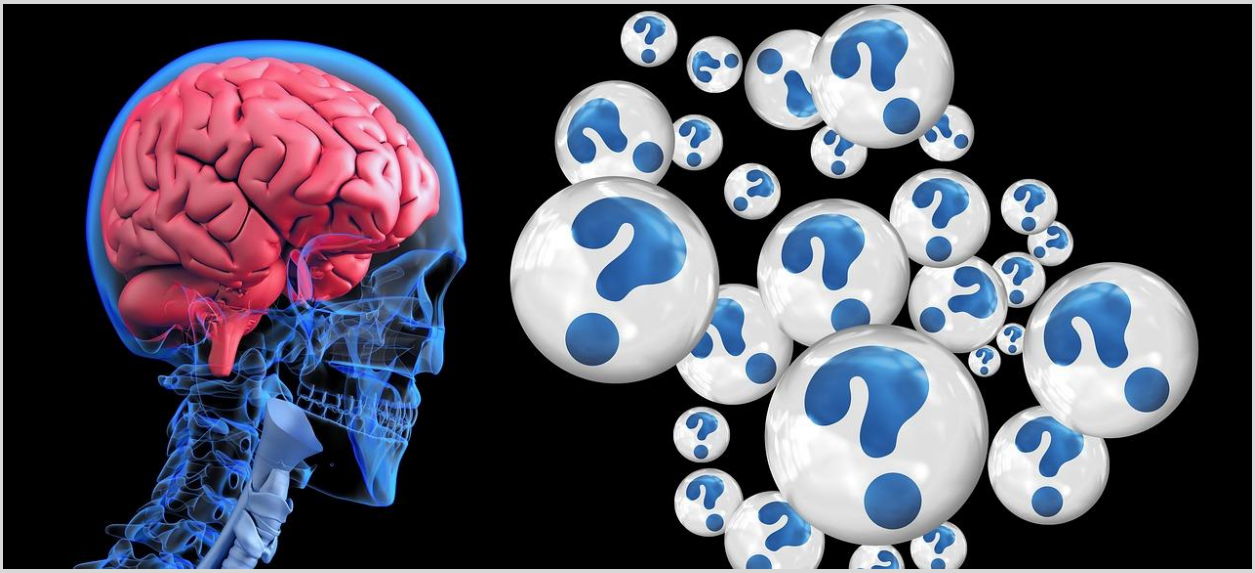

Layperson's Primer on Alzheimer's, framed in the context of biotech super startup AC Immune. Investment guide follows.

In this special report, I thought it might be useful to shed light--in more of a layperson's context--on 1) what is currently known in the scientific/medical community about Alzheimer's disease and, 2) a top investment opportunity.

What is Alzheimer's?

Alzheimer's disease (AD) is a brain disorder that seriously affects a person's ability to carry out daily activities. Symptoms include memory loss, confusion, trouble performing familiar tasks, and changes in personality and behavior. There is no cure for Alzheimer's disease, but medications are available that can help with memory and behavioral problems.

AD is the most common form of senile dementia, accounting for up to 70% of cases.

The clinical symptoms of AD usually occur after age 65, but changes in the brain which do not cause symptoms and are caused by Alzheimer's, may begin years or in some cases decades before. Although the symptoms of AD begin in older people, it's not a normal part of aging.

At this time there is no cure for Alzheimer's, but there are treatments that can help some patients with the signs and symptoms, so they do not affect them as gravely. There are also treatments which slow down the disease so the damage to the brain does not occur as quickly. There are also certain personal habits that people can learn which may help to delay the onset of the disease.

While it is not yet known exactly what causes Alzheimer's, there are a number of risk factors which may make a person more susceptible. Some of these risk factors are genetic; changes to four different genes have been found which increase the risk.

The current lifetime risk for a 65-year-old person to get Alzheimer's disease is estimated to be at 10.5%. It is the sixth leading cause of death in the US, resulting in about 83,500 deaths a year.

According to the Mayo Clinic, there's no specific test today that confirms you have Alzheimer's disease.[1] Your doctor will make a judgment about whether Alzheimer's is the most likely cause of your symptoms based on the information you provide and results of various tests that can help clarify the diagnosis.

Doctors can nearly always determine whether you have dementia, and they can often identify whether your dementia is due to Alzheimer's disease. AD can be diagnosed with complete accuracy only after death, when microscopic examination of the brain reveals the characteristic plaques and tangles.

Treatment

Current Alzheimer's medications can help for a time with memory symptoms and other cognitive changes. Two types of drugs are currently used to treat cognitive symptoms:

Cholinesterase inhibitors. These drugs work by boosting levels of a cell-to-cell communication by providing a neurotransmitter (acetylcholine) that is depleted in the brain by AD. The

[1] https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/diagnosis-treatment/drc-20350453

improvement is modest. Cholinesterase inhibitors can improve neuropsychiatric symptoms, such as agitation or depression, as well. Commonly prescribed cholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon).

Memantine (Namenda). This drug works in another brain cell communication network and slows the progression of symptoms with moderate to severe AD. It's sometimes used in combination with a cholinesterase inhibitor.

Steve's Take:

As noted above, efforts to treat Alzheimer's disease have been singularly abject failures. Such efforts have been traditionally grounded in one of two alternative theories: First, that the pathology is driven by plaques of amyloid-beta (Aβ) proteins or, secondly, by bundles of their tau counterparts instead. Until now, the majority of treatments to enter the clinic have just targeted Aβ plaques, but the case for aiming for tau bundles in addition to, or instead of, these plaques is steadily gaining traction.

Rising Swiss star AC Immune SA (Lausanne) is one of the few companies with a drug targeting tau bundles, and one of the very few with programs in both tau and Aβ. Its lead candidate is crenezumab, which has made it as far as Phase 3 for Alzheimer's treatment and Phase 2 for prevention in partnership with Genentech/Roche. The company has other antibodies and vaccines for Alzheimer's, in addition to various other diseases.

Andrea Pfeifer, co-founder and CEO of AC Immune, sat down with Evelyn Warner of Labiotech.eu to explain the approach her company hopes will break through this so-far impenetrable wall.

Pfeifer started out as toxicologist in oncology before she moved into entrepreneurship, says Warner. She left Germany after her PhD at the University of Würzburg for a stint at the NIH, but moved back for personal reasons:

> *"It was by pure chance that I ended up in Nestlé for two years, which turned into sixteen years," she told Warner.*

Pfeifer eventually left Nestlé because she saw the opportunity to help people even more when she met the founders of AC Immune, where she found her niche as a co-founding CEO.

Warner posed several prescient questions on the direction of AC Immune's promising, workable approaches for successful AD treatment.[2] The following are excerpts from that interview.

> *Q: What excited you about joining the company? What was it about the technology that drew you in?*
>
> *A: The SupraAntigen and Morphomer platforms produce highly specific antibodies, vaccines and small molecules that bind to misfolded proteins. These proteins are difficult to target because they are still recognized as the body's own proteins, even though they are harmful. The line between harmful and benign comes down to a conformational change in protein structure that adds another level of complexity to the challenge of hitting a target.*
>
> *Also, our scientific founders were very established, and they were all very successful in initiating products--they were scientists, but they also had a lot of entrepreneurial spirit.*
>
> *Q: What do you think makes Alzheimer's so challenging?*
>
> *A: One of the three pillars of our R&D strategy is biomarker development, because this allows you to select patients and follow their treatments. I think that in areas where we don't yet have a treatment, it's exactly because of a lack of diagnostic.*

> *When we entered the field, it was clear to us that we needed a safe and pathological protein-specific antibody for efficacious treatment. Aβ plaques and tau bundles occur normally in the body, and it's by a still unknown mechanism that these proteins change their structure and conformation to become pathological.*
>
> *At this point, they can aggregate to form the fibers that are hallmarks of Alzheimer's.*

[2] https://labiotech.eu/alzheimers-disease-acimmune-andrea-pfeifer/

We were extremely lucky that crenezumab is particularly sensitive to structures called oligomers, the most toxic subunits of the pathological proteins. These are what really kill neurons when you put them together, and crenezumab has a really high affinity for them.

At the time we started developing crenezumab, oligomers hadn't reproducibly been isolated, but with a little bit of luck, we got things right. For tau, it's much more complicated because there are many subtypes, and we have to make sure that we're binding them all. We did a long selection process for this.

When we started the company in 2003, there were about 23 antibodies against Aβ in development, so we were definitely late; but now there are only two left in late stage Phase 3 clinical development, aducanumab from Biogen and crenezumab from us. The really challenging thing is that we don't know how much we actually need in the brain in order to really have an effect.

Today, between 1% and 5% of what you find in the plasma goes into the brain. It's a low concentration, but people showed that this concentration is actually enough to have the antibody act. You need to have this concentration to be effective, and it's probably related to equilibrium so that the microglia absorb it and activate the complex.

The reason why crenezumab is given in such a high amount--60 milligrams per kilogram--is of course linked to this. The studies showed that even 15mg has an effect, but the higher the better the percentage that goes into the brain. In a way, we've solved the problem, but the biggest challenge in developing an Alzheimer's drug is perhaps delivering drugs in a high enough quantity to the brain.

Q: How do you select patients and design a clinical trial for such a long-term disease?

A: We pre-select the patients for Aβ positivity using Aβ imaging; more and more we use tau imaging as well, using a PET imaging agent we developed. Studies are increasingly done in patients who have Aβ plaques and cognitive impairment, but not yet any clinical symptoms. We want to go as early as possible, and it's very important. It's even more essential to find the right population with biomarkers before you start.

A: How would you characterize the roles of A-beta and tau proteins?

Tau in Alzheimer's is often described as an Aβ-mediated tauopathy, meaning it works well as a predictor. AC Immune started its first program in 2007, and in 2012 we made the first deal. It wasn't really known how an antibody could treat tau until a year or so before that, and now it's known with certainty that tau can infect cells in a prion-like way. Companies now choose their assets based on whether they can inhibit that spreading.

Aβ came first because genetically it's very strongly linked to Alzheimer's, so it's probably the starter while tau is the spreader.

Bottom Line:

Why buy AC Immune?

The amyloid hypothesis is one hypothesis for understanding and treating AD, says Seeking Alpha.[3] But it has lost some support following several high-profile Phase 3 failures. The market for a successful treatment of Alzheimer's disease is enormous, and AC Immune is well positioned with a strong cash balance, confident partners, and a growing pipeline.

AC Immune is trading well below its IPO price, with expectations for its leading candidate diminished due to recent failures by other drug companies. But the company is in a strong financial position, and their leading candidate still holds promise. The market for the treatment of AD is huge, and AC Immune is now among the frontrunners.

Leerink Partners' Paul Matteis rates the odds of success for AC Immune's crenezumab at 35%.

The latest update from AC Immune's first-quarter 2017 financial results showed CHF 138 million in cash and cash equivalents (all results are reported in Swiss francs, which are at close to parity with US dollars at the moment). I agree with those who believe with their high cash balance, the company appears well positioned for further development of its pipeline. In addition to their

[3] https://seekingalpha.com/article/4087044-ac-immune-compelling-speculative-investment?page=2

partnership with Genentech, they have partnerships with Janssen (of Johnson & Johnson), Biogen, and Piramal Healthcare on other drug candidates.

While much is made of AC's leading candidate crenezumab, they also have multiple candidates based on the competing tau hypothesis of AD treatment, as well as candidates designed to treat Down syndrome, glaucoma, and Parkinson's disease. This added diversification provides some downside protection if crenezumab fails in Phase 3.

Analysis: High Risk/High Reward

There are currently only a handful of drugs cleared by the FDA to treat Alzheimer's disease, and they are focused on treating the symptoms. The current market for Alzheimer's treatment is estimated to be several billion dollars, but could grow considerably if a drug that successfully treats or prevents the disease is approved. While odds are against any given candidate, the potential jackpot is gargantuan.

Let's do some numbers:

AC Immune's IPO price was $11 in September of 2016 and it soared 45% on the first day. After struggling for months falling well below its IPO price last summer, AC Immune has fought back and continues to rebound. As of today (January 22, 2018), its share price is now 23% ($13.57) higher than its IPO price.

All said and done, AC Immune's 1-year return is a wretched -1.12%. It's market cap is $755.4 million; definitely small-cap territory. But among the analysts covering it, the average rating is a Buy (as of December, 2017), with a 12-month mean price target of $21.67. That's an upside spread of 63%.

With no negative news coming out of the company's own drug trials, and with the stock trading at a significant discount to mean price target, there couldn't be a better time to get involved.

High Risk

While the upside in royalty payments from its big-pharma partners is massive if they succeed in creating an FDA-approved treatment for AD, there is significant risk as well.

AC Immune is a young company that has never taken a candidate through to commercialization, so there is execution risk. The science of AD is uncertain, so it is entirely possible that increases

in beta-amyloid in the brain of Alzheimer's patients is a side effect and not a cause of the disease or its symptoms. If this turns out to be the case, then AC Immune's leading candidate crenezumab won't amount to a hill of beans.

There is also a risk that even if the amyloid hypothesis holds true, that crenezumab could still fail to deliver the promised results.

Investing in AC Immune is definitely risky, but at the current depressed prices, with a promising, distinctly specialized candidate for treating Alzheimer's disease, and a strong business model, it's a rational bet rather than a pure gamble. I believe the name warrants a small-stake buy for the highly risk-tolerant portfolio.

Thank You for Subscribing!
Steve Walker