Neurology company Ovid Therapeutics Inc. is already tapping into the expertise of its new CEO, veteran dealmaker Jeremy Levin. The biotech is in-licensing molecules that have reached Phase III testing but are not approved in the U.S., and where there is a mechanism-based rationale for development in rare and Orphan diseases of the brain.

Hardly the first company to attempt to repurpose failed drugs, Ovid may have an ace up its sleeve in the form of extremely close ties to patients and their families, who will have a role in shaping development of the company’s drug candidates.

Ovid’s first deal, announced Thursday, brings in a candidate from H. Lundbeck A/S that is slated to enter Phase II in 2016 to treat Angelman syndrome and Fragile X. The deal includes exclusive, worldwide rights to gaboxadol, a selective extrasynaptic GABA A receptor agonist that Lundbeck and former partner Merck & Co. Inc. had taken through Phase III testing for insomnia.

In that setting, a combination of the U.S. regulatory requirements for demonstrating the lack of abuse potential and the pharmacokinetics of gaboxadol scuttled both the development program and the partnership. But according to Ovid, the PK problem that dogged the compound in the sleep setting will not be an issue in Angelman and Fragile X, where lower doses and lower peak concentrations are desired.

Angelman is a rare genetic disorder that is characterized by developmental delay, severe speech impairment, seizures, and movement and balance disorders (ataxia).

No drugs have been approved for Angelman and only two clinical trials of drugs have been run in the population, one testing levodopa and one minocycline; therefore, no endpoints have stood the test of regulatory review. In addition, the instruments used to assess key symptoms, including motor dysfunction and cognitive impairment, are not optimized for use in Angelman patients.

This is one area where Ovid will benefit from collaborations with two parent-led advocacy groups, the Angelman Syndrome Foundation (ASF) and the Foundation for Angelman Syndrome Therapeutics (FAST). The organizations maintain databases of patients and providers who treat Angelman, will provide input to the company’s clinical trial advisory group and will help recruit patients for trials.

Levin plans to extend the model to other rare neurological diseases to build Ovid and keep it independent: in-licensing unapproved compounds with a large body of data, well understood pharmacology and a mechanistic link to disease, and collaborating closely with patients to ensure successful development.

Levin, who has been chairman of Ovid since 2014, was most recently president and CEO of Teva Pharmaceutical Industries Ltd.; he previously led business development for Bristol-Myers Squibb Co. and Novartis AG.

GLIMPETING THE PATHWAY

Ovid was founded last year by President and CSO Matthew During, a neuroscientist and physician whose lab pioneered the use of AA V in the brain.

“In the last five years, we’ve come to better know the genetic basis of Orphan neurological disorders, and also have animal models — predictive genetic models — that recapitulate the human phenotype,” During told BioCentury. “And knowledge of small molecules, and cloning out receptors and subreceptors in the brain, have flourished in parallel over this time.”

Instead of screening libraries of compounds, During sought out drug candidates that had made it through Phase III testing but were not approved in the U.S.

“They had to have known pharmacology, a unique mechanism, and had to match the neurological disorder,” he said.

Gaboxadol, now dubbed OV101, is one of six small molecules During has identified. The chemical names of the other five are not disclosed, but Levin disclosed the planned indications for three of them: OV201 is for Lewy body dementia, OV301 is for Dravet syndrome and OV401 is for Prader-Willi.

According to During, the molecules have extensive human data and have shown no rate-limiting toxicities. And
because they have not been approved in the U.S., there will not be generic competition before Ovid’s IP expires. For example, he said gaboxadol has patent protection at least through 2025.

NEW PURPOSE
While gaboxadol didn’t pan out in sleep disorders, During and Levin said the molecule’s pharmacology is particularly suited for Angelman and Fragile X. Lundbeck originally hoped gaboxadol would be differentiated in insomnia in part by not being regulated as a drug of abuse. In 2004, Lundbeck partnered the compound with Merck and told BioCentury it believed gaboxadol was the only molecule in development for insomnia that targeted the GABA binding site on GABA A receptors, and not the benzodiazepine binding site.

Gaboxadol binds to GABA A receptors with alpha4/delta subunits. At the time, Bjarke Ebert, then head of electrophysiology at Lundbeck, said the alpha4/delta subtype does not have a benzodiazepine binding site unlike most GABA A receptors. And unlike most GABA A receptors, he said, the alpha4/delta subtype is expressed outside of synapses.

But Lundbeck and Merck dropped gaboxadol in 2007, saying the “overall clinical profile” did not support continued development.

According to During, the problems were twofold. First, patients experienced hallucinations in a study in drug abusers that FDA requested to support approval as a nonscheduled hypnotic. However, During said the abuse study used three times the normal dose for insomnia, and he noted hallucinations are not uncommon in drug abusers.

Second, During said, Phase III efficacy results in the U.S. were not as good as those in Europe because of a PK problem. “In Phase III in normal individuals, they saw good results in women, but not in men,” he said.

“For the hypnotic use, Lundbeck and Merck needed to get a very high Cmax. It required super rapid absorption and high Cmax. When dosing in Americans, high meat consumption impacted not the area under the curve, but the Cmax. But we don’t want high Cmax,” he said.

The doses of gaboxadol used in animal models of Angelman are lower than those required for sedation.

“The key in Angelman and Fragile X and Rett syndromes is that synaptic dysfunction leads to reduction of GABA, and that leads to a reduction of tonic inhibition,” During said. “There is an exquisite need for low doses of GABA in the extrasynaptic spaces.”

Tonic inhibition is a basal level of inhibition on neurons that prevents over-excitability in order to maintain normal function. Two other companies have development programs for neuroactive steroids that act on delta-containing GABA A receptors. Ganaxolone from Marinus Pharmaceuticals Inc. is expected to complete a Phase II study in Fragile X this year. Sage Therapeutics Inc. is developing SAGE-217 for Rett and Dravet syndromes and expects to begin Phase I testing this year.

Marinus spokesperson Lisa Caperelli said neurosteroids including ganaxolone exert anticonvulsant and anxiolytic effects via a dual mechanism of action at GABA A receptors. At nanomolar concentrations, they enhance tonic inhibition at extrasynaptic receptors by potentiating endogenous GABA, which is plentiful throughout the CNS.

At higher concentrations, they directly activate both synaptic and extrasynaptic GABAA receptors.

“WHAT IS IMPORTANT TO ONE INDIVIDUAL WHOSE CHILD IS NOT YET WALKING MAY BE DIFFERENT FROM WHAT IS IMPORTANT TO AN INDIVIDUAL WHOSE CHILD IS WALKING.”

EILEEN BRAUN, ASF

Sage has not disclosed the structure or precise mechanism of SAGE-217, except to say the molecule is a novel neuroactive steroid that acts as a positive allosteric modulator of synaptic and extrasynaptic GABA A receptor subtypes.

MOTOR MECHANISM
Preclinical studies suggest gadoxodol could correct synaptic dysfunction and restore tonic inhibition in Angelman patients, leading to an improvement in symptoms such as motor dysfunction.

The condition is usually caused by loss of function of the maternal gene encoding ubiquitin protein ligase E3A (UBE3A; E6AP). Recent in vitro and in vivo studies showed that the mechanistic cause of ataxia in mice with a deficiency in maternal UBE3A is a decrease in tonic inhibition in cerebellar granule cells.

Normally, tonic inhibition is maintained when GABA — an inhibitory neurotransmitter — binds extrasynaptic GABA A receptors that contain the delta subunit. In the mouse models, a decrease in UBE3A induces a surplus of the GABA transporter GAT1, which in turn increases the uptake of GABA into neurons, and thus reduces concentrations of GABA in the extrasynaptic space.

In the mice, treatment with gadoxodol rescued motor function, improving gait and balance, and decreasing abnormal clasping reflexes. Results were published in Science Translational Medicine in 2012.

AMELIORATING SYMPTOMS
According to three parents of Angelman patients who spoke to BioCentury, even a small improvement in motor function could make a huge difference in quality of life, not just for the child with the condition, but for the entire family.

Eileen Braun, executive director of ASF and mother of a 24-year-old daughter with Angelman, noted there is a wide range of ability in Angelman. “If a child is walking,” she said. “Anything we can do to improve quality of life for people with Angelman syndrome is hugely important for my daughter and patients with Angelman syndrome.”

Without a treatment that can reduce disability, lifelong care is a huge concern.

“Right now, because there is not a currently available comprehensive treatment, families are looking at lifelong care for individuals,” Braun said. “Long after parents pass away, these individuals will live on and will continue to have Angelman syndrome.”
Paula Evans, chairperson of FAST and mother of a 10-year-old daughter with Angelman, said motor function affects patient families every day.

“My daughter walks, but would I bring her to a playground and sit on a bench and check my messages? No. Everything she does she needs help with, from the time she gets up to the time she goes to bed,” Evans told BioCentury.

“If my daughter is able to feed herself, if she can get a spoon or a fork to her mouth, that’s a huge benefit, not only to Ainsley but to the whole family,” she said.

Rebecca Burdine, CSO of FAST and mother of a nine-year-old daughter with Angelman, said an improvement in motor function that would enable her daughter to communicate using a device would be a huge benefit.

“My daughter does not walk. If she had an improvement in motor function so she could push a button on an iPad to tell me what she wants for dinner, that would be enormous,” she said.

Burdine is an associate professor in the Department of Molecular Biology at Princeton University. Her lab is researching how organs form and function in vertebrate embryos, with a focus on the heart and kidney.

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PAULA EVANS, FAST

NAILING THE METRICS

Figuring out how to measure motor function and other symptoms that could be improved by gaboxadol, such as cognitive function, is one of Ovid’s biggest challenges.

“The biggest problem we are faced with is designing the best clinical trial, and the hardest aspect is to select the best endpoint,” During said.

He said Ovid plans to include endpoints assessing not only motor function, but also cognition and frequency of seizures.

The minocycline trial provided some clues. But the study, which was funded by FAST and conducted by academics, also highlighted the need for a randomized, controlled study with carefully selected endpoints. The open-label study in 25 patients ages 4-12 showed significant improvement in mean raw scores on the communication and fine motor subdomains of the Bayley Scales of Infant and Toddler Development 3rd Edition (BSID-III). BSID-III is a measure of development used to assess the cognitive, language and motor abilities of children ages 1 to 42 months.

“One of the issues with previous trials is that the scales are pretty noisy and are not optimized for children with Angelman,” During said.

For example, Burdine noted one of the tasks used to assess cognitive ability involves stacking four blocks on top of each other.

“My daughter cannot. The question is, does she understand the task? I would argue she understands but cannot make her arms do that,” Burdine said.

Burdine, Evans and During all said it is possible that an improvement in motor function in Angelman children could actually change the understanding of their cognitive ability, because poor motor function impairs their ability to communicate.

To help select endpoints for the Phase II study, Ovid is assembling a clinical trials advisory group that will include clinicians, geneticists and clinical trials experts and will seek input from ASF and FAST.

Braun noted ASF is funding research into biomarkers and metrics to help evaluate the efficacy of drug candidates for Angelman.

During said the organizations also can help identify investigators and centers that may participate in the studies. He said FAST has a list of investigators with a specific interest in Angelman. And ASF told BioCentury it has established Angelman-specific clinics in Boston and North Carolina.

Importantly, both organizations can help Ovid recruit study participants.

“It’s a frightening prospect to take your non-verbal child who cannot communicate side effects — to enroll them in a trial is really daunting. You run the risk in a disorder like Angelman syndrome of not getting patients,” said Evans.

“It is really critical for us as a patient organization to be available to our community to answer questions. They need to know literally from step A, how will I be considered for a trial, all the way to what we think gaboxadol may be able to do,” she said.

During said details of the trial design will be firmed up over the coming months, but he estimated the double-blind, placebo-controlled study will enroll 30-50 patients in each arm, with 1:1 randomization.

COMPANIES AND INSTITUTIONS MENTIONED

Angelman Syndrome Foundation (ASF), Aurora, Ill.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Foundation for Angelman Syndrome Therapeutics (FAST), Downer’s Grove, Ill.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Marinus Pharmaceuticals Inc. (NASDAQ:MRNS), Radnor, Pa.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Ovid Therapeutics Inc., New York, N.Y.
Princeton University, Princeton, N.J.
Sage Therapeutics Inc. (NASDAQ:SAGE), Cambridge, Mass.
Teva Pharmaceutical Industries Ltd. (NASDAQ:TEVA), Petah Tikva, Israel

REFERENCES
