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Synaptic synopsis

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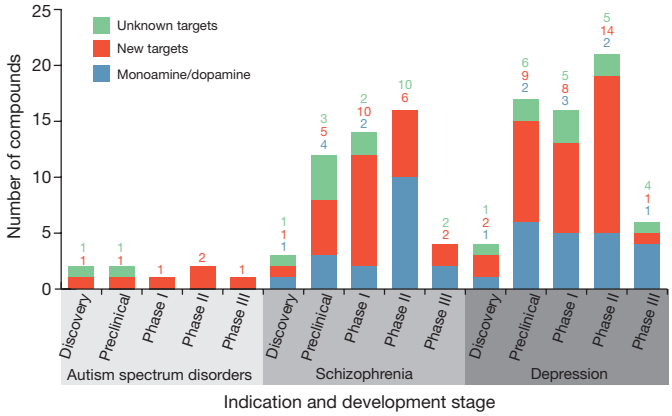

Figure 1. Dopamine departure. Compounds in disclosed company-sponsored programs.
Source: BCIQ: BioCentury Online Intelligence

The early promise that neurotransmitter research would unlock the door for neurological diseases has devolved into sagging interest from several pharmas following repeated failures in clinical trials. Now, genetic findings are pointing to new targets in the synapse and reawakening commercial interest in fields such as autism spectrum disorders, schizophrenia and depression.

Although the behavioral features of those three conditions are quite dissimilar, new hypotheses about their origins suggest they all are diseases of connectivity. The common thread is synaptic dysfunction and disrupted communication between different brain regions.

The last decade has seen companies pursue compounds directed at new targets, in particular related to glutamate signaling because it contributes to the pathology of ASD, schizophrenia and depression.

In addition, data from recent academic-driven, large-scale genetic studies are pushing companies to pursue public-private partnerships (PPPs) as a way to explore new therapeutic real estate.

According to **Atlas Venture** partner Bruce Booth, academic research is injecting new life into the field.

"As industry has pulled back, academic research is advancing on the mechanistic basis of many of these diseases," he told *SciBX*.

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> ***—Bruce Booth, Atlas Venture***

Transmitting

There are more than 15 drugs approved for schizophrenia, at least 15 for depression and 2 for ASD. The majority are based on the early theory that the conditions are caused by an imbalance in monoamine neurotransmitters, most notably dopamine and serotonin.

The two ASD drugs, Risperdal risperidone and Abilify aripiprazole, are indicated for irritability associated with the disorder. Both drugs were first developed as antipsychotics and act on dopamine receptors.

Risperdal is marketed by **Johnson & Johnson**. Abilify is marketed by **Otsuka Pharmaceutical Co. Ltd.**, a subsidiary of **Otsuka Holdings Co. Ltd.**

The dopamine hypothesis of schizophrenia dates back to the 1960s, when dopaminergic antagonists such as haloperidol were approved. Since then, the most significant improvements have been in reducing side effects, with the last big breakthrough being the approval of atypical antipsychotics such as clozapine in the 1970s.

Similarly, the monoamine hypothesis of depression emerged in the 1960s with the use of monoamine oxidase (MAO) inhibitors and tricyclic antidepressants that inhibit monoamine reuptake transporters. In the 1990s, selective serotonin reuptake inhibitors such as fluoxetine entered the market, alleviating many of the cholinergic side effects of the earlier generation.

Although the dopamine antagonists and monoamine reuptake inhibitors represented a major leap forward in psychiatry, the molecules have drawbacks that limit their use or result in their discontinuation.[1]

For example, depression drugs only work in about two-thirds of the patient population and carry black box warnings of an increased risk of suicide in children, adolescents and young adults.[2]

Nevertheless, there are at least 30 companies pursuing new compounds in all stages, from discovery to Phase III trials, that work via the traditional dopamine and monoamine systems. These represent one-third of disclosed compounds in company-sponsored programs for the three disorders combined, and most aim to improve tolerability or reduce side effects.

Glutamate is the new dopamine

According to Mriganka Sur, a professor of neuroscience at the **Massachusetts Institute of Technology**, the field has gone as far as it can with receptors and transporters for dopamine and monoamines.

"We need to go beyond these neuromodulators for the next steps," he told *SciBX*.

The shift is under way. Over the last five years, companies have begun refocusing their activities toward glutamate-related targets, following clinical, imaging and genetic studies that tied glutamate synapses to schizophrenia, depression and ASD.

More than half of the disclosed compounds from discovery to Phase III trials in all three disorders target nondopaminergic and nonmonoaminergic systems (*see* **Figure 1, "Dopamine departure"**).

Many of the new compounds target signaling through glutamate synapses—at least 15 compounds in development for the 3 disorders target glutamatergic systems (*see* **Table 1, "Glutamate mates"**).

Table 1. Glutamate mates. Compounds in development for autism spectrum disorders (ASD), schizophrenia and depression.

Target	Company	Product	Development stage	Indication
Glutamatergic targets				
Glycine transporter type 1 (GlyT1; SLC6A9)	**Roche** (SIX:ROG; OTCQX:RHHBY)	Bitopertin (R1678)	Phase III	Schizophrenia
NMDAR NR2B subtype (GRIN2B; NR2B)	**AstraZeneca plc** (LSE:AZN; NYSE:AZN)	AZD6765	Phase II	Depression
GRIN2B (NR2B)	**Addex Therapeutics Ltd.** (SIX:ADXN); **Johnson & Johnson** (NYSE:JNJ)	ADX71149	Phase II	Depression; schizophrenia
NMDAR	Johnson & Johnson	Esketamine	Phase II	Depression
NMDAR	**Naurex Inc.**	GLYX-13	Phase II	Depression
Metabotropic glutamate receptor subtype 5 (mGluR5; GRM5)	Roche	RG7090	Phase II	Depression
GRIN2B (NR2B)	**Cerecor Inc.**	CERC-301	Phase I	Depression
NMDAR	Naurex	NRX-1074	Phase I	Depression
mGluR2 (GRM2)	**BrainCells Inc.**	BCI-838	Phase I	Depression
AMPA glutamate receptor (GRIA; GLUR)	**Pfizer Inc.** (NYSE:PFE)	PF-04958242	Phase I	Schizophrenia
mGluR5	**Seaside Therapeutics Inc.**	STX110	Preclinical	ASD
mGluR4 (GRM4)	**Domain Therapeutics S.A.**	DT1687	Preclinical	Schizophrenia
mGluR2	Addex Therapeutics	mGluR2 negative allosteric modulator (NAM)	Preclinical	Depression
mGluR7 (GRM7)	Addex Therapeutics	mGluR7 NAM	Discovery	Depression
mGluR5	**Heptares Therapeutics Ltd.**	mGluR5 modulator	Discovery	ASD; depression
Other receptor targets				
σ-1 Receptor	**M's Science Corp.**	SA4503	Phase II	Depression
Nicotinic acetylcholine receptor α_7 (CHRNA7)	**Targacept Inc.** (NASDAQ:TRGT)	TC-5619	Phase II	Schizophrenia
CHRNA7	**AbbVie Inc.** (NYSE:ABBV)	ABT-126	Phase II	Schizophrenia
κ-Opioid receptor (OPRK1; KOR); OPRM1 (MOR)	**Alkermes plc** (NASDAQ:ALKS)	ALKS 5461	Phase II	Depression
Corticotropin-releasing factor receptor 1	**Neurocrine Biosciences Inc.** (NASDAQ:NBIX)	561679	Phase II	Depression
Arginine vasopressin receptor 1A (AVPR1A)	Roche	RGS7314	Phase II	ASD
CHRNA7	**Aniona ApS**	NSD-761	Preclinical	Schizophrenia
Muscarinic acetylcholine receptor M1 (CHRM1; HM1)	Heptares Therapeutics	HM1 agonist	Preclinical	Schizophrenia
Nonreceptor targets				
Enzyme replacement therapy	**Curemark LLC**	CM-AT	Phase III	ASD
Helminth-based treatment	**Coronado Biosciences Inc.** (NASDAQ:CNDO)	CNDO-201	Phase II	ASD
Phosphodiesterase-10 (PDE-10)	**Omeros Corp.** (NASDAQ:OMER)	OMS824	Phase II	Schizophrenia
PDE-10A	**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502)	TAK-063	Phase I	Schizophrenia
PDE-10A	Roche	RG7203	Phase I	Schizophrenia
PDE-10	**EnVivo Pharmaceuticals Inc.**	EVP-6308	Phase I	Schizophrenia
PDE-1	**Intra-Cellular Therapies Inc.**	IC200214 (ITI-002)	Preclinical	Schizophrenia

In schizophrenia, the link to glutamate first arose from clinical evidence that NMDAR blockers such as phencyclidine (PCP) produce schizophrenia-like symptoms. The link gained further support recently from genetic findings associating NMDARs with the disorder.[3]

The emerging glutamate model suggests that reduced activity of glutamate receptors removes an important brake on dopamine signaling, leading to hyperactivity of pathways that cause psychosis.

In addition to glutamate binding to the NMDAR, glycine binding has an allosteric effect that enhances receptor activity. Impaired binding at either site can therefore alter receptor-mediated signaling.

Several companies are thus developing compounds to augment or supplement glutamatergic transmission, either by acting as agonists at NMDARs or other glutamate receptors or by inhibiting activity of the glycine transporter type 1 (GlyT1; SLC6A9).

The most advanced glutamate-based molecule for schizophrenia is

Roche's bitopertin (RG1678), a GlyT1 reuptake inhibitor that is in Phase III testing.

Addex Therapeutics Ltd. and Johnson & Johnson have a Phase II NMDAR antagonist in development for both schizophrenia and depression, and **Pfizer Inc.** has a Phase I schizophrenia compound that targets AMPA glutamate receptor (GRIA; GLUR).

In depression, the connection to glutamate arose through imaging and postmortem studies that showed altered levels of glutamate in the brains and serum of patients with mood disorders.[4,5]

At least seven companies have compounds that hit glutamatergic targets in Phase II for depression, in addition to the Addex and Johnson & Johnson compound.

For ASD, the glutamate connection emerged in the last two years when genomewide association studies revealed a large number of mutated proteins involved in pathways that converge on glutamate synapses.[6]

Seaside Therapeutics Inc. and **Heptares Therapeutics Ltd.** have early stage preclinical programs targeting metabotropic glutamate receptor subtype 5 (mGluR5; GRM5) for ASD.

Beyond glutamate, other new targets for schizophrenia, depression and ASD include receptors for cholinergic, opioid, vasopressin and steroid signaling systems.

In addition, at least six companies are focusing on nonreceptor or transporter targets including phosphodiesterases, which are intracellular signaling enzymes that affect long-term memory formation and working memory.

Sorting the synapse

According to Sur, the next generation of discovery in ASD, schizophrenia and depression will be driven by genetics. "Genes and synapses are essential drivers of a new understanding of these diseases," he told *SciBX*.

Genetic studies, largely in ASD,[7] have revealed mutations in proteins that lead to impaired synaptic structure and function. Links between mutations in synaptic proteins found in ASD, schizophrenia and depression tie the three disorders together and suggest that disrupted connectivity might be a common pathology among them.

However, the plethora of genes emerging from genomewide association studies will need some sorting. Academic and industry leaders alike acknowledge the complexity of pinpointing the targets with the greatest translational potential.

"A major challenge is to determine whether risk factor genes that have been identified are potential points of therapeutic intervention or whether they are entrées for modifier genes that would represent better drug targets," said Kenneth Rhodes, VP of neurology research at **Biogen Idec Inc.**

"There are 1,200–1,500 proteins involved in making the synapse; not all are equally effective," added Sur.

Magali Haas, CSO and CTO for the advocacy group **One Mind for Research**, said that the way forward should involve external innovation models and investment in precompetitive partnerships.

At least 8 PPPs were announced in 2012 and 2013 that specify a focus on schizophrenia, depression or ASD, with investments ranging from $2 million to $48 million.

Patient advocacy also has a growing role, with **Autism Speaks** playing a role in multiple PPPs.

The organization has partnered with Seaside, providing $2 million to the biotech to discover genetic and protein biomarkers. It also partnered with **Sigma-Aldrich Corp.** with an undisclosed amount of funding to develop rat models with modified autism-associated genes.

Autism Speaks also helped form a large-scale PPP, dubbed European Autism Interventions—A Multicenter Study for Developing New Medications (EU-AIMS). The PPP involves a consortium of pharmas, biotechs and academics led by Roche and **King's College London**.

The project is backed by the **Innovative Medicines Initiative** (IMI), which is a joint enterprise between the EU and the **European Federation of Pharmaceutical Industries and Associations**, and aims to develop and validate new translational approaches in ASD. EU-AIMS received funding for 5 years totaling €35.9 million ($48.1 million) in 2012.

IMI also has backed a large-scale consortium focused on schizophrenia.

The Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) consortium comprises 19 commercial and academic organizations led by **H. Lundbeck A/S**. NEWMEDS received €24 million ($34.6 million) from IMI in 2009 to develop new animal models, imaging technologies and clinical trial tools.

In 2012, the not-for-profit group **Sage Bionetworks** formed the CommonMind Consortium with **Takeda Pharmaceutical Co. Ltd.**, Roche and five U.S.-based universities with the goal of producing an open-source database of genomic information for neuropsychiatric diseases.

The precompetitive consortium will gather data and samples from patients and postmortem brain samples collected by the consortium member institutions. The consortium has received $3 million in funding, including $2 million from the **National Institute of Mental Health**.

Although the synapse is the hot topic of the moment, momentum is already building to explore how connections between different brain regions might be altered in these disorders and to view the brain as an integrated organ rather than a discrete collection of receptors and transporters.

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Addex Therapeutics Ltd. (SIX:ADXN), Geneva, Switzerland
Atlas Venture, Cambridge, Mass.
Autism Speaks, New York, N.Y.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Heptares Therapeutics Ltd., Welwyn Garden City, U.K.
Innovative Medicines Initiative, Brussels, Belgium
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
King's College London, London, U.K.
Massachusetts Institute of Technology, Cambridge, Mass.
National Institute of Mental Health, Bethesda, Md.
One Mind for Research, Rutherford, Calif.

Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan
Otsuka Holdings Co. Ltd. (Tokyo:4478), Tokyo, Japan
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sage Bionetworks, Seattle, Wash.
Seaside Therapeutics Inc., Cambridge, Mass.
Sigma-Aldrich Corp. (NASDAQ:SIAL), St. Louis, Mo.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan