米国製薬業界週報 U.S. Pharmaceutical Industry Newsletter

Targeting the Complement Pathway in Neurodegenerative Diseases

Ted Yednock, Ph.D., Chief Scientific Officer, and Douglas Love, President and CEO, Annexon Biosciences

Based in South San Francisco, Annexon Biosciences is targeting the classical complement pathway to treat neurodegenerative and ophthalmic disorders. We spoke with Dr. Ted Yednock, Annexon's Chief Scientific Officer, about the company's pipeline. Toward the end of our conversation, Douglas Love, Annexon's President and CEO, joined to talk about the company's partnering strategy.

You are targeting the complement pathway, and my understanding is that, in the case of Alzheimer's disease, complement mediated neurodegeneration is more of an adjunct to the amyloid hypothesis rather than an alternative to it. Is that correct?

Yednock: Yes, and what is exciting about it to us is that complement mediated neurodegeneration seems to be a pathway common to nearly all neurodegenerative diseases. The complement pathway is a way of amplifying and propagating a neurodegenerative response, regardless of the way it was initiated.

We are inhibiting C1q, which is the initiating molecule of the classical complement cascade. It has been shown to function normally in development for eliminating excess or redundant synapses. Then it appears to be reactivated through the normal aging process. In development, we know that C1q can distinguish between weak and strong synapses. As we go through the developmental window, the weak synapses are eliminated by the classical complement pathway being activated and calling in immune cells that then phagocytose or eliminate the synapses directly.

During the normal aging process, C1q appears to be accumulating on synapses. It is not activating, and it is not eliminating the synapses as it does in development, unless there is some sort of secondary hit. An inflammatory response, for example, will allow a number of other complement components to be expressed that allow C1q to activate the complement pathway, causing the synaptic elimination process.

In Alzheimer's for example, amyloid itself can activate C1q, and other ligands are accumulating, such as CRP, which can activate C1q. With this initiation of a disease process, then C1q can play a very important role in activating the complement cascade and propagating the neurodegenerative response.

With ANX005 and ANX007, in inhibiting C1q, are you thereby dampening down the inflammatory response?

Yednock: Exactly. It is inhibiting the classical pathway at its initiating point. We are inhibiting C1q and all the downstream complement components that come after it.

Will ANX005 and ANX007 not only work to stop or slow neurodegeneration, but also prevent damage and allow synapses to repair themselves?

Yednock: Yes. We know from the developmental pathway that by eliminating C1q during the early developmental window, synapses that otherwise would have been eliminated are retained, and they are still functional in the adult. We know that by blocking C1q, we will prevent synapses from being eliminated. In the case of neurodegenerative disease, we believe that by inhibiting C1q and preventing the synaptic loss, we are protecting the neurons first of all, which is very important, and we hope that by inhibiting the inflammatory response we are shifting the balance from synaptic elimination towards synaptic regeneration or synaptic formation.

In treatments that are targeting amyloid beta, one of the big issues has been whether you can attack the disease early enough before the damage has occurred. In this case, does inhibiting the complement pathway offer any advantage in terms of being able to arrest the degeneration before it has progressed too far?

Yednock: We believe so. The reason for that is that synaptic elimination is very closely associated with neurodegeneration and, in fact, precedes it. In neurodegenerative diseases, one of the first pathological findings is that synapses are declining. It is an early part of the process that precedes neuronal death, but then synaptic elimination is happening throughout the entire neurodegenerative process. In fact, the synapse number is a very good correlate with neuronal function and cognition. Unlike amyloid, for which there really is not a very good correlation between the level of amyloid and cognitive function, with synapse number there is a very strong association.

Are there any challenges or difficulties involved in designing or dosing ANX005 or ANX007 to inhibit C1q in the entire classical complement pathway without affecting the body's innate immune response to viruses and bacteria?

Yednock: The complement pathway is important for immune defense. Fortu-

nately, in the immune defense system, there is a lot of redundancy. By targeting C1q, we are selectively inhibiting the classical pathway, but we are leaving the lectin and the alternative complement pathways fully intact. These will still be available for inhibiting bacteria and viruses. We think it is particularly important that we are doing this in adults, so that the immune system has already matured and has already developed immunity against a number of these different pathogens.

Ted Yednock, Ph.D

Douglas Love

Please describe the developmental status of ANX005 and ANX007.

Yednock: Both are going to enter the clinic next year, 2017. We will have three separate development programs. One will be in Alzheimer's and Huntington's disease. Another will be in an ophthalmic indication. The third will be in an antibody-mediated autoimmune disease.

Lastly, please tell us about your partnering strategy.

Love: We will be running multiple phase 1 programs over the course of 2017. In both the neurodegenerative indications, as well as in the ophthalmic space, we are open to discussions about collaborations. We would like to work with partners that have expertise and capabilities in the respective areas of ophthalmology and neurology. From a regional perspective, we have started to look into the incidence and prevalence of the diseases we are targeting in different regions, such as Japan. We see that there is a reasonably high level of incidence and prevalence for those diseases in Japan. We do not presently have capabilities and expertise in that market, so if we were able to align with a strong Japanese partner, that would be of interest to us.

Profiles

Ted Yednock, Ph.D.

Dr. Yednock was previously Chief Scientific Officer for Prothena Corporation, Head of Research for Elan Pharmaceuticals and a Scientist at Athena Neurosciences. While at Athena, he was the scientific inventor of Tysabri, a blockbuster monoclonal antibody for the treatment of multiple sclerosis. Dr. Yednock earned his B.S. in biology and chemistry from the University of Illinois and his Ph.D. in anatomy and cell biology from the University of California San Francisco.

Douglas Love

Mr. Love previously served as Head of Operations for Elan Pharmaceuticals, where he led the Tysabri multiple sclerosis and Alzheimer Immunotherapy franchises. Mr. Love is a corporate attorney by training, and prior to joining Elan served as an associate at the law firm Orrick, Herrington & Sutcliffe, Corporate Counsel at Amgen, Inc., and as Section Corporate Counsel at Genentech Inc where he led the bio-oncology legal team. Mr. Love holds a J.D. with great distinction from McGeorge School of Law, Sacramento, CA, and a B.S. in business administration from the University of Southern California.