Science Translational Medicine Podcast

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Host – Orla Smith

Hello, I'm Orla Smith. Welcome to the *Science Translational Medicine* Podcast for May 25th, 2011. In this show, I will be speaking with Dr. Steven Paul of Weill Cornell Medical College about a new antibody for treating Alzheimer's disease.

Alzheimer's disease affects 30 million people worldwide, and this eye-popping number is set to quadruple in the coming decades. There are currently no drugs that delay the onset or slow the course of this tragic neurodegenerative disorder that begins with mild memory loss and ends with total incapacity. Two studies published in the May 25th issue of *Science Translational Medicine* from the groups of Ryan Watts and Mark Dennis at Genentech now report that an antibody against a brain enzyme called BACE1 may have potential for treating Alzheimer's disease.

Dr. Steven Paul who wrote a Perspective to accompany the papers now joins us on the line to discuss the new findings.

Interviewer – Orla Smith
Welcome, Dr. Paul, and thanks for joining us.

Interviewee – Steven Paul
Thank you.

Interviewer – Orla Smith
So what does the enzyme BACE1, also called beta secretase, do in the brain and how is it implicated in Alzheimer's disease?

Interviewee – Steven Paul
Well, BACE1, or beta-secretase 1, is an enzyme that processes the amyloid precursor protein at the N-terminus and is one of two main enzymes or enzymatic cleavages that occur to release the amyloid beta peptide, which is a peptide that aggregates and deposits in the brain of patients who develop Alzheimer's disease—the peptide that forms the so called amyloid plaques or neuritic plaques in the brain. So by inhibiting BACE1 one should theoretically inhibit the formation of this peptide and reduce a number of these plaques or prevent these plaques from forming in the first place.

Interviewer – Orla Smith
So why did the Genentech researchers decide to develop an antibody against BACE1 rather than a small molecule drug for example?

Interviewee – Steven Paul
Well, that's a good question. I think that the scientists at Genentech being very, very proficient in developing antibodies—human monoclonal antibodies for treating a variety of diseases—had this technology at their disposal and, you know, took the chance that it would be possible to inhibit this enzyme with an antibody as opposed to a small molecule drug. Most investigators in industry pursuing BACE inhibitors are pursuing small molecule drugs since they're more likely to get into the brain and get into neurons where BACE is expressed and therefore were more likely or are more likely to inhibit the enzyme potentially for therapeutic purposes.

Interviewer – Orla Smith
What trick did they use to get their antibody across the blood-brain barrier?

Interviewee – Steven Paul
Well, they used a trick that had been suggested many years ago by Bill Partridge and colleagues. They used a mechanism that is known to get large proteins across the blood-brain barrier—a mechanism called receptor mediated transcytosis. This is a mechanism that is known to shuttle things like insulin and transferrin into the brain, and they created an antibody that would bind to one of these receptors—in this case the transferrin receptor—and then using the other variable region, the other arm of the antibody, they would tackle, if you will, BACE1. So by using these bispecific antibodies they were able to get an antibody across the blood-brain barrier in sufficient concentrations to actually have an effect on inhibiting BACE and the production of Aβ. And the trick they used, which was really quite simple but elegant I guess in its simplicity, is that by lowering the affinity for the transcytosis receptor—in this case the transferrin receptor—they found that the antibody not only bound to this receptor located on the endothelial cells of the capillaries that formed the blood-brain barrier but were also able to not only transcytose the antibody but to release it into the brain parenchyma surrounding neurons. In the past, high affinity antibodies, these receptors, got to the capillary endothelial cell membrane but didn't get released into brain to the same extent as what the scientists at Genentech found with their antibodies.

Interviewer – Orla Smith
What did they find when they tested their anti-BACE1 antibody in animal models?

Interviewee – Steven Paul
Well, remarkably they found a significant inhibition of BACE1. They had actually shown earlier than that—earlier than the in vivo experiments—that in vitro the antibody was quite specific inhibiting BACE1 and not a closely related enzyme called BACE2, or cathepsin D. And they found, in fact, by engineering the antibody using this transcytosis receptor, if you will, they were able to get sufficient concentrations of the antibody in brain to the target, which was BACE1, of course, and they observed significant

reductions in the production of Aβ by inhibiting the enzyme they could inhibit the processing of APP, the amyloid precursor protein, to the Aβ peptide.

Interviewer – Orla Smith
So will passive immunization with a therapeutic antibody have potential for treating Alzheimer's disease?

Interviewee – Steven Paul
Well, that's a very good question and frankly is largely unanswered. What this particular antibody and others will do is test a specific hypothesis, the amyloid cascade hypothesis. And indeed, if that hypothesis is correct, we could see a slowing of the progression of the disease or ultimately even a prevention of the disease. The caveat, however, is that we now know through lots of biomarker studies—imaging studies and cerebrospinal fluid biomarker studies—that amyloid deposition is a very early event. Probably begins some 10 to 20 years before the onset of dementia. And, in fact, by the time a patient becomes even mildly impaired cognitively it appears that amyloid deposits have already pretty much peaked or plateaued in the brain. So the open question on the table so to speak is whether anti-amyloid therapies will, in fact, work in patients who already have mild to moderate disease or even mild cognitive impairment or what we call the prodrome of AD. And, of course, these are hypotheses that can be tested. Having said that it is quite possible that treating patients who are presymptomatic—let's say several years before the onset of MCI, mild cognitive impairment, or AD—might be even more effective. And the field is going to have to work this out over time. But, at least we have better tools, better drugs to reduce the formation of these Aβ peptides and potentially reduce the formation of amyloid, so we now can test these hypotheses.

Interviewer – Orla Smith
Can this new method for getting antibodies across the blood-brain barrier be applied to other therapeutic antibodies for treating other diseases?

Interviewee – Steven Paul
Yes, I think one of the exciting features, if you will, of the work by the group at Genentech has been or is—because what they've done is really resurrected an old idea showing that it now works pretty well—that these antibodies can be engineered to get across the blood-brain barrier and then theoretically could be useful for treating a variety of neurodegenerative disorders and potentially other brain disorders. So there are a whole variety of potential targets—whether they be neuropeptide transmitters or whether they be receptors for neurotransmitters or whether they be other pathological proteins such as tau or Huntington's or any of the α synucleins for Parkinson's. So I think it's a very, very exciting approach, and you could call it a new approach, if you will, to potentially treating a variety of brain disorders.

Interviewer – Orla Smith
Dr. Paul, thank you so much for joining us today and for taking the time to discuss these two fascinating papers.

Host – Orla Smith
That was Steven Paul of Weill Cornell Medical College in New York. Check out the papers by Yu *et al.* and Atwal *et al.* and the accompanying Perspective by Dr. Paul on the *Science Translational Medicine* Web site at stm.sciencemag.org.

I'm Orla Smith, thanks for listening!

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