Big Things Sometimes Come from Small Places

A short history of Alzheimer's Disease and a New Approach to Treating the Disease from a Small Company in Berwyn, PA

When Dr. Maccecchini, the CEO and founder of Annovis Bio (NYSE:ANVS), was completing her PhD in biochemistry in 1978, little was known about Alzheimer's as a disease compared to what we know today. Prevalent in the late 70's was the "cholinergic hypothesis" of Alzheimer's, which ascribed the memory loss and other symptoms associated with Alzheimer's to a deficiency of a neurotransmitter called acetylcholine, which is a chemical important to proper memory function. But medications to correct the acetylcholine deficiency were shown to improve attention slightly, but to have no effect on the progression of the disease.

Alzheimer's was discovered over 100 years ago by a young psychiatrist named Dr. Alois Alzheimer, after he noticed unusual changes in the brain tissue of a female patient who died with severe dementia. He described what we now call plaques and tangles, which led to new approaches to remove the plaques and the tangles.

In the late 80's, researchers discovered that in Down Syndrome and Alzheimer's patients the amyloid protein was present in plaque. By the 90's researchers determined that mutations increasing the production of amyloid led to Alzheimer's disease. Thus the "amyloid hypothesis" became the prevailing theory of the cause of Alzheimer's. The amyloid hypothesis states that high levels of amyloid lead to a high number of plaques, which dramatically "increases the risk for developing clinical Alzheimer's." (Bright Focus Foundation, "The History of Alzheimer's Disease").

Therefore, for the next 20 years the most favored approach to treating Alzheimer's disease was to remove the amyloid and plaque.

Unfortunately, drug candidates targeting amyloid and plaques have failed in numerous clinical trials. In fact, over $40 billion has been spent to develop drugs to treat amyloid. But these approaches have resulted in over 500 failed clinical trials and we still have no drug that slows the progression or reverses the effects of Alzheimer's.

A few years ago, researchers started directing their efforts in targeting the protein Tau, which forms into tangles. Tau, just like amyloid, damages and destroys brain cells. Unfortunately, newly released data show that drug candidates targeting Tau are also failing in clinical trials.

Touted as a potential groundbreaking drug for Alzheimer's, developed by Roche and AC Immune, it was announced in September that in a 500-patient phase two clinical trial, their anti-tau drug candidate semorinemab failed to meet its endpoints of improving cognitive function. In sum, every drug candidate targeting the amyloid, Tau have failed.

A recent article in Scientific American, sums up the problem:

"Finding drugs to treat dementia is especially difficult because the brain is relatively inaccessible and harder to test and deliver compounds to, explains Simon Lovestone, a professor of translational neuroscience at the University of Oxford, UK. Less is known about the biology of the condition than, say, cancer."

TIME FOR A NEW APPROACH TO TREATING ALZHEIMER'S DISEASE

Enter Dr. Maria Maccecchini, a brilliant scientist with over 65 patents, many of them focused on neurodegenerative diseases. With a PhD in biochemistry from the Biocenter of Basel and two post-doctoral degrees, one at the Roche-Institute of Immunology, and another at Caltech, she has a had long and successful career. She has worked for Bachem Bioscience, the US subsidiary of Bachem AG, Switzerland and was head of Molecular Biology for Mallinckrodt. In 1992, she founded Symphony Pharmaceuticals, focused on protecting nerve cells from dying, ultimately selling the company to Transgenomic in 2001.

In May of 2008, she founded Annovis Bio to develop better therapeutics for Alzheimer's, Parkinson's and other neurodegenerative diseases . She took the company public on the NYSE American in January 2020, raising $14 million. She and her team have taken a new approach to treating Alzheimer's disease. "The drug industry invested a lot of time and money into the hypothesis that sticky brain plaque causes Alzheimer's disease, but this idea, while interesting, has ultimately been proven wrong," she stated. "Lately we have seen that the tau hypothesis also does not improve memory and learning and does not slow the course of the disease, so we have pioneered a new approach."

During her 30 years of research on neurodegenerative diseases she discovered that chronic and acute brain insults lead to high levels of neurotoxic proteins and inflammation. To understand her approach, it is important to understand that in healthy nerve cells communication within nerve cells as well as with other nerve cells and body parts is carried by small packages containing neurotransmitters, nerve growth factors and other important molecules. This flow of information is called axonal transport – the information highway of the nerve cell. For a nerve cell to be healthy, axonal transport needs to be unimpaired from the cell body through the axon to the synapses and back. High levels of neurotoxic proteins limit the flow and speed at which neurotransmitters travel along the axon resulting in compromised nerve function and impairment of the information highway causing a toxic cascade leading to nerve cell death that results in the loss of cognitive and motor function.

Thus she developed ANVS401, Annovis' lead compound, which is the only drug to attack multiple neurotoxic proteins simultaneously. In a proof of concept study with mild cognitive impaired patients, ANVS401 lowered the levels of APP/AB, tau/p-tau and aSYN back to the levels seen in healthy volunteers. Remarkably, the drug lowered the levels of three neurotoxic proteins known to cause Alzheimer's and Parkinson's. By doing so, the drug improved the information highway and lowered inflammation. In three animal studies of cognition, ANVS401 increased memory and learning in Alzheimer's and Downs Syndrome mice and in traumatic brain injury rats.

In three further animal studies of function, ANVS401 normalized movement and function in Parkinson's and Frontotemporal Dementia mice and preserved sight in glaucoma rats.

A recent article published in the prestigious *Alzheimer's & Dementia*: The Journal of the Alzheimer's Association, further validated Annovis' lead compound as the only drug to improve axonal transport, the information highway of the nerve cell. The publication of peer-reviewed data was from a study conducted at Dr. William Mobley's lab at the University of California San Diego's Department of Neurosciences. Professor Mobley, MD, PhD, is one of the world's leading experts on Down Syndrome and axonal transport. The paper supports the basic hypothesis of the efficacy of Annovis' drug, that it

lowered levels of neurotoxic proteins, normalized axonal transport, lowered inflammation and led to normal mouse behavior.

Annovis is currently in two phase 2 clinical trials in Alzheimer's and Parkinson's with up to 15 clinical sites. The endpoints of the trials are the steps of toxic cascade: a decrease in neurotoxic protein levels, increase in neurotransmitters and neurotrophic factors, lowering of inflammatory proteins and lowering of neurodegenerative markers. The Company expects to receive interim results from these trials in the first quarter of 2021. If the results meet the clinical endpoints, this could lead to a partnership with a major biopharma for a phase 3 clinical trial. This new approach could change forever the way the scientific community thinks about Alzheimer's and Parkinson's. Indeed, Dr. Maccecchini's novel idea for treating neurodegeneration could make all the difference in the world. Big things sometimes come from small places. At a current market cap of only $35 million, when the results from the trial are announced in the first quarter, the stock could experience an explosive breakout to levels more in line with industry comps, which trade at significantly higher market caps.