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# Building tools against autism

*By Lev Osherovich, Senior Writer*

As information about the genetic underpinnings of autism spectrum disorder has proliferated, so too have questions about how subtle changes in a seemingly diverse set of genes can lead to similar clinical pathology. This month, an academic-industry consortium headed by **King's College London** and **Roche** launched with €29.6 million ($38.9 million) to develop research tools and diagnostics for the disorder and to help select clinical endpoints for future trials.

Up to 40% of autism spectrum disorder (ASD) cases are now thought to stem from either single mutations or a combination of multiple genetic variants. For example, a trio of recent exome sequencing studies identified spontaneous mutations that substantially increase the risk for ASD.[1–3]

However, the underlying causes of the majority of ASD cases that lack a clear genetic component remain mysterious. As a result, only a handful of companies are pursuing ASD therapeutics.

The new consortium, dubbed the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS), hopes to change that by uncovering common pathophysiological features across a range of ASD cases, identifying biomarkers for stratifying patients and developing preclinical and clinical assays to assess drug efficacy.

The consortium's work has been subdivided into six projects concerning cellular assays, animal models, MRI methods, PET radioligands, biomarker identification and clinical research network building.

The consortium is being funded by the **Innovative Medicines Initiative** (IMI), Roche and other industry participants, and the patient advocacy group **Autism Speaks** (*see* **Table 1, "Participants in the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS) consortium"**).

Autism Speaks is contributing about €500,000 ($656,000) as a grant to academic researchers in the consortium; industry partners will contribute about €10 million ($13 million) in services, reagents and facilities; IMI will provide about €19 million ($25 million) in grant support over 5 years.

> **"The goal of the consortium is to speed up the development of infrastructure that would facilitate the development of new treatments."**
>
> ***—Declan Murphy, King's College London***

## Framing the challenge

According to Declan Murphy, professor of psychiatry and brain maturation at King's College London and leader of the consortium's U.K. team, the challenges in understanding ASD include the apparent heterogeneity of the genetic causes of the disease, a lack of good preclinical models and the complex behavioral manifestation of the disease in the clinic.

"This is a mental health disorder, and there are a lot of pharmas getting out of the area. We don't understand the biology well enough," said Murphy. "The goal of the consortium is to speed up the development of infrastructure that would facilitate the development of new treatments."

The key questions, he said, are "can we stratify individuals with

**Table 1. Participants in the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS) consortium.**

| Academic centers and research organizations | Companies |
|---|---|
| **Autism Speaks**, New York, N.Y. | **Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland |
| **Biozentrum of the University of Basel**, Basel, Switzerland | **Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind. |
| **Birkbeck, University of London**, London, U.K. | **Servier**, Neuilly-sur-Seine, France |
| **Campus Bio-Medico University**, Rome, Italy | **Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J. |
| **Central Institute of Mental Health**, Mannheim, Germany | **Pfizer Inc.** (NYSE:PFE), New York, N.Y. |
| **European Molecular Biology Laboratory**, Heidelberg, Germany | **Galenica Ltd.** (SIX:GALN), Berne, Switzerland |
| **French Alternative Energies and Atomic Energy Commission**, Saclay, France | **deCode genetics ehf**, Reykjavik, Iceland |
| **Institute of Education**, London, U.K. | **NeuroSearch A/S** (CSE:NEUR), Ballerup, Denmark |
| **Karolinska Institute**, Stockholm, Sweden | |
| **Max Planck Institute of Experimental Medicine**, Goettingen, Germany | |
| **Pasteur Institute**, Paris, France | |
| **Radboud University Nijmegen**, Nijmegen, the Netherlands | |
| **University Medical Center Utrecht**, Utrecht, the Netherlands | |
| **University of Cambridge**, Cambridge, U.K. | |
| **University of Ulm**, Ulm, Germany | |

autism? Can we develop assays and biomarkers that are predictive of outcomes? Can we demonstrate efficacy in mice and humans?"

Luca Santarelli, global head of Roche Neuroscience and point person for the pharma's involvement with EU-AIMS, said the consortium is operating on the hypothesis that there is set of shared disease mechanisms that apply to the bulk of ASD patients.

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***—Luca Santarelli, Roche***

Roche's RO5028442, a small molecule with an undisclosed target, is in Phase I testing in autistic patients. Roche also has another autism compound, the arginine vasopressin receptor 1A (AVPR1A) antagonist RG7314, in Phase I testing in healthy volunteers.

"Genetics offers a very wide variety of potential reasons why brain physiology might be altered leading to ASD," said Santarelli. "On one hand, you have many mutations that can lead to ASD. On the other hand, you have a lot of complex phenotypes. What we need is a more reductionist, simple model that explains how different types of genetic lesions may lead to common alterations in the brain."

Thus, he said, one of the consortium's goals is to understand the common features of brain pathophysiology across the autism spectrum.

"It's more than likely that we will converge on a handful of common pathways that lie downstream of a variety of genetic risk factors," agreed Robert Ring, VP of translational research at Autism Speaks.

## Game plan

Santarelli and Ring said the theory they favor is that ASD is a disorder of brain connectivity in which alterations in a range of genes lead to changes in synaptic structure and function. According to this theory, some patients with ASD may have overly excitable synapses, whereas other patients may suffer from the opposite problem.

"We clearly have an interest in the balance of inhibition and excitation in certain brain regions. There is a very fine-tuned balance between these activities both in development and adulthood," said Santarelli. "With this hypothesis in mind, it's clear that we need appropriate cell and animal models to dissect the biology. In this consortium, cell models and animal models are the two pillars. We will start with modeling these mutations in cell systems and iPS [induced pluripotent stem] cells from patients, then we will move into animal models."

In parallel with model building, the consortium will search for imaging data or other biomarkers to shed light on the functional consequences of brain connection problems in ASD.

Academic centers participating in the consortium will develop functional MRI methods and PET radioligands for *in vivo* imaging. The consortium also hopes to uncover proteomic biomarkers of the disease that can be used to guide treatment decisions and assess efficacy of future interventions.

The hope, said Santarelli, is to classify patients with ASD into less than 10 functional categories that will help guide what kind of therapy would be most appropriate.

Knowing how autistic brains are different from normal brains also will help guide selection of endpoints in future trials. Thus, Autism Speaks will work with clinics within the consortium to build a patient registry and a clinical trial network.

IMI requires that the money be spent in the EU, so it brought in Autism Speaks to insure that the consortium does not repeat the work of other autism research consortia in the U.S., such as the Biomarkers Consortium, managed by the **Foundation for the National Institutes of Health**, and the Autism Epidemiology Network of the **Centers for Disease Control and Prevention**. Autism Speaks will help coordinate between EU-AIMS and American researchers to avoid duplication of effort.

Murphy said that the consortium's work will be openly accessible.

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### REFERENCES

1. Sanders, S.J. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10945
2. O'Roak, B.J. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10989
3. Neale, B.M. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature11011

### COMPANIES AND INSTITUTIONS MENTIONED

**Autism Speaks**, New York, N.Y.
**Centers for Disease Control and Prevention**, Atlanta, Ga.
**Foundation for the National Institutes of Health**, Bethesda, Md.
**Innovative Medicines Initiative**, Brussels, Belgium
**King's College London**, London, U.K.
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland