BIOTECHNOLOGY

Cenna Biosciences Inc.

Putting a new spin on amyloid beta target in AD

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Contact: Nazneen Dewji, PhD, CEO
Business: Disease-modifying peptides for Alzheimer's disease
Founded: March 2006
Founders And Advisors: Nazneen Dewji; S. Jonathan Singer, PhD; Sterling Johnson, Corporate Development Advisor; Cary Miller (Morrison and Foerster)
Employees: 2
Financing To Date: $14 million in funding and grants
Investors: Founders; National Institutes of Health

Cenna Biosciences Inc. thinks it has come up with a way to target amyloid beta in a way that will succeed where other companies have failed in Alzheimer's disease.

Amyloid beta, which refers to fragments of proteins that form plaques in the brain, has been for many years and remains a favored target for Alzheimer's disease, but attempts so far to target buildup have met with failure.(*See "Beyond A-Beta: New Approaches To Alzheimer's"* — START-UP, *June 2012*.) Many approaches in the past have involved targeting enzymes that cleave amyloid beta out of its precursor, amyloid precursor protein, resulting in a lot of off-target effects, explains Nazneen Dewji, co-founder and CEO of Cenna Biosciences. Also, drugs were given too late, when the damage was already done.

Cenna is aiming for disease-modifying drugs – the Holy Grail in Alzheimer's research. The San Diego-based start-up has developed technology that creates peptide drug candidates that bind the amyloid precursor protein, to prevent amyloid beta buildup in the first place.

The company's lead candidate is the peptide P8, which in a transgenic mouse model of AD, inhibited Abeta production by over 50%. The start-up plans to deliver it intranasally. The approach was detailed in an article by Dewji and colleagues in PLOS ONE published on April 29, 2015. Cenna is aiming to file an IND for the lead candidate by the end of the year and estimates it will cost $5 million to get the drug to that stage, of which $1.5 million has already been granted by the National Institutes of Health.

Founded in 2006, Cenna Biosciences is a spin-off of research dating back to the 1990s at the **University of California, San Diego** by Dewji and S. Jonathan Singer, both professors at UCSD, with funding from the NIH. The pair went on to get an exclusive license for the technology from UCSD and formed Cenna. The company has only two employees, preferring at this time to outsource work to contractors as needed.

Cenna's peptides are covered by five issued composition-of-matter patents in the US and one pending application. The firm also has one issued patent in Australia, one in select European countries and one in China. Applications are pending in Canada and Asia.

Research at UCSD and carried on by Cenna has been supported by a total of $14.15 million raised over the past 12 years, mostly from the NIH. Other sources include the Affordable Care Act's therapeutic tax credit ($250,000) and funding from founders Dewji and Singer ($646,000).

Dewji estimates that P8 could conceivably reach the market within five years, but for now, the company's sights are on getting to the IND stage. The latest grant of $1.5 million from the NIH will be used to conduct pharmacokinetic and pharmacodynamic studies, as well as other preclinical work. Cenna is seeking another $3.5 million to do toxicology studies on the lead candidate, and to advance work on a backup candidate and develop other leads in the firm's portfolio.

The company hasn't yet decided on the clinical trial design for P8, beyond intranasal administration. Cenna has succeeded in getting its peptides through the blood-brain barrier to the brain with this method in animal studies. Intranasal delivery is tried and tested for the peptides, but the start-up is also investigating other routes of administration, such as patches and films. "There are lots of really neat little tricks these days for getting peptides into the bloodstream," Dewji says.

Current approved treatment options for AD – such as **Allergan PLC**'s NMDA receptor antagonist *Namenda* (memantine) and **Eisai Inc./Eisai Co. Ltd.**'s acetylcholinesterase inhibitor *Aricept* (donepezil) – are aimed at relieving symptoms, rather than modifying disease, and have modest effects.

Like other companies, Cenna sees vast unmet need and market potential for a disease-modifying drug for Alzheimer's. Today, some 8 million people have Alzheimer's in the seven major markets, including 5 million in the US. Cenna points out that in the US alone, treatment costs $200 billion annually and this is rising by 19% every year. With better nutrition and health care people are living longer, and of those who live to the age of 90, one in two will have Alzheimer's. By 2020, roughly 80 million people in this country alone will be over the age of 65 and 12 million of them will have Alzheimer's disease.

Research with the amyloid beta target has focused on two main classes of drugs targeting amyloid beta – beta and gamma secretase inhibitors or modulators and monoclonal antibodies – both of which have downsides, Dewji explains. Beta and gamma secretase inhibitors cleave APP but also 50 to 60 other proteins, some of which – "Notch" in particular – have critical functions in the cell. This can result in many undesirable off-target effects, which makes it hard to take the drugs for long, clearly a disadvantage for a chronic disease like Alzheimer's, she says.

Cenna's peptides bind to APP at sites that are different from the beta and gamma catalytic sites and so do not affect the catalytic activities of the enzymes. The binding is believed to prevent the subsequent processing of APP to produce amyloid beta. "The great advantage of our approach is that we can stop the very production of amyloid beta – before it has a chance to accumulate in the brain. And our approach is very specific – affecting only one reaction," Dewji says. Monoclonal antibodies, on the other hand, bind and clear amyloid beta once it is formed and deposited in the brain. Furthermore, the intravenous delivery with monoclonal antibodies is cumbersome, Dewji says.

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But the failures in the field create a challenge for Cenna in educating people about the target and the value of the company's approach. "Unfortunately, what's happened is with all the failures people think of Abeta and their eyes glaze over – they say, 'Oh it's a bad target,'" Dewji acknowledges. "It's not – it's a terrific target. We have a way of avoiding the very things that make the therapies fail. I am hoping they come around to our way of thinking," she adds.

Cenna's approach of targeting APP as a precursor is interesting and novel, says James Hendrix, PhD, director of global science initiatives at the Chicago-based Alzheimer's Association. Most approaches have been focused on using small molecules to target the secretase enzymes. Finding the specific site that is particular to APP and targeting it with a peptide is really a challenge, but Cenna has "apparently been able to overcome that," he says.

Hendrix also notes another Alzheimer's study is testing whether an intranasal spray of insulin can improve cognition in Alzheimer's disease, so other researchers are also seeing the potential for this method of administration.

Edny Inui, PhD, senior scientific analyst at Informa's *BioMedTracker*, comments that Cenna's approach of adding a peptide of the NH2-terminal domain of PS-1 is novel, but questions remain about whether it will be an effective disease-modifying treatment for Alzheimer's. "While it would reduce total Abeta production, I'm not convinced that alone would slow the progression of the disease. While decreases in Abeta were associated with modestly positive cognitive data with aducanumab, we have not seen that play out in a larger study yet," she says. Inui adds that although Cenna's approach is likely better than targeting gamma secretases, there are late-stage drugs targeting beta secretase that have not encountered any major safety issues to date.

Dewji responds that some studies of BACE inhibitors have been encouraging in terms of reducing Abeta, but concerns about potential side effects associated with this approach have been growing, particularly with long-term use, based on published preclinical studies.

For Cenna, financing is also a challenge – development of Alzheimer's drugs is very expensive, costing upward of $200 million to get a candidate through Phase III, according to Dewji. She would like to either partner the drug or have it be acquired by a big pharma that has the expertise and experience to market a drug for Alzheimer's.

Another challenge lies in diagnosis. Ideally in the future, everyone over 65 would get a baseline assessment of Abeta and risk could be identified many years before symptoms of dementia, Dewji says.

Currently, Abeta may be measured on PET scans or in cerebrospinal fluid. PET imaging is a significant and important advance in the diagnosis of Alzheimer's disease and mild cognitive impairment, but it is not 100% accurate and it is expensive, she says. Measurement of biomarkers in CSF is also very useful and the two tests together give significant information, but that method is also not 100% accurate. CSF measurement is also invasive as it requires a spinal tap. "You want a really good reliable diagnostic marker. That's really the biggest challenge," Dewji says.

Hendrix says that he is cautiously optimistic about early intervention. Using biomarkers to identify amyloid plaque buildup early and prevent it is likely the best way to treat this kind of chronic progressive disease. "I would rather prevent damage that occurs in Alzheimer's disease than try to repair the damage, so if we can go in early we may have a better outcome as well," he says. **SU**

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– Emily Hayes