Approaches to age-related disorders evolve

Although specific age-related disorders such as Alzheimer's disease continue to be a focus of R&D investment and dealmaking activity, companies are also beginning to approach aging in a broader way.

BY SUZANNE ELVIDGE

The world's population is aging. According to the World Health Organization, the global population of people aged over 60 is predicted to be around 2 billion by 2050, or 22% of the population, an increase from 11% in 2000. The concomitant increase in the prevalence of age-related diseases—such as Alzheimer's disease, age-related macular degeneration, osteoporosis, cardiovascular disease, diabetes and cancer—is placing a growing and substantial strain on healthcare budgets. Thus, the need for new approaches to treat or prevent such disorders is high, particularly for diseases such as Alzheimer's disease, for which the effectiveness of current treatments is very limited.

Persistence with Alzheimer's disease

Alzheimer's disease, the most common form of dementia, is the focus of two of the top five aging deals from the past 12 months (**Table 1**), with companies persisting despite the catalog of expensive late-stage clinical failures in the field. A recent study found that the industry invested in 1,120 unique pipeline drugs for Alzheimer's disease from 1995 to 2014, but the overall success rate in reaching approval was just 0.5% (*Nat. Rev. Drug Discov.* **14**, 161–162; 2015). Furthermore, the drugs that were approved only treated disease symptoms, as opposed to modifying disease progression.

Such failures may be dampening investment and dealmaking activity in the field. "Failure rates are high, and pragmatically, the money spent on an Alzheimer's trial could fund a number of oncology trials. It's not that companies don't want to work in the area, but there is a penalty, and it takes investment away from somewhere else," said Eric Karran, director of research strategy at Alzheimer's Research UK.

Many putative disease-modifying drugs in development for Alzheimer's disease are based on the amyloid hypothesis, which proposes that the accumulation of a fragment of amyloid precursor protein (APP), β-amyloid, is behind the neuronal loss and neurodegeneration associated with the disease. One of the key deals of 2014, an agreement between Eli Lilly and AstraZeneca that could be worth up to $500 million for AstraZeneca, focuses on preventing the production of β-amyloid by targeting β-secretase cleaving enzyme (BACE). The 50:50 partnership to develop AZD3293, AstraZeneca's BACE inhibitor, brought Lilly—a long-term investor in the field—back into the race to develop a BACE inhibitor after it had to drop its own BACE inhibitor, LY2886721, owing to liver toxicity (*Nat. Rev. Drug Discov.* **13**, 804; 2015). A phase 2/3 trial of AZD3293 is planned, with Lilly leading the clinical development.

Some researchers have questioned the amyloid hypothesis, however, pointing out inconsistencies between β-amyloid levels and normal cognition, and suggesting that research on Alzheimer's disease needs to expand beyond a focus on β-amyloid plaques (*Alzheimers Res. Ther.* **6**, 37; 2014). Another approach to treating Alzheimer's disease involves targeting the tangles of tau protein that develop in the brain. An agreement between Johnson & Johnson and the Swiss biotech company AC Immune focused on ACI-35, AC Immune's therapeutic vaccine targeting tangles of tau protein, as well as on other tau vaccines. Johnson & Johnson's Janssen has gained rights to ACI-35, which was the first vaccine for Alzheimer's disease to enter clinical trials and is now in phase 1b. This is AC Immune's third major collaboration involving drugs targeting the tau protein.

Uncertainty over the optimal approaches for targeting Alzheimer's disease will remain high until a clinical trial clearly demonstrates a disease-modifying effect. Recently, however, there have been tentative suggestions of such an effect in trials of Lilly's solanezumab, an antibody to β-amyloid. Although the primary endpoints were missed in two phase 3 trials, an extended subgroup analysis suggested that solanezumab has a positive effect in mild disease (*Alzheimers Dement. (NY)* doi:10.1016/j.trci.2015.06.006; 2015), and another phase 3 trial is ongoing.

"If it is successful, this could transform the field as the first disease-modifying drug for Alzheimer's disease, and tell us a lot about the disease process," said Karran. "This could bring companies back into the area."

Table 1. Top three aging deals by value (July 2014–July 2015).

Companies involved	Headline	Deal value (US$ million)	Date announced
Calico; AbbVie	Calico will create an R&D facility focused on aging and age-related diseases in the San Francisco Bay Area. To fund the facility, AbbVie and Calico will each provide up to $250 million, with the possibility to both contribute a further $500 million.	1,500	September 2014
Johnson & Johnson (Janssen Pharmaceuticals); AC Immune	Johnson & Johnson to develop AC Immune's tau-targeted therapeutic vaccine against Alzheimer's disease, ACI-35, from phase 2 onward in a $509 million deal.	509	January 2015
Eli Lilly; AstraZeneca	Eli Lilly and AstraZeneca enter into a partnership to develop AZD3293, a BACE inhibitor for Alzheimer's disease. Lilly will take the lead on the phase 2/3 trials.	500	September 2014

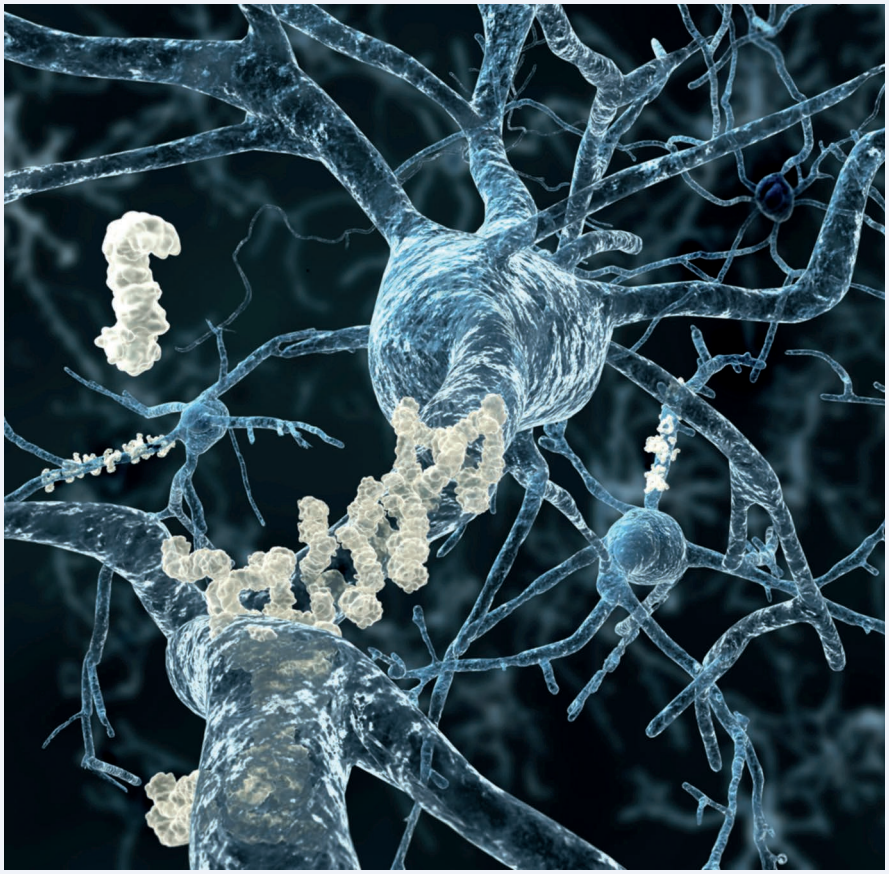
A broader approach for age-related disorders?

Although the focus at the moment is still largely on treating individual diseases such as Alzheimer's disease, more researchers and companies are beginning to look at aging overall, with interest in a potential central mechanism leading to progressive decline and a focus on healthy lifespan, or 'healthspan'.

"Many big pharma companies, including AbbVie, Pfizer and Johnson & Johnson, have programs in aging and healthspan," said George Vlasuk, president and CEO at Navitor Pharmaceuticals, a company focusing on the mTORC1 signaling pathway as a target for intervention in age-related diseases. "While previous overhyping about drugs for aging led to skepticism, there is now a recognition of real science behind the mechanisms of aging and aging-related diseases."

Part of the skepticism might originate from investments in the area that have appeared to fail, at least in the short term. For example, back in 2008, GlaxoSmithKline (GSK) invested $720 million to buy Sirtris, a biotech company that developed drugs targeting sirtuins, which have been implicated in age-related diseases such as type 2 diabetes and cancer. But after little apparent progress, GSK shut down Sirtris in March 2013 and moved its projects in-house.

"Sirtris was a trailblazing effort to look at an overall mechanism of action for aging. It was the first real aging-based company, but I believe it was ahead of its time, and its story got lost



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behind the hype because the deal with GSK fell way short of its expectations, leaving a wariness about the area," said Vlasuk, who was previously Sirtris' CEO.

One sign that the skepticism about broad-based strategies for targeting age-related disorders could be abating is the biggest deal of the past year, between Calico and AbbVie. This deal, signed in September 2014 and potentially worth up to $1.5 billion, is to create an R&D facility in the San Francisco Bay Area that will focus on aging and age-related diseases, including neurodegeneration and cancer. Calico, established in 2013, is focused on age-related diseases and has the might of Google behind it, as well as a leadership team that includes Art Levinson and other key figures from Genentech.

Another intriguing recent development is an effort to tackle a major outstanding question in the field: could it be possible to design clinical trials and gain regulatory approval for a therapeutic to intervene in aging, rather than treat a specific age-related disorder such as type 2 diabetes?

According to Nir Barzilai of the Albert Einstein College of Medicine in New York, treating one disease might mean simply exchanging it for another; for example, reducing the incidence of cardiovascular disease might mean that more people will die from another age-related illness such as Alzheimer's disease.

"It's aging that makes people ill. The new paradigm is to develop drugs that delay aging and therefore delay the onset of aging-related diseases, rather than treating the individual diseases," explained Barzilai. "Delaying aging by just two years could lead to huge savings in healthcare and social costs."

One potential therapeutic in this field is metformin, an oral antidiabetic drug that has been available since the 1950s. It is safe and well tolerated, and it delays aging in animal models.

Barzilai and his colleagues are planning a clinical trial dubbed Targeting Aging with Metformin (TAME), which will involve thousands of people who have or are at risk of one or two of the following diseases: cancer, heart disease and cognitive impairment (*Nature* **522**, 265–266; 2015). The aim is to see whether the metformin delays death, onset of diabetes or the development of diseases that the subjects do not already have.

"The metformin trial is an intriguing opportunity, and makes a great start," said Vlasuk.

The next step will be to get the regulatory bodies to accept therapeutics that delay aging rather than treat individual diseases. The US Food and Drug Administration (FDA) seems open to the idea, having held a meeting to discuss the TAME trial in June 2015.

"We are really glad to see dialogue happening at the FDA, as this area has previously been seen by some as pseudoscience," said Vlasuk. "Delaying aging and therefore reducing age-related diseases will be well worth the investment."

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