

Science AMA Series: We are Drs. Brenda Moore and Todd Golde, neuroscientists at the University of Florida. Our findings reveal the potential for a drug therapy to be developed that could one day stop the progression of Alzheimer's. Ask Us Anything!

Golde_{Lab}¹and *r/ScienceAMAs*¹

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Abstract

Hello Reddit, I am Brenda Moore, Ph.D., a neuroscientist in Dr. Todd Golde's lab at the University of Florida. We conduct disease-oriented research with a focus on Alzheimer's and other neurodegenerative diseases. And I am Todd Golde, M.D., Ph.D., director of the Evelyn F. and William L. McKnight Brain Institute at UF, where I oversee, champion and facilitate neuroscience and neuromedicine research programs across our campus. I am also director of the 1Florida Alzheimer's Disease Research Center consortium of institutions. We recently published a study featured on the cover of the Journal of Experimental Medicine titled Short A β peptides attenuate A β 42 toxicity in vivo. Our research shows that short Abeta peptides were not toxic in two animal models — a mouse and a fruit fly — and in fact were protective from the toxic effects of Abeta 42. The accumulation of Abeta 42 in the brain is widely recognized as key in promoting Alzheimer's disease. Our findings hold the potential for a drug therapy that could go beyond treating the symptoms of Alzheimer's and target the disease's progression. To read our paper and news release, visit <http://bit.ly/2nocJPI>. We will answer your questions at 1 pm EST — Ask Us Anything! Thank you everyone for your great questions, we enjoyed answering them!

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GOLDE_LAB [R/SCIENCE](#)

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Thanks for doing this AMA. What do you think the is most effective way for regular people to donate to Alzheimer's research for prevention and cure?

[Goldblatt1](#)

(Todd) There are numerous national philanthropic organizations that support Alzheimer's research, including the National Alzheimer's Association, BrightFocus Foundation and the American Federation for Aging Research, among others. There are also local initiatives, so I would suggest contacting your local universities or research institutions. Thank you for your interest in supporting this important cause. We need all the help we can get!

Hi Brenda, and thank you for doing this AMA.

You write:

Our findings hold the potential for a drug therapy that could go beyond treating the symptoms of

progression of Alzheimer's. Ask Us Anything!, *The Winnower* 5:e151740.06659, 2018, DOI: [10.15200/winn.151740.06659](https://doi.org/10.15200/winn.151740.06659)

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Alzheimer's and target the disease's progression.

I'll be honest, that seems a bit much for a set of experiments mostly conducted in flies. That said, I think it is great that you are passionate about the prospects of your work to help AD patients.

My questions for you:

- how is this going to be different from the myriad of other drugs that have targeted the abeta pathway and failed in AD patients (Abeta antibodies, GSIs, BACE inhibitors etc.)?
- if you were CEO of a biotech company trying to decide whether to advance this compound to clinical testing, what are the key experiments you'd want to see to convince yourself that it has a shot where so many other Abeta-targeting drugs failed?

[SirT6](#)

(Brenda) Most in the field believe that Abeta accumulation triggers the disease. It is necessary but not sufficient. The accumulation occurs a decade or so more before symptoms. The real issue is not that the therapy per say was the wrong therapy, it was just initiated at the wrong time. Dr. Golde has written a number of reviews that can be found on Pub Med about this issue. The key to using any drug in a prevention setting will be that it's safe enough. Our data supports that GSMS are one class of compounds to treat Alzheimer's disease would be safe.

So after reading the article I deemed that your findings are only suggestive that this only slows the progression of Alzheimer's. So my question for you is how can this discovery be used to perhaps stop brain degeneration or even cure Alzheimer's. Furthermore, how does this discovery mark an important step in fighting fighting neurodegenerative diseases? Thanks for your time.

[wetardedpanda4](#)

(Todd) As Brenda alluded to in a previous response, we believe that targeting Abeta can prevent or delay Alzheimer's. Current clinical trials suggest that targeting Abeta production in the symptomatic phase of the disease will have little, if any, benefit. Even delaying the onset of symptoms of Alzheimer's disease by 5 years would have a huge public health impact. We must continue to try to develop these strategies that are safe enough for primary or secondary prevention. Notably, we must also develop new therapeutic strategies that may be more effective in the symptomatic stages of the disease.

What challenges came with finding the drug? What brought you guys to Alzheimer's?

[AmazingDayAmazingDay](#)

(Todd) See the comment about GSMS as background. Working with Dr. Eddie Koo at UCSD the Golde Laboratory initially found that some anti-inflammatory agents acted as GSMS. This was somewhat of an accidental discovery, but really launched the field. These initial compounds were not very potent and didn't get in the brain very well. These are properties that prevented re-purposing of these drugs for use in Alzheimer's disease. It's been challenging to find new GSMS that get in the brain, are potent and don't have side effects. The side effects in most cases don't appear to be related to the action of the drugs on Abeta. So we think that with concerted efforts, we can find really safe GSMS and that these could be effective in delaying Alzheimer's disease. I started working on Alzheimer's disease as an M.D. Ph.D. student some 30 years ago and stuck with it. (Brenda) I wanted to work on Alzheimer's due to a family member and watching my mother deal with this difficult situation.

Thank you for doing this! My questions are regarding the shorter peptides' protection.

So the A β 36-40 are non-toxic, and seem to be the preferred pathways versus the longer A β 40-42 peptides.

Are there currently-known direct ways to promote the shorter peptides?

Also, what sort of challenges could you foresee with actual patients?

[TBSquared](#)

(Brenda) Our lab was involved with the discovery of compounds that actually decrease toxic Abeta 42, but increase the shorter Abeta peptides. These compounds are called gamma secretases modulators (GSMs). (Todd) Numerous GSMs have been studied, but it has been challenging to find the right molecule. At least one GSM program remains in clinical development. Our hope is that these findings will spur more research in this area to continue to the search for optimal GSMs that will one day work in patients.

Hello. Great work here, and I too am a Drosophila biologist!

One question about the paper in the link you posted in the experiments where you overexpressed AB42 with other AB forms. Did you check to see whether levels of AB42 expression were changing by adding another UAS-transgene? I have coexpressed multiple genes before, and sometimes adding another UAS-transgene reduces the overall expression of both transgenes. I worry that some of the rescue may be from reduced overall expression of AB42. (I am not saying all of the rescue is due to this, especially since the climbing behavior is robust.)

Have you tried feeding any of these flies the gamma secretase modulators?

[rubber ducky](#)

Contact us offline by email and we can discuss this technical issue with you.

As a best guess that absolutely no one will hold you to, how long do you guys suppose it could be until any such potential drug therapy could be available / helping people?

Thanks for your work! The world needs people like you.

[Pinkerdog](#)

(Todd) GSMs have been in early phase clinical trials and we hope additional compounds will be tested in the future. Unfortunately, prevention studies in Alzheimer's disease take a very long time to complete and we think a GSM will work best in that setting. It would be unlikely to have any drug available for prevention of Alzheimer's disease within a decade. We wish the process was more rapid.

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(Brenda) We agree! But trying to change aging is probably harder than trying to treat or prevent Alzheimer's disease.