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Product Discovery & Development

Alzheimer's rewind

By Lev Osherovich
Senior Writer

A string of Phase II and III failures in Alzheimer's disease has prompted companies to look for new targets beyond the well-known players in the core mechanism of AD — the production and accumulation of beta amyloid deposits in the brain. The next wave of candidates includes more than 20 clinical stage small molecules for targets that indirectly affect beta amyloid production and/or toxicity, or aim for solutions that might be disease-modifying even as they ameliorate symptoms.

Among the latest casualties are gamma secretase inhibitors, which first entered the clinic more than a decade ago. The two most advanced molecules, one in Phase III and one in Phase II, have shown safety signals that suggest the basic approach to the target will need to be refined. A handful of clinical and preclinical programs aiming to create a second generation of molecules are already underway.

Meanwhile, the AD field is awaiting the results of the remaining Phase III candidates, a trio of immunotherapeutics against beta amyloid. Behind them are at least 11 more clinical stage immunotherapies *(see "Awaiting mAb Data")*.

Gamma ghost town

Gamma secretase, the proteolytic complex that processes amyloid precursor protein (APP) into the neurotoxic beta amyloid form, was first proposed as a target in the 1990s and at least a dozen candidates have reached the clinic in AD.

Data presented at the **Alzheimer's Association** International Conference (AAIC) in July highlighted the difficulty of finding a therapeutic window for hitting the target.

Eli Lilly and Co. presented the results of a follow-up to the Phase III IDENTITY and IDENTITY-2 trials of its semagacestat (LY450139) gamma secretase inhibitor.

Those trials were suspended last year when a safety monitoring committee uncovered evidence of cognitive worsening in treated patients compared with placebo (*see BioCentury, Aug. 23, 2010*).

New data from a follow-up of 1,534 patients showed that seven months after dosing was stopped, patients who had received once-daily 100 and 140 mg oral semagacestat, respectively, had ADAS-Cog11 scores that were 7.29 and 7.68 points lower than baseline. Patients who got placebo showed a 6.19 point decline compared with baseline.

These data mean the harmful effect was not reversed after treatment was suspended. The rate of cognitive decline after termination of dosing was the same as placebo.

> ***"Semagacestat produced an effect on cognition. Unfortunately it wasn't the effect we wanted."***
>
> **Eric Siemers, Eli Lilly**

"Semagacestat produced an effect on cognition," said Eric Siemers, the senior medical director at Lilly who presented the findings. "Unfortunately it wasn't the effect we wanted."

Doubts about the target were compounded by results from a Phase II trial of **Bristol-Myers Squibb Co.**'s BMS-708163, a gamma secretase inhibitor that was intended to be more selective for APP processing.

The rationale for greater APP selectivity was to not interfere with the processing of other gamma secretase substrates such as Notch 1 (NOTCH1), which is involved in normal tissue regeneration in the gastrointestinal tract and skin.

Bart de Strooper, professor of human genetics at the **Catholic University Leuven**, said his own studies using improved gamma secretase assays suggest that BMS-708163 in fact blocks NOTCH1 processing at least as potently as semagacestat.

de Strooper led a team that discovered the key enzymatic components of gamma secretase in the 1990s.

Although BMS's Phase II trial met its primary endpoint of establishing a well-tolerated dose, it did not improve cognition endpoints or have the expected effect on biomarkers of efficacy.

Data from the double-blind, placebo-controlled, international Phase II CN156-013 trial in 209 patients with mild to moderate AD showed doses below 100 mg/day had acceptable tolerability and were associated with discontinuation rates similar to placebo. Patients given 100 mg/day or more had higher discontinuation rates than placebo patients, mostly due to GI or dermatological side effects.

However, doses below 100 mg/day showed no effects on the secondary efficacy endpoints of improving ADAS-Cog and ADCS-ADL scores vs. placebo. Indeed, the 100 and 125 mg cohorts showed "trends for cognitive worsening," according to Howard Feldman, VP of global clinical research in neuroscience at BMS.

It's not yet known whether patients who received high-dose BMS-708163 developed the same sort of irreversible cognitive decline seen with semagacestat or whether the harmful effects will

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wear off.

Furthermore, lower 25 and 50 mg doses of BMS-708163 showed no significant difference in beta amyloid in the cerebrospinal fluid (CSF) at the trough level of drug concentration vs. placebo, although the 100 mg dose led to a 40% reduction.

The pharma said the trial was not powered to determine efficacy but that measurements of CSF beta amyloid at post-dosing peak suggested the compound could inhibit gamma secretase at well-tolerated doses.

Bristol-Myers said BMS-708163 at doses below 100 mg/day thus provides a "potential therapeutic window" for evaluation in Phase III studies.

The company is awaiting the result of a second Phase II trial in early stage or predementia AD patients before deciding how to proceed. In that study, patients were started at 125 mg BMS-708163 daily but were shifted to a 50 mg dose after the tolerability problems in the first trial came to light.

Interim results of the second trial, whose primary endpoints are safety and tolerability, are expected this fall.

Probing deeper

Trying to avoid neurological toxicity with next-generation compounds will require guesswork, because the mechanism through which it occurs with gamma secretase inhibitors is not fully understood.

In his presentation on semagacestat at AAIC, Siemers discussed several hypotheses. He concluded the most probable was that inhibiting the enzyme outright prevented the normal processing of other substrates, of which "there are at least 50."

Siemers cited recent preclinical studies about the role of NOTCH1 and other gamma secretase substrates in normal neuronal function to suggest "you could make a plausible story about how these pathways could contribute to the cognitive effects of semagacestat."

> ***"Companies are making decisions based on failures of drugs that were developed using old knowledge."***
>
> **Bart de Strooper, Catholic University Leuven**

Finding a molecule that blocks the cleavage of APP but leaves all other gamma secretase substrates unaffected is a tall order, Siemers told BioCentury.

"If you had a real honest-to-God modulator that affected just APP, this might work, but I think it would be very difficult to come up with something that doesn't hit any of the 50-odd other substrates," he said.

Part of the challenge is the specific form of gamma secretase that produces beta amyloid has not yet been fully characterized.

"There are at least four different gamma secretase complexes," said de Strooper. "We have to modernize gamma secretase drug development to include these different enzymes and their different substrates."

de Strooper said it was not surprising that high doses of the Lilly and BMS compounds, which shut down every form of gamma secretase, would have adverse effects.

Lilly has thrown in the towel on gamma secretase.

So has **Elan Corp. plc**, which announced on Aug. 1 that it had terminated development of ELND007, a Phase I gamma secretase inhibitor from the same discovery program that led to semagacestat. Elan's other Phase I gamma secretase inhibitor, ELND006, was discontinued last October due to liver toxicity.

Semagacestat was one of several compounds that came out of a nine-year Elan-Lilly partnership to discover gamma secretase inhibitors. The biotech was not involved in the clinical development of semagacestat, but retained royalty and co-promotion rights.

Still, de Strooper said the failures of first-generation programs should not discourage further efforts against the target.

"Companies are making decisions based on failures of drugs that were developed using old knowledge," he said. "We simply started the clinical trials at a point when we didn't understand the molecule."

However, de Strooper added, sorting out which version of gamma secretase to hit and how to do it safely will require "a great deal more preclinical work before we advance anything else into the clinic."

de Strooper cited preclinical data from his laboratory and others supporting the idea that certain forms of beta amyloid contribute more to AD pathogenesis than others, so that future efforts should subtly tweak gamma secretase activity to change the relative ratios of the various beta amyloid fragments it produces.

"We have found that the absolute amount of amyloid beta is not the critical factor in AD, but rather the ratios of various species," said de Strooper. "If you have a compound that affects APP cleavage, you first have to characterize its effect on these various peptides."

Next up

A handful of companies are developing next-generation gamma secretase modulators (GSMs) that they hope will block the production of toxic beta amyloid fragments without affecting gamma secretase's other activities.

For example, **EnVivo Pharmaceuticals Inc.** in July started a Phase I trial of EVP-0962 GSM. That compound, which reduces beta amyloid formation with minimal effects on NOTCH1, is an NSAID derivative with improved solubility and brain penetration compared with previous NSAID GSMs.

An earlier NSAID, **Myriad Genetics**

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PO Box 1246
San Carlos CA 94070-1246
Voice: 650-595-5333
Fax: 650-595-5589
www.biocentury.com

DAVID FLORES
President & CEO

KAREN BERNSTEIN, Ph.D.
Chairman & Editor-in-Chief

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Inc.'s Flurizan tarenflurbil, failed a Phase III AD trial in 2008. A closely related compound, **Chiesi Farmaceutici S.p.A.**'s CHF 5074, is in Phase II testing.

Eisai Co. Ltd. is pursuing an alternative chemical class — diarylcinnamide GSMs — with similar NOTCH1-sparing properties but higher potency than NSAID GSMs. Its E2212 is in Phase I.

Also in this class, **NeuroGenetic Pharmaceuticals Inc.** has preclinical compounds that it acquired from TorreyPines Therapeutics Inc. when the latter reverse-merged with **Raptor Pharmaceutical Corp.** in 2009.

Another strategy is to alter the cleavage site of APP itself so gamma secretase cuts it differently. The goal is to reduce levels of beta amyloid 42, thought to be the most toxic form, and increase levels of the smaller beta amyloid fragments that are thought to be less toxic or perhaps beneficial, including beta amyloid 38, 39 and 40.

This is what **Satori Pharmaceuticals Inc.** aims to do. The company has compounds that "change the cleavage site of APP itself without affecting the whole pool" of other gamma secretase substrates, said CEO Jeff Ives.

Satori gave a first glimpse of the mechanism of its preclinical compounds at AAIC.

The company presented cell culture and animal model data for compounds in two distinct chemical classes that increase relative levels of beta amyloid 38 and beta amyloid 39, respectively.

Neither compound class affected absolute levels of APP processing, suggesting they do not affect the catalytic activity of gamma secretase. This may mean other gamma secretase substrates are likely to be left undisturbed by Satori's compounds.

The biotech is selecting a lead AD compound for an IND filing in 2012. Ives said the Phase I trial will monitor levels of beta amyloid fragments in the CSF.

At least two pharmas — **AstraZeneca plc** and **Roche** — also are keen on altering the relative ratios of beta amyloid fragments using GSMs. The companies presented preclinical data at AAIC on aminopyrimidine compounds that reduce beta amyloid 42 production and increase production of smaller fragments in cell culture.

Ives believes efficacy trials of GSMs will need to be done in patients with prodromal or early stage AD, which can be detected through brain imaging abnormalities and abnormal CSF biomarkers before significant neuronal degeneration and cognitive deficits appear.

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AD pipeline: APP processing/beta amyloid production

At least nine clinical compounds aim to treat Alzheimer's disease (AD) by targeting the proteolytic processing or production of amyloid precursor protein (APP). At least eight programs are in research/preclinical development. *Source: BioCentury Online Intelligence*

Company	Product	Description	Status
AC Immune S.A.	ACI-91	Oral small molecule that modulates beta-site APP-cleaving enzyme 1 (BACE1)	Ph II
Bristol-Myers Squibb Co. (NYSE:BMY)	BMS-708163	Gamma secretase inhibitor	Ph II
Chiesi Farmaceutici S.p.A.	CHF 5074	Gamma secretase modulator	Ph II
Sonexa Inc./ Zenyaku Kogyo Co. Ltd.	ST101	Inducer of alternative cleavage of APP	Ph II
QR Pharma Inc./ Raptor Pharmaceutical Corp. (NASDAQ:RPTP)	Posiphen	Amyloid precursor protein (APP) translation inhibitor	Ph I/II
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523)	E2212	Gamma secretase modulator	Ph I
Eli Lilly and Co. (NYSE:LLY)	LY2886721	BACE1 inhibitor	Ph I
EnVivo Pharmaceuticals Inc.	EVP-0962	Gamma secretase modulator	Ph I
TransTech Pharma Inc.	HPP854	BACE1 inhibitor	Ph I
AstraZeneca plc (LSE:AZN; NYSE:AZN)	Not available	Gamma secretase modulator	Preclin
Comentis Inc./ Astellas Pharma Inc. (Tokyo:4503)	Not available	BACE1 inhibitor	Preclin
Genentech Inc./ Roche (SIX:ROG; OTCQX:RHHBY)	Anti-BACE1/anti-TfR	Bispecific human mAb with low affinity against transferrin receptor and high affinity against BACE1	Preclin
NeuroGenetic Pharmaceuticals Inc.	Not available	Gamma secretase modulator	Preclin
Noscira S.A.	NPM-05	Alpha secretase enhancer	Preclin
Roche (SIX:ROG; OTCQX:RHHBY)	Not available	Gamma secretase modulator	Preclin
Satori Pharmaceuticals Inc.	Not available	Gamma secretase modulator	Preclin
Intra-Cellular Therapies Inc.	Not available	Compound targeting gamma secretase activating protein (GSAP)	Res

AD pipeline: Serotonin modulators

At least 11 serotonin receptor modulators are in clinical development to treat Alzheimer's disease (AD). Whether targeting serotonin signaling would have a disease-modifying effect in AD or would merely alleviate the symptoms is under debate. *Source: BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Status
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	SB-742457	Serotonin (5-HT6) receptor antagonist	Ph II
H. Lundbeck A/S (CSE:LUN)	Lu AE58054	Serotonin (5-HT6) receptor antagonist	Ph II
Nanotherapeutics Inc.	PRX-3140	Serotonin (5-HT4) receptor agonist	Ph II
Suven Life Sciences Ltd. (NSE:SUVEN; BSE:530239)	SUVN-502	Serotonin (5-HT6) receptor antagonist	Ph I compl
Abbott Laboratories (NYSE:ABT)	ABT-354	Serotonin (5-HT6) receptor antagonist	Ph I
Avineuro Pharmaceuticals Inc.	AVN-322	Serotonin (5-HT6) receptor antagonist	Ph I
Pfizer Inc. (NYSE:PFE)	PF-5212377 (SAM-760)	Serotonin (5-HT6) receptor antagonist	Ph I
Pfizer Inc. (NYSE:PFE)	PF-4995274	Serotonin (5-HT4) partial agonist	Ph I
Biotie Therapies Corp. (HSE:BTH1V)/ **Roche** (SIX:ROG; OTCQX:RHHBY)	SYN-120	Serotonin (5-HT6) receptor antagonist	Ph I
RaQualia Pharma Inc. (JASDAQ:4579)	RQ-00000009	Serotonin (5-HT4) partial agonist	Ph I
Theravance Inc. (NASDAQ:THRX)	TD-5108	Serotonin (5-HT4) receptor agonist	Ph I

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"Future trials for early intervention in prodromal AD will be critical," said Ives. "There's a feeling that there's no sense in running future trials in mild to moderate patients because we know that the insult has already taken place and it's too late to intervene."

Ives noted that amyloid-related biomarkers may be the only way to assess efficacy in early stage AD trials. This is because conventional measures of cognitive function like ADAS-Cog are unreliable in the early stages of disease before cognitive functioning is severely compromised.

Last year, the Alzheimer's Association issued guidelines for the use of AD biomarkers such as blood and CSF amyloid levels, magnetic resonance imaging (MRI) and positron emission tomography (PET) brain scans. Industry and academic researchers are still working out how to standardize these tests, and FDA has not indicated how it will interpret these data *(see BioCentury Aug. 8, 2010)*.

Meanwhile, **Merck KGaA**'s Merck Serono S.A. unit is developing a cell culture assay to explore how to target gamma secretase activating protein (GSAP; PION), a recently discovered co-factor of gamma secretase.

The Merck Serono team reported that **Novartis AG**'s Gleevec imatinib, which has previously been shown to interact with GSAP, inhibited the ability of gamma secretase to cleave APP but not NOTCH1.

Gleevec is marketed to treat a range of cancers.

Intra-Cellular Therapies Inc. has a discovery program targeting GSAP for AD (*see SciBX: Science-Business eXchange, Sept. 16, 2010*).

Other avenues

At least four companies are pursuing small molecule approaches to other targets involved in beta amyloid formation *(see "APP processing/beta amyloid production")*.

Lilly's LY2886721 inhibits another APP protease, beta site APP-cleaving enzyme 1 (BACE1). Because BACE1 acts earlier in the pathway that leads to beta amyloid production, hitting it could in principle avoid the challenge of sparing NOTCH1 or other gamma secretase substrates.

However, mouse genetic studies by academic researchers have hinted at deleterious neurodevelopmental consequences of inactivating BACE1, raising potential safety concerns for that strategy.

LY2886721 has completed Phase I testing, and the company is planning a Phase II trial, Siemers told BioCentury.

Partners **Astellas Pharma Inc.** and **CoMentis Inc.** have preclinical compounds targeting BACE1. In 2010, the companies halted clinical development of a previous BACE1 inhibitor, CTS-2116 (ASP1702), after Phase I testing in AD.

Meanwhile, **QR Pharma Inc.** is taking an entirely different approach to reducing beta amyloid production by lowering levels of APP itself.

At AAIC, the company presented a potential therapeutic mechanism for Posiphen, a positive enantiomer of phenserine the company acquired from TorreyPines Therapeutics Inc.

President and CEO Maria Maccecchini told BioCentury it now appears that Posiphen enhances the activity of aconitase 1 (ACO1; IRP1). IRP1 is a multifunctional protein that, among other things, represses translation of APP.

Earlier this year, QR reported that 30 patients with mild cognitive impairment (MCI) showed improvements in CSF biomarker levels when treated with Posiphen for 10 days in a Phase I/II trial compared with baseline. The company is hoping to start a Phase II/III trial in MCI patients this year.

Another approach is to use small molecules or polymers that alter the biophysical environment in the brain, preventing or reversing beta amyloid aggregation.

In September, Elan and partner **Transition Therapeutics Inc.** said they were planning a Phase III trial of ELND005, a formulation of scyllo-inositol. The compound disaggregates beta amyloid *in vitro* and in mice.

Last year, ELND005 missed the primary endpoints of improving Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) and Neurophysiological Test Battery (NTB) in a Phase II trial. Trial arms testing 1,000 and 2,000 mg doses were discontinued

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AD pipeline: Antioxidation / anti-aggregation

At least eight compounds in clinical development aim to treat Alzheimer's disease (AD) by mitigating beta amyloid toxicity through anti-oxidant or anti-aggregation effects. The specific targets and/or mechanisms of action for most of these compounds are not firmly established. *Source: BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Status
Scigenic Co. Ltd./ Whanin Pharmaceutical Co. Ltd. (KOSDAQ:016580)	INM-176 (WIN-026)	Antioxidant and anti-amyloid herb extract	Ph III
Prana Biotechnology Ltd. (ASX:PBT; NASDAQ:PRAN)	PBT2	Metal protein-attenuating compound (MPAC)	Ph II
Transition Therapeutics Inc. (TSX:TTH; NASDAQ:TTHI)/ **Elan Corp. plc** (NYSE:ELN)	ELND005 (AZD-103)	Small molecule that disaggregates beta amyloid fibrils	Ph II
Evotec AG (Xetra:EVT)/ **Roche** (SIX:ROG; OTCQX:RHHBY)	EVT-302	Monoamine oxidase B (MAO-B) inhibitor	Ph I
Intellect Neurosciences Inc. (OTCBB:ILNS)/ **Viropharma Inc.** (NASDAQ:VPHM)	OX1 (Oxigon)	Antioxidant and anti-amyloid compound	Ph I
Bellus Health Inc. (TSX:BLU)	NRM8499	Prodrug of tramiprosate	Ph I
Noscira S.A.	NP-61	Beta amyloid modulator	Ph I
ProteoTech Inc.	Exebryl-1	Small molecule targeting beta amyloid protein accumulation	Ph I

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in 2009 due to increased rates of infection and death vs. placebo.

Biomarker data presented at AAIC showed patients in the 250 mg arm had significantly reduced CSF beta amyloid 42 at 78 weeks compared with placebo. But those patients also had significantly increased ventricular volume.

Ventricular dilation accompanies AD progression and can transiently reduce CSF beta amyloid concentration. Thus, it's not certain whether ELND005 ameliorates or accelerates disease progression.

Still other companies are looking at serotonin receptors, which may provide symptomatic solutions but also may prove to be disease modifying. Preclinical studies suggest that modulating serotonin signaling can enhance neuronal survival and functioning in the presence of beta amyloid while simultaneously reducing the production of more beta amyloid *(see "Serotonin Modulators")*.

Pfizer Inc. has a pair of compounds that hit two different serotonin receptors, with opposite effects on serotonin signaling. One compound, PF-05212377/SAM-760, is an antagonist of serotonin (5-HT6) receptor. Another molecule, PF-04995274, is a partial agonist of serotonin (5-HT4) receptor.

Both compounds improved cognitive endpoints in rodent models of AD compared with untreated controls and were well tolerated in healthy volunteers in Phase I testing.

It's not clear whether hitting the 5-HT6 and 5-HT4 receptors would prevent disease progression or merely forestall its clinical manifestation. Both receptors are abundant in the brain regions affected by AD, and previous reports by academic researchers suggest serotonin signaling generally is depressed in AD patients and preclinical models of AD.

Supporting the disease-modifying idea, mouse data from a team at **Washington University** suggest that broadly agonizing serotonin signaling with selective serotonin reuptake inhibitors (SSRIs) can decrease levels of beta amyloid in the brain. Data were published in the *Proceedings of the National Academy of Science* in August.

At AAIC, **GlaxoSmithKline plc** presented data from two Phase II trials of its own 5-HT6 receptor antagonist, SB-742457.

In one 576-subject trial, once-daily 15 and 30 mg SB-742457 each missed the co-primary endpoints of significantly improving Change plus Caregiver Input (CIBIC-plus) and ADAS-Cog scores from baseline to week 24 vs. placebo.

In the second 684-subject trial, once-daily 15 and 35 mg SB-742457 as an add-on to donepezil each missed the co-primary endpoint of significantly improving Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores from baseline to week 24 vs. placebo.

High-dose SB-742457 met the co-primary endpoint of significantly improving ADAS-cog scores from baseline to week 24 vs. placebo, but low-dose SB-742457 missed that endpoint. Similar results were observed at week 48.

The results are in line with two previous Phase II trials of SB-742457.

GSK spokesman David Daley said that the company is "exploring the data from both the monotherapy and adjunctive therapy studies to help our decision on what the next steps for SB742457 might be."

H. Lundbeck A/S also has a 5-HT6 receptor antagonist in Phase II testing for AD. Data for Lu AE58054 are expected 1H12.

Meanwhile, Roche has partnered with **Biotie Therapies Corp.** to put the latter company's 5-HT6 receptor antagonist, SYN-120, through a Phase I imaging study for AD. Data are due in 1H12. That compound was initially discovered at Roche and was then outlicensed to Synosia Therapeutics AG, which Biotie

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acquired this year.

Indeed, Roche is casting a wide net for mechanisms to treat AD.

In September, the pharma bought back **Evotec AG**'s EVT 302 reversible monoamine oxidase type B (MAO-B) inhibitor for $10 million up front and up to $820 million in milestones.

The biotech originally acquired EVT 302 from Roche and developed it for smoking cessation, but the compound failed a Phase II trial for that indication in 2009.

The compound is now ready for a "12-month AD trial" according to Jonathan Savidge, who recently stepped down as Evotec's VP of business development. Savidge is now associate practice executive at **Campbell Alliance Group Inc.**, a biotech and pharma consultancy.

Savidge said EVT 302's precise mechanism of action in AD is unclear but may involve antioxidant and anti-inflammatory effects. He said EVT 302 is not expected to directly affect beta amyloid production, but blocking MAO-B could slow down the neurodegenerative effect of amyloid plaques.

"With an MAO-B inhibitor, you wouldn't necessarily get an improvement in cognitive behavior, but you would slow the rate of decline," said Savidge.

Besides EVT 302 and ELND005, at least six other small molecules in clinical development for AD are thought to detoxify beta amyloid through a range of antioxidant and/or antiaggregation mechanisms. These include an herbal extract, a metal chelator and several compounds thought to directly disaggregate beta amyloid or block its aggregation *(see "Antioxidation/Anti-aggregation").*

COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Association, Chicago, Ill.
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Biotie Therapies Corp. (HSE:BTH1V), Turku, Finland
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Campbell Alliance Group, Inc., Raleigh, N.C.
Catholic University Leuven, Leuven, Belgium
Chiesi Farmaceutici S.p.A., Parma, Italy
CoMentis Inc., South San Francisco, Calif.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Elan Corp. plc (NYSE:ELN), Dublin, Ireland
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
EnVivo Pharmaceuticals Inc., Watertown, Mass.
Evotec AG (Xetra:EVT), Hamburg, Germany
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Intra-Cellular Therapies Inc., New York, N.Y.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Myriad Genetics Inc. (NASDAQ:MYGN), Salt Lake City, Utah
NeuroGenetic Pharmaceuticals Inc., San Diego, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
QR Pharma Inc., Berwyn, Pa.
Raptor Pharmaceutical Corp. (NASDAQ:RPTP), Novato, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Satori Pharmaceuticals Inc., Cambridge, Mass.
Transition Therapeutics Inc. (TSX:TTH; NASDAQ:TTHI), Toronto, Ontario
Washington University, St. Louis, Mo.

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BioCentury Publications, Inc.
BioCentury International Inc.

Main Offices
PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

Chicago: +1 312-755-0798; Fax: +1 312-755-0658

Washington, DC: +1 202-462-9582; Fax: +1 202-667-2922

Oxford, UK: +44 (0)1865-512184; Fax: +1 650-595-5589

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