Developing new pharmacotherapies for autism

C. Ecker1, W. Spooren2 & D. Murphy1

From the 1Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, London, UK, and 2F. Hoffmann-La Roche Ltd, Basel, Switzerland


Developing new pharmacotherapies for autism spectrum disorder (ASD) is a challenge. ASD has a complex genetic architecture, several neurobiological phenotypes and multiple symptom domains. However, new opportunities are emerging that could lead to the development of ‘targeted’ and individualized pharmacological interventions. Here, first we review these important new insights into the aetiology and neurobiology of ASD with particular focus on (i) genetic variants mediating synaptic structure and functioning and (ii) differences in brain anatomy, chemistry and connectivity in this condition. The characterization of the genotypic and phenotypic differences underlying ASD might in the future be invaluable for stratifying the large range of different individuals on the autism spectrum into genetically and/or biologically homogeneous subgroups that might respond to similar targeted interventions. Secondly, we propose a strategic framework for the development of targeted pharmacotherapies for ASD, which comprises several different stages in which research findings are translated into clinical applications. The establishment of animal models and cellular assays is important for developing and testing new pharmacological targets before initiating large-scale clinical trials. Finally, we present the European Autism Interventions – A Multicentre Study for Developing New Medications (EU-AIMS) Initiative, which was set up in the context of the EU Innovative Medicines Initiative as the first European platform for integrated translational research in ASD. The EU-AIMS Initiative consists of academic and industrial partners working in collaboration to deliver a more ‘personalized’ approach to diagnosing and treating ASD in the future.

Keywords: autism, biomarkers, drug development, personalized medicine, translational research.

Introduction

Autism spectrum disorder (ASD) is a life-long neurodevelopmental condition for which no cure yet exists. Discovering novel treatments for ASD remains a challenge; its aetiology and pathology are largely unknown, the condition shows wide clinical and phenotypic diversity, and case identification is solely based on symptomatology. Hence, large-scale clinical trials are typically based on samples of biologically and clinically heterogeneous individuals, and potential treatment effects often remain undetected.

Yet, there is an increasing need for effective treatment development. It is currently estimated that 1% of all children have ASD [1], and the condition is more common than paediatric cancer, diabetes and AIDS combined. Furthermore, the high prevalence rate of ASD is growing (by approximately 10–17% annually), and consequently so is the disease burden on affected individuals, their families and carers, and society as a whole. However, new opportunities are emerging that might help in the development of novel treatments and biomarkers for the condition. More than ever, there is thus a strong need to establish multidisciplinary, integrated platforms that could facilitate translational research to develop ‘targeted’ pharmacotherapies and personalized interventions for ASD.

Here, we review the findings of recent studies that might provide new and tractable opportunities to identify ASD biomarkers across a variety of scientific disciplines and that underpin the discovery of new pharmacological targets. In addition, we present the first European platform, the European Autism Interventions – A Multicentre Study for Developing New Medications (EU-AIMS) initiative, which was set up to facilitate evidence-based target-drug discovery in ASD.
Heterogeneity of ASD: a complex challenge for developing biomarkers and treatments

Autism spectrum disorder is a group of conditions in which heterogeneity, both causative and phenotypic, is emerging as a dominant characteristic [2]. Although a number of candidate genes have been proposed to underlie ‘the autisms’ [3], recent genetic findings suggest that idiopathic autism (i.e. in contrast to ASD with known aetiology as a result of, for example, Fragile X and Rett syndromes) is not a single-gene disorder. Rather, it seems that ASD susceptibility is mediated by a pattern of small and individually rare genetic variants, copy number variations (CNVs), which give rise to the ‘broader autism phenotype’. Individuals with this phenotype demonstrate (i) various degrees of symptom severity, (ii) different neurocognitive profiles, (iii) several associated comorbid conditions and (iv) potentially different neurobiological features. It is thus perhaps not surprising that the diagnosis of ASD is still solely based on symptomatology assessed via behavioural observations and/or clinical interviews. Whilst the behavioural diagnosis of ASD has clear advantages in the clinical setting, the aetiological and phenotypic heterogeneity of ASD is less beneficial in the search for biomarkers and in the development of treatments for the condition. For example, most clinical trials conducted in this field to date have shown small to moderate effect sizes [4]. This might indicate a lack of suitable pharmacotherapies for individuals with ASD. On the other hand, it remains unclear whether such small effect sizes in large-scale clinical trials might also be due to the high degree of clinical/phenotypic heterogeneity within the ASD population (e.g. strong effects within biologically homogeneous subgroups might be masked by small effects across all individuals with ASD). Thus, it is unlikely that ASD is treatable using a ‘one-size-fits-all’ approach. There is a strong need for developing targeted treatments and interventions that will be effective in some but not in all individuals with ASD and lead to large effects within particular autistic subgroups (Fig. 1). The stratification of patients into more homogeneous subgroups will therefore be crucial not only for the development of biomarkers and treatments, but also for the design of large-scale clinical trials. Current evidence suggests that a potential patient stratification could be based on the autism genotype and/or on its neurobiological phenotype.

Genotypic stratification of individuals with ASD

Autism spectrum disorder is known to be one of the most heritable psychiatric conditions, with an estimated heritability of 80% [5]. Despite the high heritability, however, the number of ‘common’ genetic variants (i.e. genetic variants common to all individuals with ASD) is surprisingly small, and many of the reported common variants for ASD lack replication. The lack of significant linkage or genome-wide association (GWA) peaks may partially be due to methodological issues; for example, the number of genetic loci investigated by GWA studies often exceeds a few hundred thousand(s), and statistically stringent thresholds – corrected for multiple comparisons – are hence required to detect reliable effects. On the other hand, these findings might also suggest that the effect size of the contribution of common alleles to ASD could be smaller than originally thought.

An increasing number of genetic studies are therefore investigating the importance of distinct and individually rare genetic variants in the aetiology of ASD. For example, it is now known that CNVs (i.e. deletions and duplications in the DNA sequence) occur in 5–10% of ASD cases and might either be inherited or can occur de novo (i.e. are present in a child but not in either parent) [2]. In addition, individual CNVs often have large effect sizes, thought to be sufficient to ‘cause’ ASD. As recently proposed by Betancur et al., [6] these findings therefore constitute a conceptual shift from a common disease–common variant (CDCV) model to a common disease–multiple rare variant (CDMV) model, where ASD is caused by multiple strong-effect variants, each of which is found in only a few people.

Although the complexity of a CDMV model far exceeds that of a CDCV model in conceptual terms, it also offers a unique opportunity to identify rare variants and/or CNVs in individuals with symptoms of autism and to stratify patients based on their particular genotype. Considering the complex genetic architecture of the condition, it is unlikely that these autism genotypes are genetically identical (in terms of ASD-related genes). However, subgroups could be established by maximizing the genotypic variability across patient groups and by minimizing genotypic variability within groups. These homogeneous autism genotypes might also be more similar in terms of their neurobiological
phenotype and hence might respond to the same or similar treatment(s).

Whilst the specific link between genotype and neurobiological phenotype remains relatively unexplored in ASD, increasing evidence suggests that the genotypic diversity underlying the condition might indeed result in similar phenotypes, which are characterized by similar ‘core’ deficits (i.e. common to all individuals with ASD). For example, it has recently been demonstrated that the multiple rare de novo variants underlying ASD are closely linked at the functional level and can be grouped together to form clusters or networks of genes based on their common functional involvement.

Most importantly, however, many of the genes forming these networks are primarily related to synapse development, axon targeting and neuron motility [7, 8]. Thus, perturbed synaptogenesis has become a common underlying theme amongst the numerous genetic variants associated with ASD at the functional level.

Synaptic CNV in ASD: a potential target for treatment

The notion that synaptogenesis might represent a common aetiological pathway for symptoms and traits of autism also implies that ASD might be treatable with drugs that specifically target synaptic molecules. For instance, many of the rare CNVs

**Fig. 1** (a) The low to medium effect size of the current ‘one-size-fits-all’ approach for treating ASD might be due to the large genetic and phenotypic heterogeneity of the condition and the presence of different ASD subgroups. (b) Thus, a more ‘personalized’ approach to treatment might be more effective in the future. Individuals are stratified into genetically or phenotypically homogeneous subgroups (i.e. based on biomarkers) that might respond well to a particular type of treatment (adapted from http://www.bayerpharma.com/).
associated with ASD play a major role in synaptic cell-adhesion molecule (CAM) pathways (2,6). CAMs (reviewed in [9]) are a group of molecules that are involved in the formation and maintenance of synaptic contacts and include molecules responsible for (i) initiating contact between pre- and postsynaptic cells, (ii) maintaining synaptic adhesion and (iii) providing ‘anchors’ for scaffolding proteins that assemble signalling molecules, neurotransmitter receptors and proteins in the cytoskeleton. During neurodevelopment, CAMs also provide a path for the so-called growth cone at the tip of the developing axon and hence support neurodevelopment even prior to synapse formation/initiation [10]. Thus, the presence of ASD-linked variations in genes and/or CNVs encoding for CAMs suggests that the development and plasticity of synaptic contacts might be atypical in ASD and affect the way the brain is connected. Furthermore, perturbed CAM pathway(s) might affect not only synaptic structure and morphology, but also function.

The best-established synaptic CNVs associated with ASD are found in genes encoding the neuroligins, neurexins and SHANK3. Neuroligins are a family of CAMs that are located postsynaptically [11] and that are involved in the formation and consolidation of both inhibitory and excitatory synaptic contacts, depending on the specific subtypes (reviewed in [9]). Once the developing axon reaches its target, neuroligins form a trans-synaptic contact with presynaptic neurexins, which is believed to initiate synaptogenesis. Furthermore, neuroligins and neurexins contain a postsynaptic density (PSD) binding domain that mediates interactions with synaptic scaffolding proteins and helps to anchor transmembrane proteins to the cytoskeleton. Thus, both neuroligins and neurexins also play an important role in determining the specificity and differentiation of synaptic contacts [9]. For example, the neuroligin 1 subtype has been found to primarily promote the formation of excitatory synapses, whereas neuroligin 2 is mainly found on inhibitory synapses and preferentially induces the formation of inhibitory contacts [12, 13]. It is noteworthy that the ASD-associated neurexin 3 [14, 15] seems to primarily promote excitatory synaptogenesis. It has therefore also been suggested that genetic variation in synaptic CNVs associated with ASD might underlie a potential disturbance in the excitation–inhibition (E/I) balance (i.e. enhanced excitation) in ASD [16]; this will be discussed in further detail below.

Another gene associated with ASD that might contribute to the E/I balance is SHANK3, which encodes for a synaptic scaffolding protein that is primarily located in the PSD [17]. The PSD is a protein-dense region located immediately behind the postsynaptic membrane, which primarily functions as a postsynaptic ‘organizing structure’ as it assembles receptors, adhesion molecules and signalling molecules that are required for synaptogenesis and synaptic signalling [18]. SHANK3 proteins interact with neuroligins to a considerable degree and are hence also essential for synapse formation and dendritic spine maturation. For example, it has recently been demonstrated in humans that mutations in SHANK3 strongly affect the development and morphology of dendritic spines (i.e. overexpression of wild-type SHANK3 significantly increased the number of spines compared with controls) and also reduce synaptic transmission in mature neurons [17]. Variations in SHANK3 primarily affect glutamatergic synapses and might hence also contribute to an E/I imbalance in ASD.

Taken together, these genetic studies highlight the important role of synaptic CNVs in the aetiology of ASD and emphasize that the various CNVs associated with ASD might be classified based on their common functional involvement in the development of brain connectivity (microscopic as well as macroscopic) and mechanisms of neurotransmission. The identification of such common genetic and neurobiological themes constitutes a crucial step in the discovery of ‘mechanism-based’ therapeutics in ASD, offering a starting point for the discovery of new pharmacological targets. Furthermore, these might be tested in genetic animal models and/or cellular assays prior to large-scale clinical trials. Given the emerging importance of synaptic genes in ASD, an increasing number of models are being developed to specifically target synaptic and/or spine pathology.

Nongenetic risk factors for ASD

Despite all the evidence indicating a predominantly genetic aetiology of ASD, more recent studies suggest that the genetic origin and/or heritability of ASD might not be as strong as originally thought [19] and that nongenetic risk factors – in addition to genetic variation – might significantly contribute to ASD susceptibility [20]. Such nongenetic risk factors include (i) epigenetic factors (see [21]), (ii) physiological conditions including immune dysre-
Animal models of and behavioural assays for ASD

The generation of predictive preclinical models that are based on understanding of the genetic architecture of ASD is crucial for the discovery of mechanism-based therapeutics in ASD (recently reviewed in [28]). Such preclinical disease models, for example using a variety of genetically engineered animal models, are invaluable not only for drug discovery but also for isolating specific aspects of the disease pathology, which can then be compared with the human phenotype for validation and translation. In addition, animal models allow the testing of drug feasibility and safety in an iterative fashion, as well as the development of behavioural assays that can be used to evaluate drug efficacy at the behavioural level.

Several animal models are now available for ASD, most of which highlight synaptic pathology/morphology and a potential E/I imbalance in ASD. For example, mouse models of SHANK3 mutations have been developed, which show significant alterations in synaptic protein levels and spine morphology as well as deficits in social interaction and repetitive behaviour (see [29, 30]). Mouse models of perturbed CAM pathways have also been developed by the manipulation of genes encoding neurexins and neuroligins. For instance, neuroligin-3 knockout mice demonstrate disrupted heterosynaptic competition and perturbed metabotropic glutamate receptor (mGluR)-dependent synaptic plasticity [31]. Similarly, mice with a deletion in the contactin-associated protein-like 2 gene (Cntnap2), which encodes a neurexin protein involved in neuron connectivity and synaptic function, have a reduced number of cortical GABAergic neurons and abnormal neuronal migration [32]. A common finding of studies using these animal models is the important role of perturbed GABAergic and glutamatergic synaptic transmission in ASD, pointing towards the possibility of developing new therapeutic approaches that specifically target mGluR5 signalling [33]. Furthermore, the available animal models also highlight the importance of reversing the effects of potential differences in spine morphology in ASD. Overall, there is increasing evidence to suggest that spine density is generally increased in ASD, resulting in an increase in local axonic connectivity (reviewed in [34, 35]). Thus, it will be important to develop and test drugs that could reduce the abnormally large number of spines and potentially decrease the severity of some behavioural deficits observed in ASD.

Phenotypic stratification of ASD

In parallel with genetic studies and animal models, an increasing number of neurobiological investigations are also now directed towards the phenotypic stratification of individuals with ASD, to resolve the wide range of autism phenotypes into biologically and phenotypically distinct subgroups. Whilst the precise neurobiology of ASD remains elusive, it is generally agreed that patients with the condition differ from healthy individuals in several key neurobiological aspects including brain anatomy, functioning, connectivity and neurochemistry, which might significantly contribute to the development of biomarkers for ASD.

Brain anatomy and functioning in ASD

Structural neuroimaging studies suggest that the brain of toddlers with ASD (2–4 years of age) is, on average, larger than that of children without ASD [36]. The overall increase in total brain volume seems to disappear by the age of 5–6 years after which no significant between-group differences are typically observed. It has therefore been suggested that the brain in ASD might undergo a period of precocious accelerated growth during early postnatal life, which is then followed by an atypically slow or arrested growth during childhood, so that no global differences are generally observed in adulthood [37]. The atypical neurodevelopmental trajectory of brain maturation in ASD also seems to be idiosyncratic for different lobes of the brain with frontal and temporal lobes being more affected...
than parietal and occipital lobes [38]. Thus, the normal temporal sequence of brain development (i.e. from ‘back to front’ [39]) seems to be disturbed in ASD, which will not only affect the development of isolated brain regions but also the way the brain is connected. ASD has therefore also been described as a ‘neural systems’ condition, which is characterized by subtle and spatially distributed neuroanatomical differences in several large-scale neurocognitive networks [40]. However, whilst the notion of an abnormally enlarged brain and associated macrocephaly (i.e. head circumference >97th percentile) might be one of the best-replicated findings with regard to ASD, it is certainly not specific to this condition nor does it affect all individuals on the autism spectrum; for example, it is estimated that only 20% of children with ASD are affected by macrocephaly (reviewed in [41]). Thus, although macrocephaly might not be well suited as a biomarker for ASD per se, general differences in brain anatomy might still offer an opportunity for patient stratification because of such variability within the ASD group. Using novel pattern classification approaches, it is now possible to distinguish between and identify (i.e. predict ‘patients’ or ‘controls’) individuals with ASD and healthy control subjects based on subtle and spatially distributed patterns of multivariate biological data. To date, most of these approaches have investigated the predictive value of neuroimaging data, utilizing information on brain structure [42, 43], functioning and connectivity (see [44, 45]). However, in the future, it will be important to extend these approaches to also incorporate information from genetic studies as well as neurochemical markers to build complex biomarker systems that could aid diagnosis, enable patient stratification and predict response to treatment(s).

### Neurochemical markers for ASD

There is also evidence to suggest that differences in brain chemistry and neurotransmission between different individuals on the autism spectrum might help to significantly reduce the large phenotype variability between individuals with ASD. The stratification of patients based on their individual neurochemical make-up is of particular importance to the development of targeted treatment strategies that maximize the individual’s response to a particular pharmacotherapy. The three neurotransmitter systems that have attracted most attention in ASD are the GABAergic, glutamatergic and serotonergic systems.

**GABA**

Evidence for atypical GABAergic synaptic transmission in ASD comes from a variety of genetic and neuroimaging studies, demonstrating inhibitory neurotransmission at several different levels in ASD (reviewed in [46]). First, GABA plays a crucial role during neurodevelopment where it acts as a tropic factor to promote synaptogenesis to influence different aspects of neuronal differentiation [47]. Thus, pathological perturbations in the GABAergic system (e.g. via genetic variation/expression) will affect the brain in a variety of ways and will influence its structure and functioning beyond atypical synaptic transmission. Secondly, in the mature brain, GABA is essential for inhibitory neurotransmission, which might be downregulated in ASD [48]. It is known that glutamate decarboxylase (GAD)65 and GAD67 proteins – the two isoforms of the enzyme that synthesize GABA in the presynaptic terminal – are reduced in the brain of individuals with ASD, which might result in reduced GABA synthesis and thus reduced inhibition [49]. These differences might be of genetic or epigenetic origin as several genetic variants highly associated with ASD were amongst a number of genes encoding for genes involved in GABA synthesis (e.g. GAD65 and GAD67 [50]) or GABA receptors (e.g. GABRB3 and GABRB5 [51]). In vivo neuroimaging studies further demonstrate significantly reduced GABA receptor binding in ASD [52, 53], which might exacerbate the existing deficits in GABA synthesis. Although measuring GABAergic neurotransmission directly in the brain in vivo poses a methodological challenge, direct evidence has recently been provide for reduced GABA concentration in the brain in ASD. In a recent magnetic resonance spectroscopy (MRS) study, a significantly reduced GABA concentration was observed [54]. Reduced GABA receptor density in both adults and children with ASD was also shown in a single-photon emission computed tomography study [55]. Finally, a recent pilot study using positron emission tomography (PET) demonstrated significantly reduced levels of GABAergic neurotransmission in adults with ASD [56]. The results of most of these studies suggest that GABAergic synaptic transmission might be reduced in patients with ASD and that region-specific variations in GABA-related receptor expression and transmitter concentration might contribute to mediating the symptoms and traits of autism. However, further studies are needed to confirm these findings.
Glutamate

Whilst GABAergic inhibitory neurotransmission appears to be reduced in ASD, there is increasing evidence to suggest that glutamatergic, and thus, excitatory neurotransmission is enhanced (i.e. the ‘hyperglutamatergic hypothesis of autism’) [48]. For example, individuals with ASD seem to have higher-than-normal serum glutamate levels [57], increased glutamate receptor mRNA [58], increased mGluR expression [59] and increased glutamate concentration as measured by MRS in both the hippocampus and the auditory cortex [60, 61]. On the basis of the findings of studies investigating GABA and glutamate in ASD, it has also been proposed that an important aspect of the pathophysiology underlying ASD might be an E/I imbalance in the brain (i.e. increased excitation relative to the amount of inhibition) [16]. The theory of imbalanced E/I has also been used to explain some of the clinical symptoms associated with ASD such as the increased incidence of seizures and/or the hypersensitivity to visual/auditory stimulation [16]. Taken together, these findings will be important for the development of drugs that could ‘normalize’ the E/I imbalance, and a variety of pharmacological compounds have recently been proposed to achieve this goal. On the basis of the hypothesis that excessive metabotropic glutamatergic signalling in ASD could cause some of the core symptoms of the condition, the findings of several studies suggest a potential beneficial effect of mGluR5 antagonists, or arbaclofen, which reduces glutamate-mediated receptor activation at synapses (reviewed in [62]). These drugs provide examples of an evidence-based approach to the development of pharmacotherapies for ASD taking into account both genotypic and phenotypic data and thus allowing in vitro validation prior to clinical trials.

Serotonin (5-HT)

There is also preliminary evidence implicating abnormalities in the serotonergic system in ASD. Unlike other neurotransmitters (e.g. GABA and glutamate), the biosynthesis of 5-HT requires the presence of a dietary source of the amino acid L-tryptophan (TRP), which can cross the blood–brain barrier. TRP is hydroxylated through the actions of the enzyme tryptophan hydroxylase to produce the intermediate 5-hydroxytryptophan (5-HTP). The resultant 5-HTP is then decarboxylated by the aromatic L-amino acid decarboxylase to produce serotonin. It has been suggested that a significant proportion of individuals with ASD might have ‘hyperserotonemia’ [63, 64]. For example, a significantly higher 5-HT concentration in whole blood sample was observed in children with ASD as well as their relatives (e.g. [65]). In vivo neuroimaging studies show that individuals with ASD have significant differences in serotonin synthesis compared with healthy control subjects, as well as a reduction in serotonin receptor binding and in the number of 5-HT transporters, particularly in brain regions involved in social communication such as the cingulate cortices [66–68]. Finally, significant genetic association between ASD and genetic polymorphisms for serotonin synthesis, transporters and receptors has been observed [69–71]. On the basis of these findings, it has also been suggested that individuals with ASD may benefit from drugs that modulate the serotonergic system. Despite the notion of hyperserotonemia in ASD, most studies have so far focused on the effects of selective serotonin reuptake inhibitors (SSRIs). The administration of SSRIs has, however, not been proven to be effective in the treatment of all individuals with ASD [4]. Nevertheless, it remains unclear whether small effect sizes in large-scale clinical trials are mainly due to the high degree of clinical/phenotypic heterogeneity within the ASD population. For instance, Hranilovic et al. reported that hyperserotonemia might only be present in about 30% of individuals with ASD [64]. It is therefore of important to develop tools that could identify those with hyperserotonemia prior to examining the effectiveness of serotonergic pharmacotherapy to specifically tailor the type of modulation required. Furthermore, other recent studies have also highlighted the potential beneficial effects of serotonin reuptake enhancers on the severity of autism-related symptoms and traits [72, 73]. In the future, such studies examining the effects of both enhancers and inhibitors in a variety of ASD subgroups might prove invaluable in developing personalized treatment strategies. Such basic clinical and pharmacological studies therefore play an important and integral role in the translational research cycle that will lead to the discovery and evaluation of new treatments for ASD.

The translational cycle in the development of targeted treatments for ASD

The translation of research findings into clinically useful biomarkers and pharmacotherapies that are based on understanding of the pathophysiology of ASD is complex and lengthy. It involves multiple stages of interdisciplinary research that are
conducted predominantly in parallel, yet inform each other. The stages of the translational research ‘cycle’ (Fig. 2) generally include the clinical and behavioural characterization of the human phenotype of the condition, followed by the identification of its genotype(s) [74]. In ASD, both genotypes and phenotypes are likely to be multifaceted, which introduces an additional level of complexity to the cycle. The identification of ASD genotypes then makes it possible to develop animal models and cellular assays that mimic the pathology or certain pathological features. For instance, animal models now exist of perturbed synaptogenesis and imbalanced E/I. These models can be used to test pharmacological compounds that target the specific aspect of pathology under controlled conditions. Such novel treatments might be designed to reduce the abnormally high spine density in individuals with ASD and/or to normalize the E/I balance. Following the successful exploration and validation of these compound using animal models, their effectiveness can then be tested in large-scale clinical trials in humans that will finally determine the effectiveness and success of a particular treatment.

Because of its multidisciplinary character, translational research for the development of stratified
<table>
<thead>
<tr>
<th>Consortium Partners</th>
<th>WP 01 In vitro system development</th>
<th>WP 02 Animal model development</th>
<th>WP 03 Translational research development</th>
<th>WP 04 Clinical research development</th>
<th>WP 05 Management of data and biological samples</th>
<th>WP 06 Project management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Academic partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>King's College London (UK)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Institute of Mental Health, Mannheim (Germany)</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radboud University of Nijmegen Medical Centre (the Netherlands)</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Cambridge University (UK)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>University Medical Centre Utrecht (the Netherlands)</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Biozentrum, University of Basel (Switzerland)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Institute Pasteur (France)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max-Planck-Gesellschaft (Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Molecular Biology Laboratory (Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Karolinska Institutet (Sweden)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Birkbeck, University of London (UK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Campus Bio-Medico (Italy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>University Ulm (Germany)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Commissariat a l'Energie Atomique et aux Energies Alternatives (Neurospin/CEA) France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Industrial partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Hoffmann-La Roche</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Eli Lilly and Company Ltd.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Institut de Recherches Servier</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Janssen Pharmaceutica</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pfizer Limited</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
medicines is a logistic challenge, particularly for ASD. It requires the orchestrated management of (i) multiple collaborating research centres, which conduct basic research at various levels of magnification; (ii) multiple control instances that assure data quality and compatibility of scientific findings between sites; (iii) ethical approval and supervision of clinical trials testing novel pharmacological agents; and (iv) the clinical evaluation of outcome measures and the distribution of pharmacotherapies in collaboration with industry. To date, however, there has been a lack of available platforms that could be utilized for conducting translational research in ASD. European efforts are therefore now directed at developing the infrastructure required to implement all stages of the translational research cycle in ASD within the same consortium.

The EU-AIMS Initiative: a European model for translational research in ASD

The EU-AIMS is a platform that was recently set up in the context of the EU Innovative Medicines Initiative (IMI) to facilitate translational research in ASD [75]. The EU-AIMS consortium consists of 14 leading European academic centres in collaboration with ‘Autism Speaks’ (world-leading charity for ASD), ‘Autism Europe’ (representing patients and carers) and industrial partners (three medium-sized enterprises and six members of the ‘European Federation of Pharmaceutical Industries and Associations’) (see Table 1). The aim of the network is to deliver new tools and standards for evidence-based drug discovery and clinical trials in ASD by integrating and translating research efforts at various levels (e.g. clinical and preclinical). EU-AIMS brings together five overlapping themes that will underpin drug discovery in five different work packages (WPs) representing the different stages of the translational research cycle.

The aim of WP1 is to develop cellular assays (e.g. using induced pluripotent stem cells [76]) that can be used to model the genetic deficits of ASD in vitro, and subsequently facilitate the identification of different cellular/molecular phenotypes of ASD and to relate phenotypes to disease-specific genetic variants. In addition, cellular assays allow the in vitro development and testing of new drugs for ASD that can then be translated into animal models and humans.

WP2 is predominantly concerned with the development of animal models and behavioural assays.
for ASD and will be informed by (and inform) WP1. The existing rodent models can be used to represent different potential pathways for ASD as well as for in vivo evaluation of treatment targets, such as GABA and serotonin.

WP3 involves the validation of biomarkers that facilitate the drug discovery process and that might be used to aid diagnosis, stratify patients and predict response to treatment. Biomarkers will be developed based on available data characterizing the human intermediate phenotype of ASD. Such phenotypic data will be based on various neuroimaging measures of brain anatomy, functioning and connectivity in ASD, in addition to electrophysiological findings and neurochemical measures acquired by PET and MRS.

WP4 facilitates clinical research development by creating an EU infrastructure of expert clinical research sites to (i) coordinate and standardize recruitment and data acquisition in several countries for large-scale clinical trials, (ii) provide expert clinical advice to inform the complex process of drug development and (iii) create a bioresource of phenotypic data in a well-characterized sample of individuals with ASD including both men and women with various stages of neurodevelopment and different autism phenotypes. Of note, an additional aim of WP4 is to develop a new EU ‘high-risk’ infant sibling network to address the important questions of early diagnosis and predictive value of biomarkers for ASD. The data acquired across WPs will then be managed and made available as a large-scale ‘bioresource’ for ASD in WP5, which represents the efforts of a large-scale integrated network of academic centres, industry, charities and affected individuals with ASD on the way to developing targeted drugs and treatments for ASD.

Conclusions

Despite the high genetic and phenotypic diversity of ASD, new opportunities are now emerging that might lead to the development of novel pharmacotherapies for patients with ASD. The mechanism-based development of targeted treatments requires extensive multidisciplinary research that is currently being conducted as part of the EU-AIMS Initiative, and globally. However, it is unlikely that a single compound will be effective in all individuals with ASD, and it is therefore important also to develop biomarkers that might be used to stratify patients depending on their genotype and/or neurobiological phenotype. These novel approaches and collaborative efforts represent a significant step towards a more personalized approach to diagnosing and treating ASD in the future, with the best possible likelihood of success.

Acknowledgements

This work was supported by the Autism Imaging Multicentre Study (AIMS) Consortium funded by the Medical Research Council, UK (G0400061); the EU-AIMS receiving support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300, which includes financial contributions from the EU Seventh Framework Programme (FP7/2007-2013), from the EFPIA companies in kind and from Autism Speaks (http://www.eu-aims.eu); the Dr. Mortimer and Theresa Sackler Foundation, the NIHR Biomedical Research Centre for Mental Health at King’s College London, Institute of Psychiatry, and South London and Maudsley NHS Foundation Trust.

Conflict of interest statement

W. Spooren is employed by F. Hoffmann-La Roche. Neither of the other authors has any conflict of interests or financial interests to declare.

References

4. Cochrane database of systematic reviews [Online].
7. Gilman SR, Rossifov I, Levy D, Ronemus M, Wigler M, Vitkup D. Rare de novo variants associated with autism implicate a
Review Article: Developing new pharmacotherapies for autism


Correspondence: Christine Ecker, Department of Forensic and Neurodevelopmental Sciences and Sackler Centre for Translational Neurodevelopment, Institute of Psychiatry, De Crespigny Park, London, SE5 8 AF, UK.

(fax: +44 (0) 207 848 0281; e-mail: Christine.ecker@kcl.ac.uk)