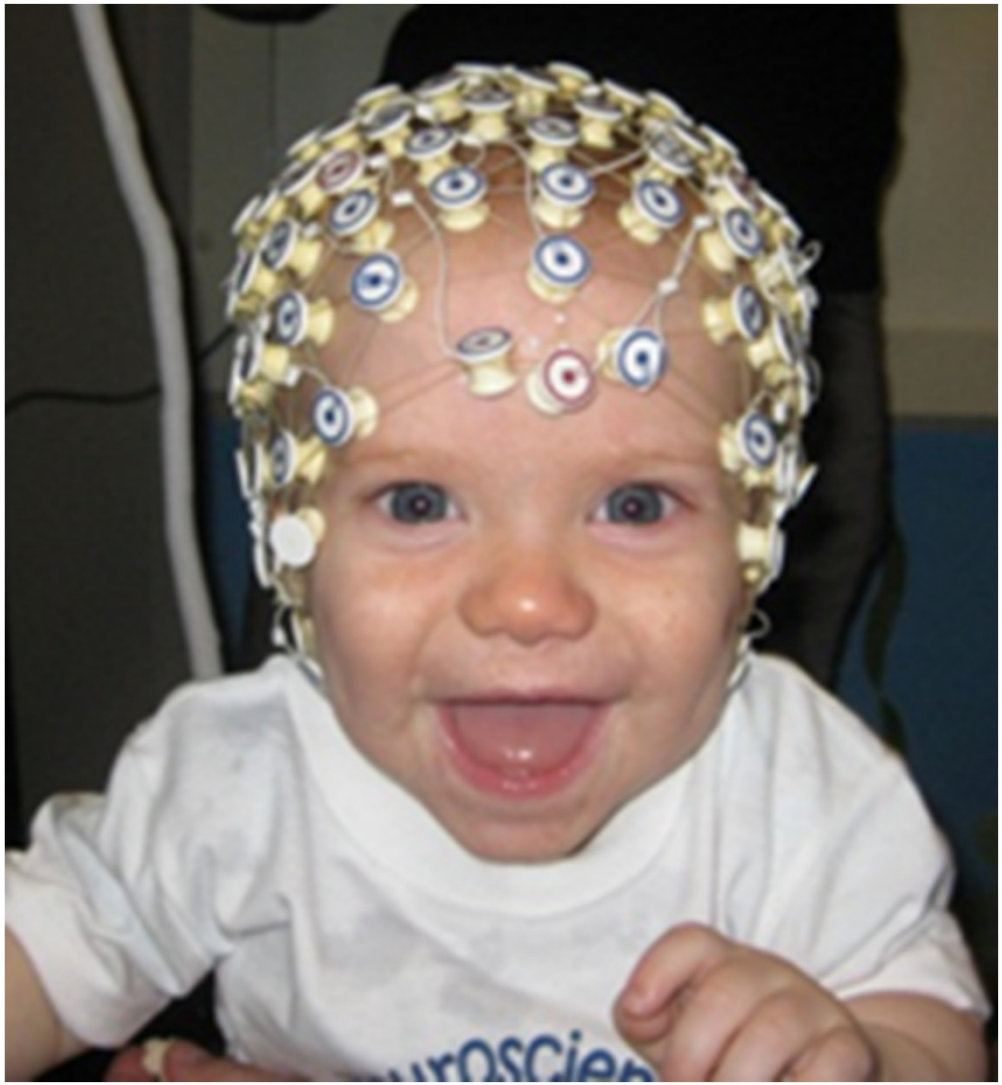
Pandina, Gahan [JRDUS]; 24.02.2016

Topic aligned with IMI-2 objectives

- Increase the success rate of clinical trials of new / re-purposed medicines
- Speed-up the drug development process and identify new treatments in areas of unmet medical need
- Develop new biological markers to diagnose diseases and assess treatments
- Improve the drug development infrastructure to better assess the efficacy, safety and quality of medicines

Potential impact for Europe

Europe to become the driver, and leader, of innovation within ASD research enabling the development, and testing, of novel / re-purposed compounds that can make a significant difference to the lives of patients and their caregivers

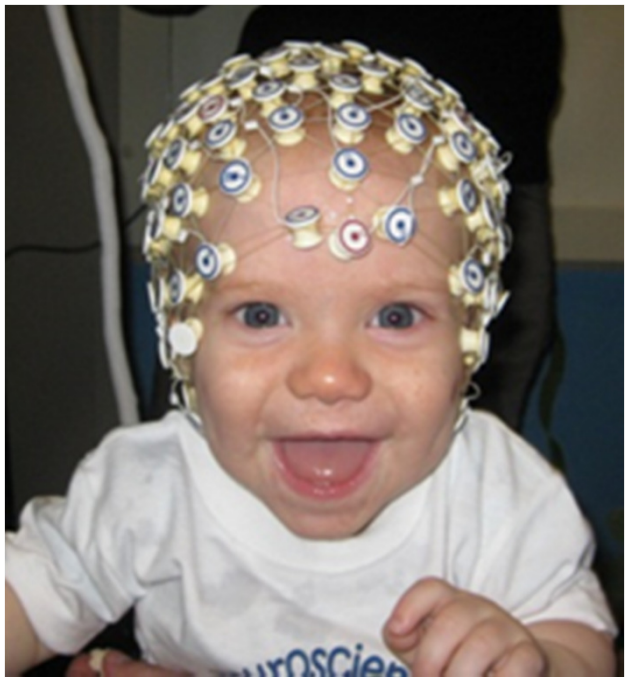


Scope and vision (I)

EU-AIMS
Autism Research in Europe

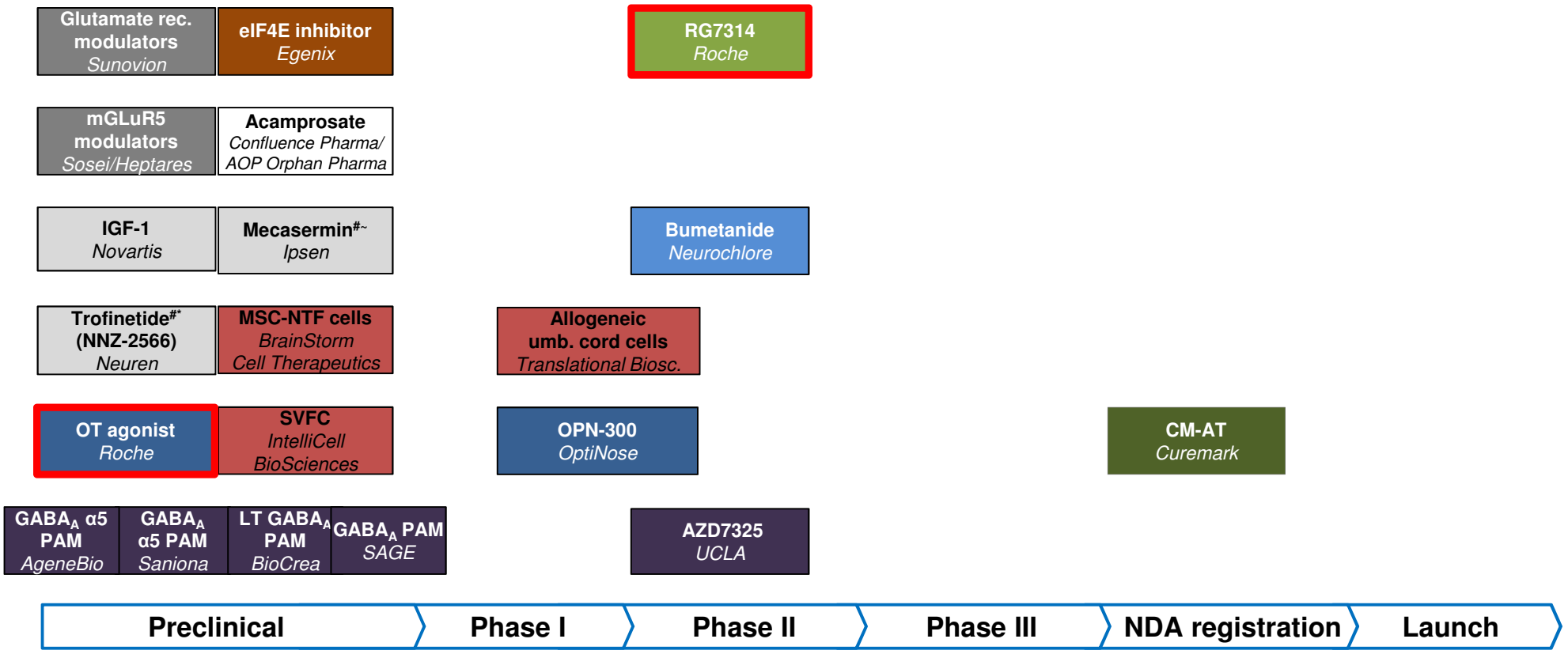
Roche

Create a world leading clinical infrastructure for research and drug development in Autism Spectrum Disorders building on key pre-existing assets in Europe



A world-class clinical infrastructure

Competitive landscape for core social & communication deficit symptoms in ASD



Modes of action

- Oxytocin agonist
- GABA$_B$ PAM
- Vasopressin 1A antagonist
- Glutamate modulator
- Insulin-like growth factor -1
- Diuretic
- eIF4E inhibitor
- Unknown
- GABA$_A$ PAM
- Chymotrypsin modulator; novel proteolytic enzyme
- Stem cell therapy

Sources: Company websites,Thomson Reuters, Pipeline, Trialtrove, clinicaltrials.gov; LAST UPDATED: 11 June 2015

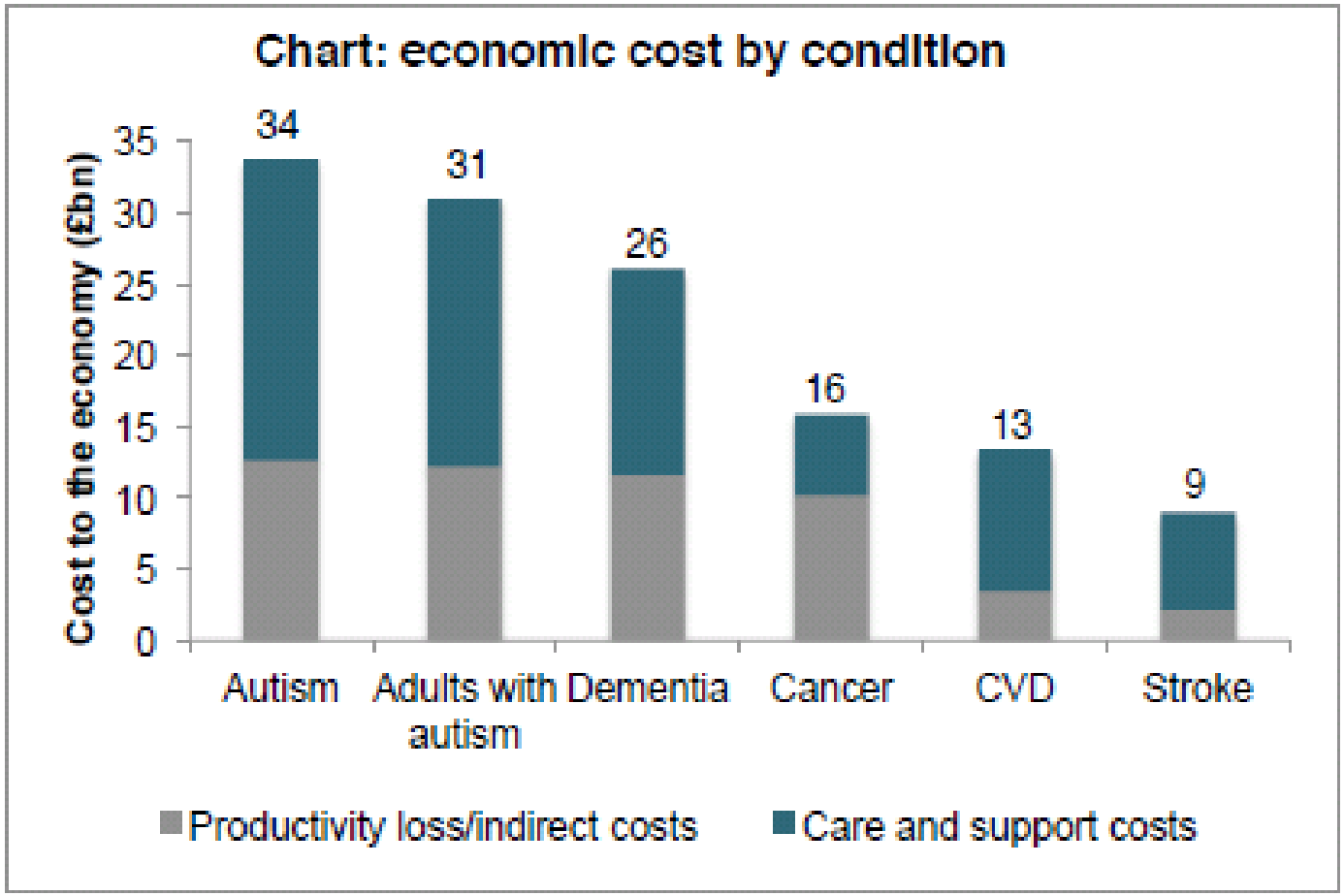
Current clinical & regulatory environment

- No aligned strategy defined between Europe and the Rest of the World
- No concerted efforts in Drug Discovery
- No operational Clinical Trial Network
- No aligned regulatory strategy – EU vs. US
- Worldwide late diagnosis and poor awareness (adults)
- Poor knowledge of patients needs across life-course
- Wide range in treatment strategy with no evidence of efficacy
- No, or poor, clinical trials experience in paediatric centres
- General lack of GCP standardization

Poor alignment and regulatory guidance across Europe and the World

Autism research spend does not match economic cost*

Autism has a higher cost to the economy than dementia, CVD, cancer or stroke



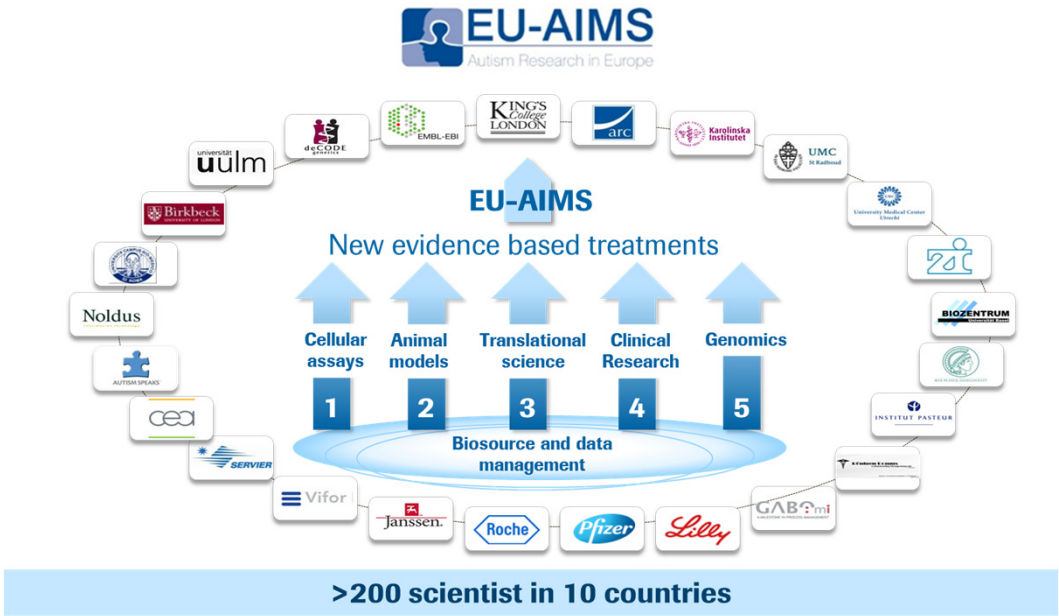
Autism among the highest of socio-economic costs

**** REFERENCE REQUIRED***

EU-AIMS - Best performing IMI project (Reuters Research)*

Scientific achievements

- Highest citation impact to date of all IMI projects (N=59)
  - 4 times the world average impact
- Highest percentage of highly cited papers (42% are in the **top decile** of publications for journal category and year of publication)



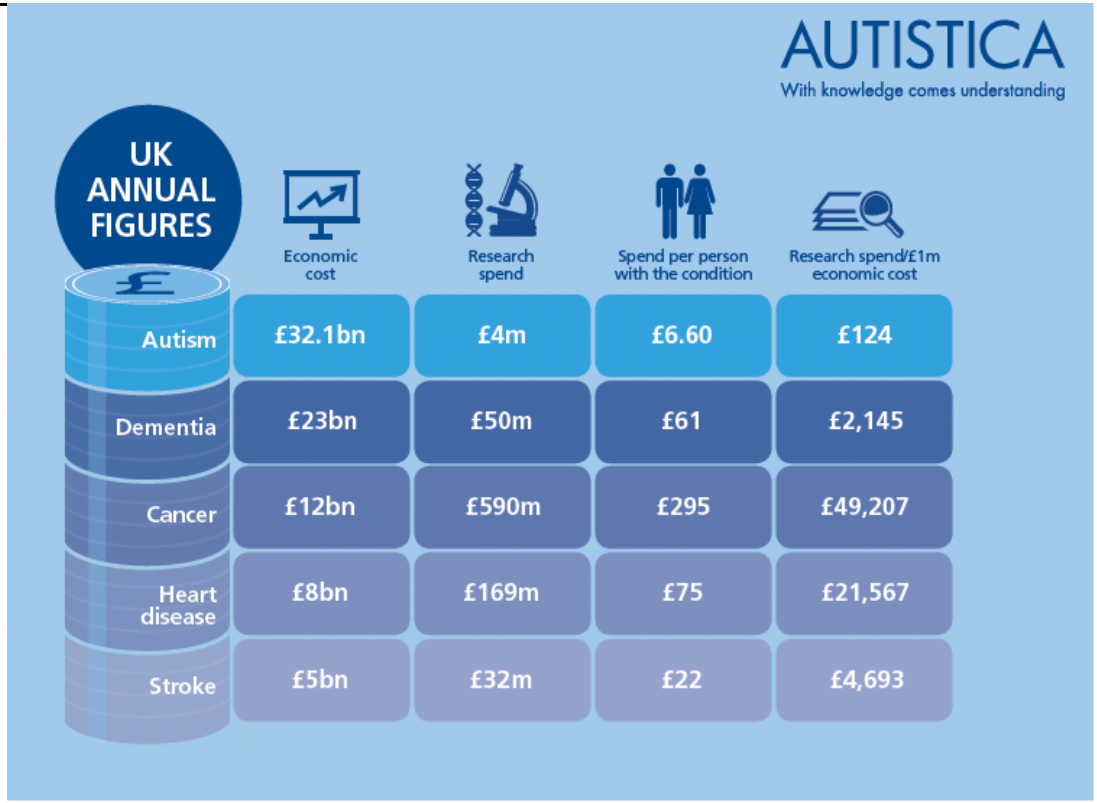
Interactions with distinct stakeholders

- External support from Autism speaks and other advocacy organizations
- Interactions with key regulatory agencies such as EMA and FDA

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

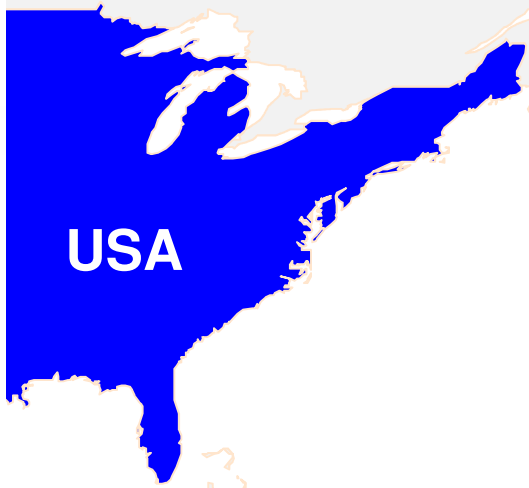
The UK economic impact of autism*

- Only 15% of people with autism will ever find full time work and many carers must give up work
- Care costs can exceed £1m a year for the most severely affected
- Our research shows autism costs the UK economy over £32 billion a year but only £4m is spent on autism research
- The UK leads the world in quantifying economic impact but we would expect a broadly similar situation in other developed nations



** Knapp, M. et al (2009). Economic cost of autism in the UK. Autism. 13 (2). P.317-336*

Understanding the Cost of Autism



Total Annual Cost of Autism Care

$127 B (€95 B) **£34 B** (€41 B)

Individual Lifetime Cost of Autism

$1.4 M (€95 M) **£0.9 M** (€41 M)

Individual Lifetime Cost of Autism

(with Intellectual Disability)

$2.3 M (€1.7 M) **£1.5 M** (€1.8 M)

Potential Impact for Europe

- Provide a deep understanding of the underlying biology of autism
- Provide Identification of patient sub-populations using validated stratification biomarkers
- Development of an European-wide infrastructure to accelerate and tailor patient recruitment to targeted (adaptive) clinical trials
- Set new standards for industry and allow potential identification of precision medicines for patients in highly characterized patient groups
- Development of a standardized approach to clinical research in ASD within Europe and the rest of the world – with full alignment with US creating a regulatory framework allow fast access to key markets
- Europe to become the driver and leader of innovation within in autism research and is likely to be first to bring a drug that will make a difference to patients

Key deliverables (I)

- **Personalised medicine through more biologically homogeneous subgroups and objective outcome markers**
  - Validated risk factors, biomarkers and stratification markers in children and adults with ASD that include fluid biomarkers, imaging, EEG/EMG, clinical end-points and genomics/proteomics
  - Initiate international 'big data' networks (e.g. linking U.S. efforts) around genetics/omics and other biomarker data including brain tissue banks
  - Biological understanding of risk vs. protective factors for common co-morbidities (e.g. intellectual disability, epilepsy and ADHD).
    - This will identify other novel molecular/systems and symptom-based approaches (e.g. that may cross clinical diagnostic boundar

Key deliverables (II)

- **Improving movement from bench to bedside**
  - Alignment to existing international efforts on ‘first in human’ proof of concept for compounds impacting on neural systems implicated in ASD
  - Shared risk for target validation, and ‘fast failing’ novel, or re-purposed, compounds and take promising compounds to trial more rapidly e.g. by linking with international (NIH) ‘fast fail’ network
  - **Carrying out large-scale trials using objective stratification tools and outcome markers e.g. international collaborations with SFARI**

Key deliverables (III)

- **Essential steps for successful trials**
  - European registry of ‘deeply phenotyped’ individuals willing to take part in clinical trials for ASD
  - A European wide clinical trials network trained to GCP standards that includes study ready and fast fail cohorts
  - Develop novel objective trial methodologies for selecting/replacing treatment arms and reducing placebo response rates
  - **Run Europe’s first GCP standard large scale multi-centre drug study in ASD**