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INmune Bio's Alzheimer's Candidate Is a Potential Best-In-Class Drug

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INmune Bio

INmune Bio's Alzheimer's Candidate Is a Potential Best-In-Class Drug

- Alzheimer's Disease (AD) is a large biotech and healthcare opportunity, costing the U.S. national healthcare system hundreds of billions of dollars.
- The Alzheimer's drug development landscape has not seen much success, but we estimate this is because the industry has not focused on the most important part of AD pathophysiology, namely chronic inflammation.
- We believe that INmune Bio (NASDAQ: INMB) has one of the best approaches in the industry for treating AD neuroinflammation.
- In our opinion, the market potential of INmune's Alzheimer's disease treatment XPro1595 in the U.S. alone undervalues the stock. We believe that further great opportunities could abound with XPro1595, a platform drug for combatting inflammation in a non-immunosuppressive and non-destructive manner.

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Info as of December 30th, 2020

Ticker:	INMB (NASDAQ)
Stock Price:	$15.67
Market Cap (M):	$211
Enterprise Value (M):	$186
Dividend/Yield:	None
Shares Outstanding (M):	13.45
Average Daily Volume (3 mo.):	144,000

Please refer to important disclosures on pages 27 and 28

INmune Bio's Alzheimer's Candidate Is a Potential Best-In-Class Drug

Alzheimer's Disease (AD) represents one of the largest, most prevalent, and economically burdensome diseases in the United States, and many pharmaceutical and biotechnology companies have attempted to treat the disease but most have completely failed to show significant benefit in clinical trials. The Alzheimer's drug treatment landscape is bleak; an estimated 150-300 drugs have failed to show benefit in clinical trials, and most of these drugs have directly or indirectly targeted amyloid proteins—fibrous, extracellular deposits of protein—in the brain that cause neuronal dysfunction. Plaques and tangles as the cause of neuronal dysfunction is a hypothesis that the scientific community has taken as a fact. This becoming fact has stalled progress in AD treatments for nearly two decades. In our opinion, the Alzheimer's field needs to move past the graveyard of failures that are the amyloid beta (AB) hypothesis, and onto another, less pigeon-holed and more broad-based, hypothesis, the hypothesis of inflammation.

On November 6th, 2020, an FDA expert panel gave a fairly negative review of Biogen's (BIIB $244.86) adacanumab, a monoclonal antibody directed against amyloid beta for the treatment of mild Alzheimer's. With the drug showing a potential effect, but two phase 3 trials and a phase 2b trial offering what could be considered as conflicting evidence, it does not look like Biogen will secure approval for adacanumab. This news resulted in a haircut of $15-20 billion dollars in market cap, indicating that the market value of an Alzheimer's approval could be worth up to $20 billion dollars. The massive potential translates our interest to a promising microcap company whose drug we think could be a best-in-class product.

We think that a company called INmune Bio (INMB $17.22) is most likely to benefit from this transition away from the amyloid beta hypothesis, and that it positions itself at the forefront of this new paradigm with a best-in-class anti-inflammatory, non-immune suppressing drug. Furthermore, we estimate INmune may be rather undervalued and that its Alzheimer's drug has a sound chance to show significant clinical benefit in Alzheimer's patients, which would be nothing short of a massive medical breakthrough as there are no approved drugs that modify the disease progression; the only drugs that exist to treat Alzheimer's simply treat the symptoms. Before diving into what INmune does and why its drug is an excellent approach to AD, we must first review and understand some context, economic burden, history, and currently understood pathophysiology of AD.

Alzheimer's Disease: Overview

According to the Alzheimer's Association, AD (Alzheimer's Disease) will cost the United States healthcare system $305 billion this year, including an estimated 18.6 billion hours of caregiver labor, accounting for $244 billion of the total. On top of that, it is estimated that over 16 million Americans provide unpaid care for people with AD or other dementias. In fact, AD is the 6th leading cause of death in the USA, and 1 in 3 seniors dies with some sort of dementia —more than breast and prostate cancer combined. It is clear that AD is a significant challenge in the United States and the world, affecting an estimated 5.8 million Americans. These patients tend to live about 8-10 years after symptoms begin.

Most people understand the significance a disease-modifying therapy could bring to their own families and loved ones. Alzheimer's, of course, progresses from mild to severe, where patients go from forgetfulness and lack of judgement to eventually having a hard time performing basic tasks like swallowing food, loss of speech, incontinence, and forgetting the identity of close friends and loved ones.

Given the massive healthcare expenditures and significant pain Alzheimer's causes to families and friends, Alzheimer's represents one of the largest unmet needs and growing market opportunities in healthcare. In fact, it has been labeled the most expensive disease in America and therefore offers a large opportunity for companies that can develop disease-modifying therapies (drugs that actually curb the disease's progression, rather than treating symptoms).

A History of Alzheimer's Pathogenesis Hypotheses

In 1906, a clinical psychiatrist and neuroanatomist, Alioz Alzheimer, reported a "peculiar severe disease process of the cerebral cortex" at a German psychiatry meeting, describing a middle-aged woman he had been following due to her abnormal behavior and mental health—aggression, paranoia, sleep problems, memory disturbance, and confusion. He recorded some other observations in similar patients, such as neurofibrillary tangles and protein plaques, as well as inflammation, throughout his career. But ultimately, much like famous artists, his work and the name "Alzheimer" was not widely recognized until he passed away.

Decades ago, two primary hypotheses arose for AD, one about amyloid beta (Aβ) aggregation and one about inflammation. This was based on the first GWAS studies that identified amyloid in sporadic disease, which was consistent with familial studies that previously demonstrated the high penetrance of AD in families that carried the gene that increases amyloid plaques. Decades ago, Howard Fillit, a geriatrician and neuroscience expert, theorized that inflammation, as measured by increased levels of TNF, a key inflammatory protein, causes AD. Four months later, the father of the Aβ hypothesis wrote a paper explaining why Aβ, a protein that can aggregate and create plaques, is the primary cause of AD. There were two major themes—one was Aβ and one was inflammation, but the data at the time supported moving in the amyloid direction. Later, in the 1990s, tau (as another misfolded and aggregating protein found in the AD brain) was categorically lumped into the amyloid beta hypothesis. Most of academia accepted these misfolded proteins as the cause, or at least the primary theory of Alzheimer's, and from then on, drugs tested for Alzheimer's were mainly focused on amyloid beta. STAT News has a brief and helpful review of Aβ and Aβ-related drugs (including BACE inhibitors) that have been tried over the years. Despite hundreds of failed amyloid beta-targeting Alzheimer's drugs, pharma as an industry continues to pursue Aβ-related Alzheimer's drugs. Our thoughts are that amyloid beta plays a role in AD, but it is not necessarily a primary driver of the disease.

Alzheimer's Disease Pathophysiology

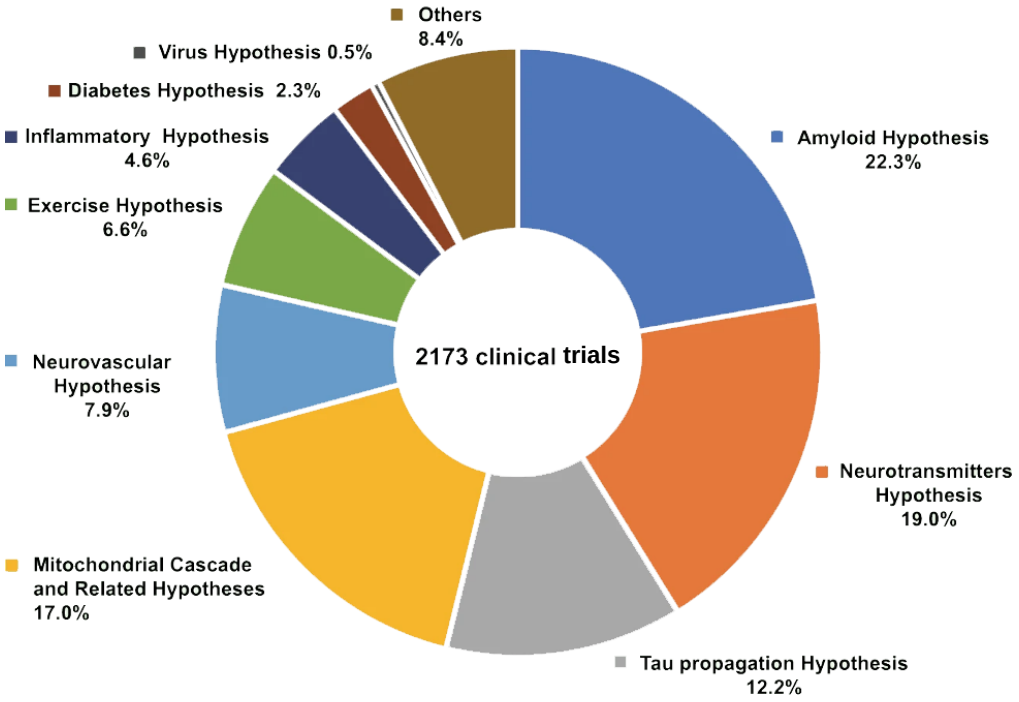
Alzheimer's Disease is characterized by plaque and fibril clumps building up in the brain and the concurrent and progressive decline in cognitive function. Neurons and their connections (axons) degenerate and die over time, leading to impaired memory, confusion, and loss of other mental functions.

Over the years, various hypotheses have arisen that attempt to nail down the cause of AD. One of the first was the cholinergic hypothesis, which attributed AD to the lack of a neurotransmitter called acetylcholine, which is critical for proper memory function. In fact, cholinesterase inhibitors, which prevent the breakdown of acetylcholine, are approved for Alzheimer's and other diseases. However, for Alzheimer's, they improve symptoms but do not affect the disease progression, only offering benefit for a matter of months.

Many of these hypotheses have attempted to reconcile hallmark observations (i.e. plaque buildup, neurofibrillary tangles, and lack of neurotransmission) of the Alzheimer's brain with disease pathophysiology—a cause or reason for

these observations, but all the pharmaceutical industry has to show for these efforts so far are these drugs that help relieve symptoms—nothing that modifies the disease's progression or underlying pathology.

Various Hypotheses of Alzheimer's Disease in Clinical Trails up to 2019



Source: Liu, P et al. (2019). History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduction and Targeted Therapy, 4(1).

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Many of these hypotheses have attempted to reconcile hallmark observations (i.e. plaque buildup, neurofibrillary tangles, and lack of neurotransmission) of the Alzheimer's brain with disease pathophysiology—a cause or reason for these. Despite the various hypotheses that have arisen, it seems that the industry and academia at large are very hesitant to drop the focus on amyloid beta and tau as the primary driver of the disease. While there is no doubt that amyloid beta and tau dysfunction play a role in AD, we believe that other biological mechanisms are overlooked because of the industry and academia's laser focus on amyloid beta and tau. For instance, we believe that systemic inflammation and neuroinflammation are a primary driver of AD, but emerging hypotheses attempt to simply tie immune/inflammatory responses back to amyloid beta, claiming that the brain's inflammation is a response to amyloid beta plaques. Even in high-profile journal reviews on AD pathophysiology, the inflammatory hypothesis is joined at the hip with amyloid beta and tau fibrils, and their effects on microglial activation. In the coming years, we expect this paradigm to shift, at least somewhat.

Undoubtedly, these interactions are relevant, but are microglia the only cells in the brain that can exhibit and propagate inflammation? Astrocytes are well recognized now as a prime player in neuroinflammation. Are the proteinous fibrils so central to the disease process, or are they simply a biomarker or hallmark that sets Alzheimer's apart from other forms of dementia, such as Parkinson's Disease (PD)? For instance, proteinous aggregates called alpha synuclein are also found in PD in a part of the brain called the substantia nigra, as opposed to the beta-amyloid buildup in the entorhinal cortex, hippocampus, and eventually the cerebral cortex, in the AD brain. In practice, pathophysiology is not so clear cut. For instance, Lewy bodies (the PD equivalent of tangles and plaques) are found widespread in AD patients and plaques and tangles are widespread in PD patients. Also, plaques and tangles are found within the brains of a large number (~30%) of "control brains" - people that die without symptoms of dementia. The difference between those that develop dementia and those who don't is the presence of inflammation in the brain.

Fortunately, the Alzheimer's Drug Discovery Foundation seems to have recognized this tunnel vision approach by big pharma years ago:

> *"The Alzheimer's Drug Discovery Foundation made the strategic decision to halt funding for anti-amyloid drugs back in 2010. The pharmaceutical industry was investing billions in these programs, and we chose to focus our efforts on advancing innovative and diverse drug targets that seemed more likely to be contributing factors to the disease. As we age, a host of biological processes occur that can damage our neurons, leading to Alzheimer's and other dementias. As Alzheimer's disease progresses, inflammation increases, our brain's ability to use energy decreases, vascular issues can worsen, and epigenetic changes accrue. The ADDF is funding multiple drugs that target each of these processes."*

In reality, it is probable that many of the hypotheses are still relevant in AD, and that many of these mechanisms play a part in AD pathophysiology, which may eventually lead to drug combination therapy for AD patients. However, as this report will outline, the inflammatory hypothesis actually encompasses other hypotheses and pathological features of AD. Thus, targeting inflammation may be a broad enough approach to AD treatment to affect significant, disease-modifying, or progression-modifying change. In the following sections, select Alzheimer's hypotheses will be examined.

The Amyloid Beta Hypothesis

The most common hypothesis is the amyloid beta hypothesis, which relates directly back to Alioz Alzheimer's findings of "clumps" in his patient's brain. The amyloid beta (AB) hypothesis has evolved over the years as various drugs have been tested, targeting different kinds of amyloid (plaques, soluble, oligomerized, etc.) in different patient populations (mild, moderate, severe). The basic viewpoint of the Aβ hypothesis is that beta-amyloid peptide aggregation is the primary mechanism that initiates neuronal degradation. The beta-amyloid aggregates into fibrils, oligomerizes, or remains soluble in some form, and each form contributes to pathology by irritating neurons or neuron's axons, in some way.

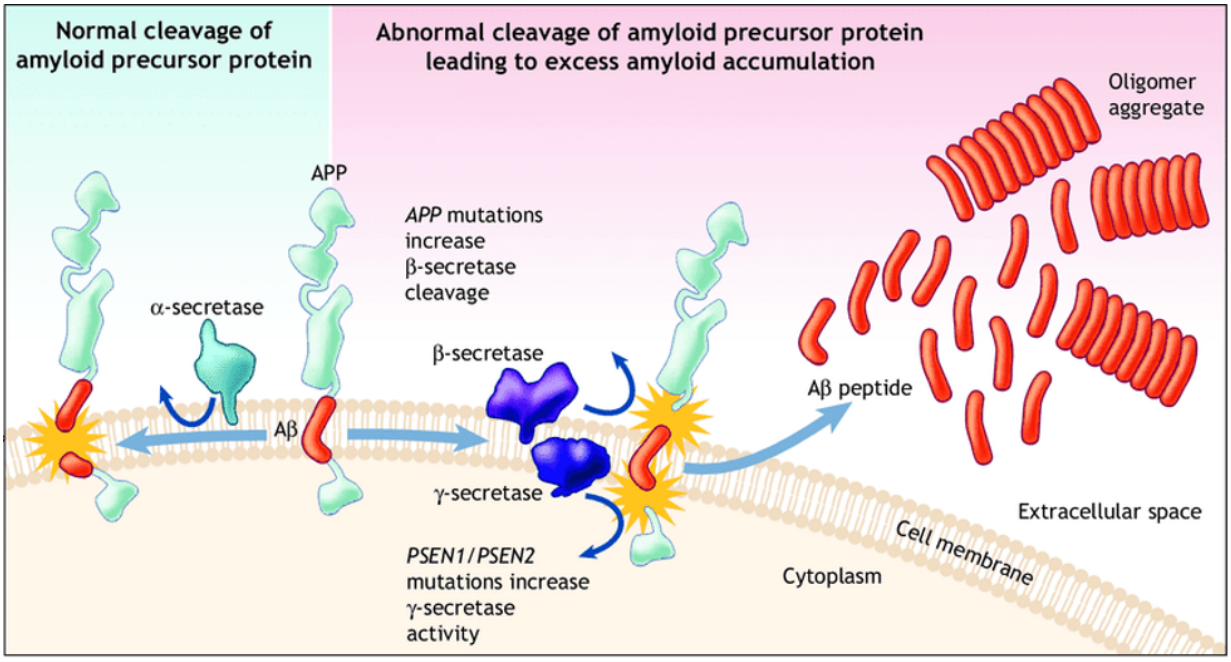
> *"Hardy and Higgins proposed the amyloid cascade hypothesis in 1992, positing that deposition of Ab in the brain is the initiating step of AD pathogenesis, leading to subsequent tau deposition, neuron and synaptic loss, and cognitive decline (Hardy and Higgins, 1992). This hypothesis has been the leading model of AD pathogenesis since it was first proposed, although portions have been revised or supplemented over time (Musiek and Holtzman, 2015; Selkoe and Hardy, 2016)"* (Long, J. M., & Holtzman, D. M. (2019). Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell, 179(2), 312-339.)*

Certain research has indicated that all Aβ drug trials have resulted in failure, and that the true underlying pathology is actually related to tau aggregates (neurofibrillary tangles), which are found inside the cells as opposed to outside the cells. Research has cited that specific problems with the Aβ hypothesis were: **1)** extracellular Aβ fibrils do not induce neurofibrillary tangles or neuronal cell death in mouse models of deposited Aβ; **2)** Aβ oligomers and fibrils did not impair memory or induce neuronal death in gene modified Aβ42 overexpressing mouse models; **3)** immunotherapy induced clearance of Aβ fibrils (drugs that induce the immune system to eat amyloid beta) in various studies did not improve symptoms or intracellular tau accumulation [1,2,3]. Furthermore, recent imaging improvements have shown that senile plaques (amyloid beta) in some elderly patients *without* dementia is as severe as those *with* dementia. This aggregated evidence suggests that Aβ is not cytotoxic, does not induce AD, and does not correlate well with AD.

Thus, there are conflicting bits of evidence surrounding the Aβ hypothesis, and in our opinion, it is more likely that Aβ plays a role in AD pathophysiology and is an important biomarker, but it is not a primary driver. According to a 2019 Alzheimer's review,

> *"In summary, the available data still strongly support the central role of pathologic Ab accumulation in mediating AD pathogenesis as outlined in the original description of the amyloid cascade hypothesis, although* ***its mechanism may be less direct than originally anticipated and requires further clarity via ongoing studies."***

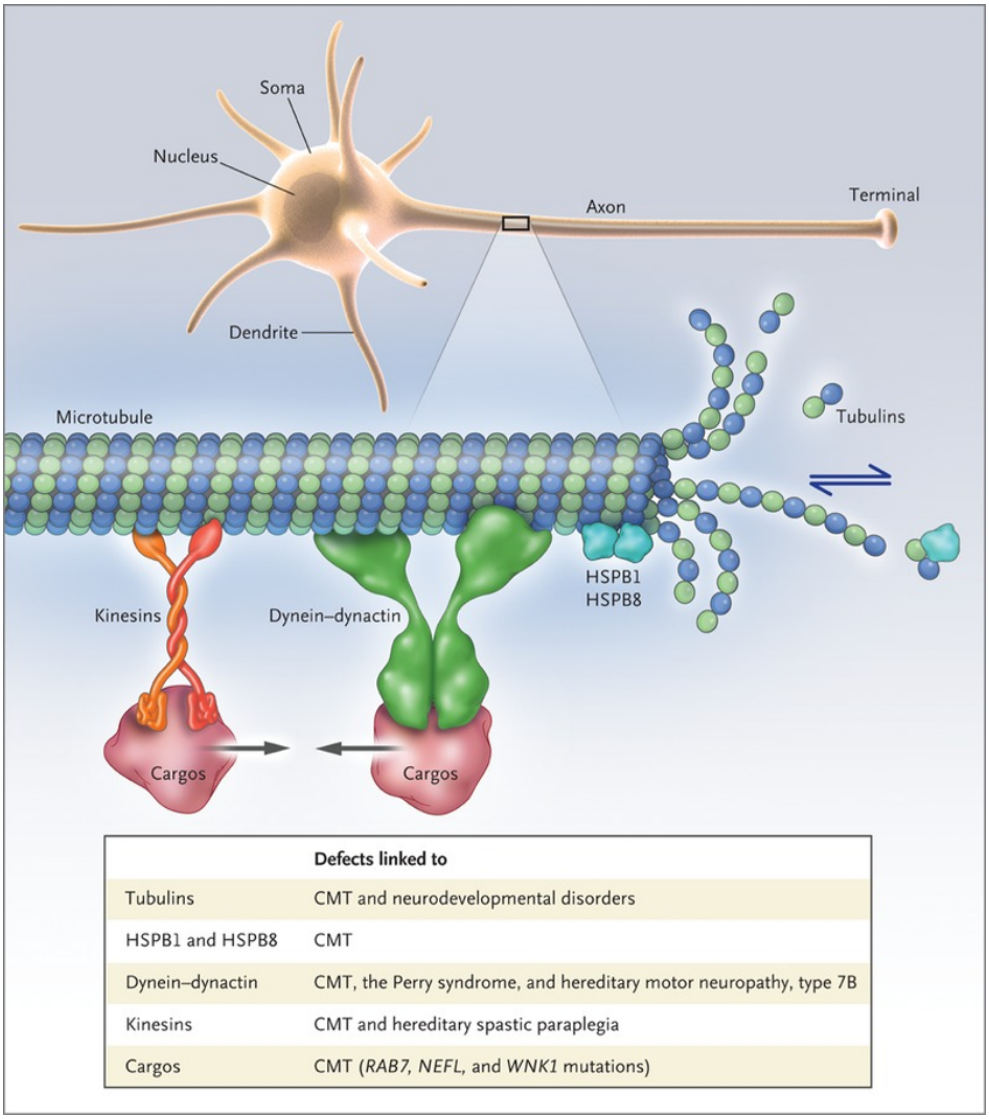
Some research suggests that tau dysfunction is actually more relevant for AD pathophysiology, although there are overlapping common mutations in the Aβ precursor protein (APP) that could link the two hypotheses and explain why Aβ might be such a relevant biomarker—that Aβ aggregation is a downstream effect of dysfunctional APP degradation, as shown below. The mutated APP protein gets clipped by enzymes improperly, and that results in the production of amyloid beta fragments that will turn into fibrils. The leftover APP-C terminal fragments—what's left of the APP within the cell's membrane after it has been clipped by the wrong secretases—are toxic to the cell, promoting axonal and synaptic defects. These defects cause tau mislocalization and contribute to tau pathology, which will be briefly summarized in the following section.



Source: Patterson, C. (2008). Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. *Canadian Medical Association Journal,* 178(5), 548-556.

Notably, a γ-secretase inhibitor, intending to reduce Aβ fibril formation (red, above), failed a large scale clinical trial, increasing AD symptoms compared with placebo, as it likely resulted in an increase in APP-C terminal fragments on the cells' surfaces, which are reportedly neurotoxic. It is also reported that, since APP and its metabolites affect multiple functions in the brain, altered APP metabolism may have various effects in the brain, and APP and accumulation of APP-C terminal fragments rather than Aβ fibrils might be more relevant in AD pathology, supporting the idea that Aβ is more of a biomarker. Overall, though, we believe these very specific approaches are narrow in focus and don't necessarily encompass the entirety of AD pathophysiology. However, these findings do support a focus beyond amyloid beta.

The Tau Hypothesis

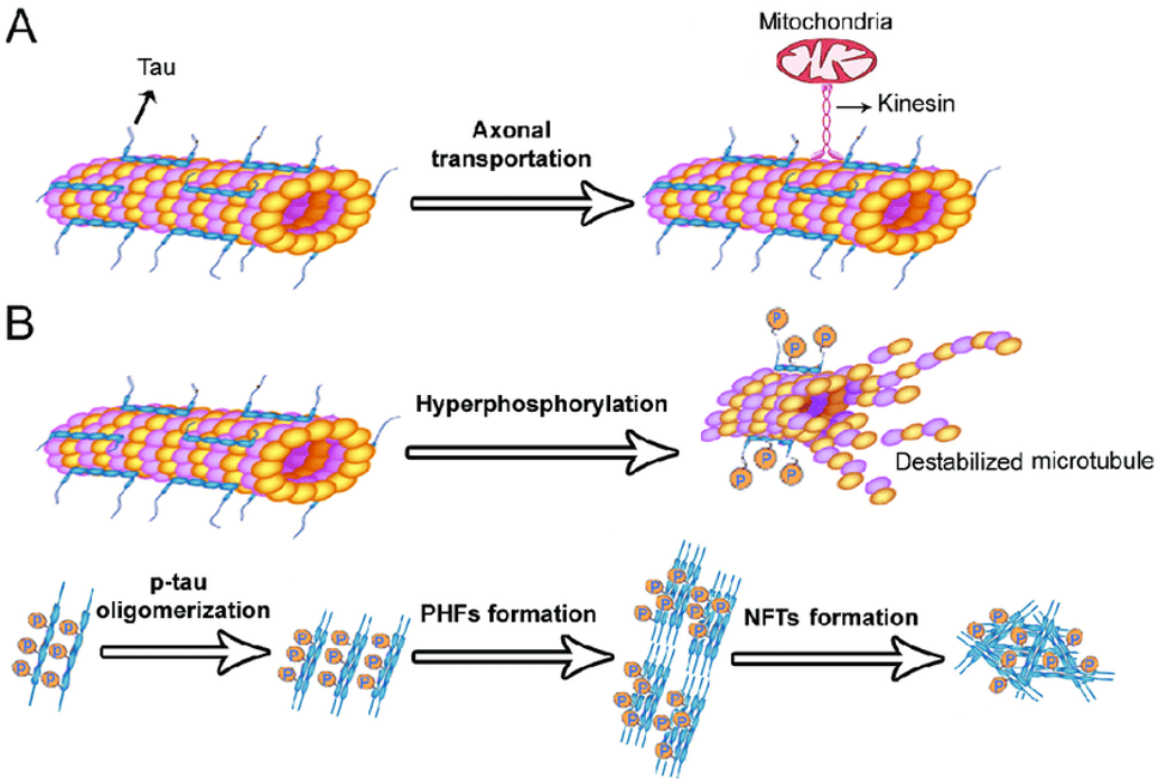


	Defects linked to
Tubulins	CMT and neurodevelopmental disorders
HSPB1 and HSPB8	CMT
Dynein–dynactin	CMT, the Perry syndrome, and hereditary motor neuropathy, type 7B
Kinesins	CMT and hereditary spastic paraplegia
Cargos	CMT (*RAB7, NEFL,* and *WNK1* mutations)

Source: Erika L.F. Holzbaur, Ph.D., and Steven S. Scherer, M.D., Ph.D. *Microtubules, Axonal Transport, and Neuropathy.* N Engl J Med, Dec 2011; 365:2330-2332.

The tau hypothesis focuses around dysfunction of the tau protein. In a nutshell, tau is used by neurons to stabilize microtubules, which are structural and transport tracks that support a neuron's cytoskeleton and transport various organelles and other substances. A graphic of microtubules that run along axons is depicted above, along with transport proteins that use the microtubule as a track. The key problem with tau in Alzheimer's is that tau is hyperpho-

sphorylated (cellular alteration of a protein's conformation/shape/function by the addition of a phosphate group somewhere on that protein), which causes tau to lose its ability to support axon microtubules. This results in destabilization of microtubules, which causes slow and steady degeneration of axons. Additionally, hyperphosphorylated tau has an increased ability to form NFTs and compromise neuronal function intracellularly, interfering with mitochondrial function.

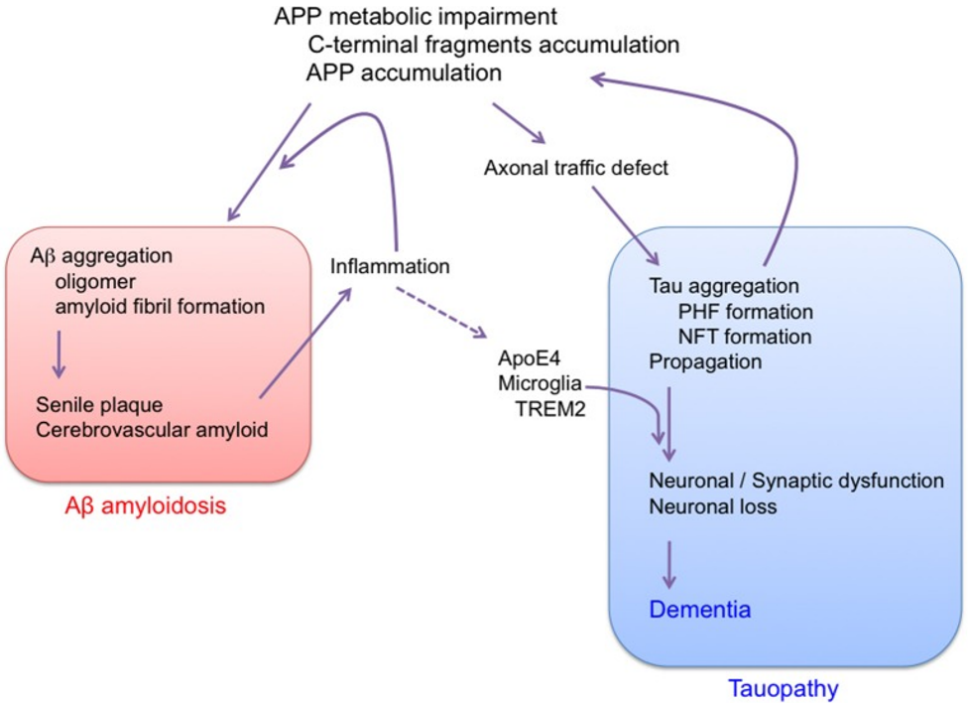


Source: Mishan, M. A. et al. *Pathogenic Tau Protein Species: Promising Therapeutic Targets for Ocular Neurodegenerative Diseases.* J Opthalmic Vis Res. 2019 Oct-Dec; 14(4): 491–505.

Also, tau has been shown to have a "seeding" effect, where misfolded tau acts in a prion-like manner to promote the misfolding of native tau monomers. In other words, tau misfolding and aggregation promotes tau misfolding and aggregation. It can also be transmitted synaptically to other distant neurons in this manner. Thus, tau dysfunction promotes tau dysfunction, and tau dysfunction has been shown to spread across the brain over time.

Notably, it has been shown in preclinical models that insulin deprivation causes tau hyperphosphorylation, which helps explain the correlation between AD and diabetes. Also of interest is that various preclinical Alzheimer's models show that Aβ can induce tau pathology, but not the other way around. However, this doesn't necessarily mean that *all* the negative effects of Aβ are caused by Aβ's effect on tau. For instance, Aβ has been hypothesized to reduce cerebral blood flow by attracting neutrophils to congest capillaries. It is then possible for this interaction to promote more Aβ via hypoxia (due to the lack of blood flow) and increased BACE1 expression, a gene that encodes beta-secretase, which cleaves APP.

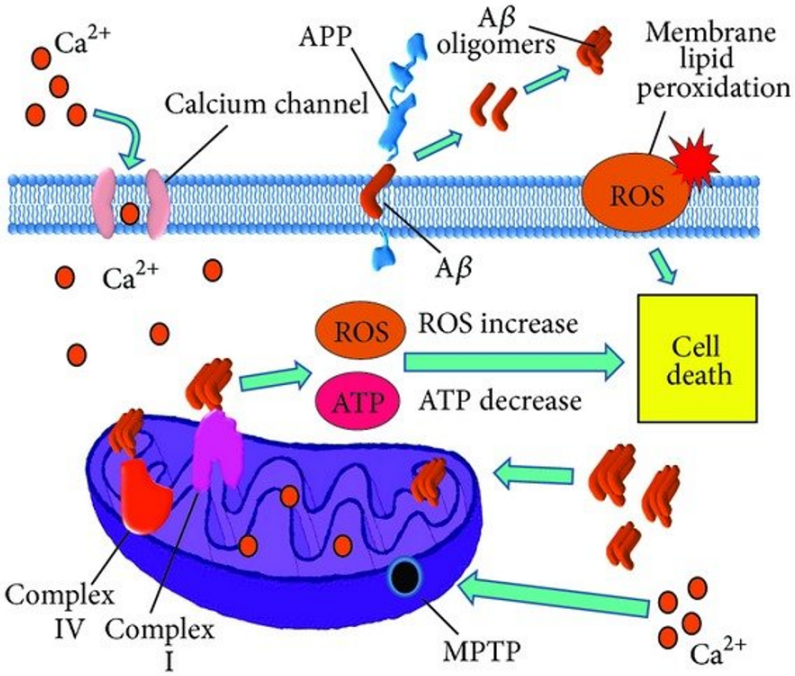
It appears that Aβ and tau are important pieces of the AD puzzle, but it is fairly clear from decades of clinical trials that Aβ is probably not a therapeutic target that can single-handedly and significantly ameliorate AD progression. It is also increasingly clear that tau pathology, triggered by impaired APP metabolism, is a more important driving factor in Alzheimer's than Aβ, which seems more like a downstream biomarker for impaired APP metabolism. A summary of the proposed web of interactions is shown below:



Source: Kametani, F., & Hasegawa, M. (2018). Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimers Disease. *Frontiers in Neuroscience*, 12.

Mitochondrial Hypothesis

Another interesting hypothesis in AD is the mitochondrial cascade and its effects on metabolism and ROS (reactive oxygen species). We already noted that hyperphosphorylated tau can affect mitochondrial function, but there's more to this theory as a standalone hypothesis. In the AD brain, mitochondrial population is reduced in neurons and oxidative stress is increased. Thus, metabolism is affected, both overall and in individual mitochondria. There is interplay between mitochondrial dysfunction, inflammation, Aβ, and tau:

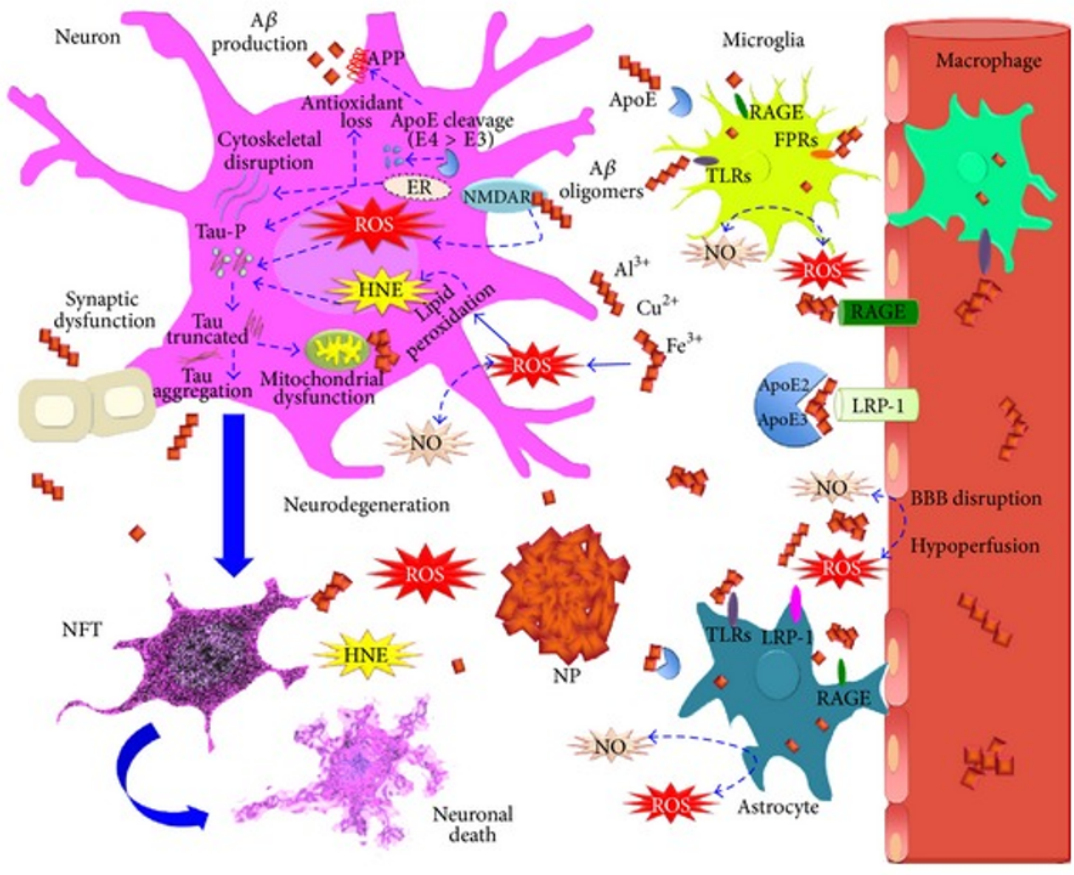


> *"Evidence indicates the critical role of Aβ metabolism in prompting the oxidative stress observed in AD patients. However, it has also been proposed that oxidative damage precedes the onset of clinical and pathological AD symptoms, including amyloid-β deposition, neurofibrillary tangle formation, vascular malfunction, metabolic syndrome, and cognitive decline."*

Source: Luque-Contreras, D. (2014). Oxidative Stress and Metabolic Syndrome: Cause or Consequence of Alzheimers Disease? *Oxidative Medicine and Cellular Longevity, 2014,* 1-11.

Amyloid beta overproduction can damage mitochondria, causing ROS production to increase (bad) and ATP production to decrease (bad). The reduction in ATP leads to impaired neurotransmission and altered ATP-dependent ion channel activity, leading to ion balance changes, i.e. calcium influx into the cell, which causes excitotoxicity. On the other hand, ROS increases lead to membrane damage and lipid peroxidation, which can trigger apoptosis (programmed cell death), and electron transport chain impairment (further impairment of mitochondrial function). In this way, amyloid beta, ROS, and metabolic impairments are subject to their own feedforward loop.

However, even though the mitochondrial cascade and oxidative stress theory sounds like another completely separate hypothesis, it is commonly tied back into the amyloid beta hypothesis, as Aβ fibrils are theorized to be a major cause of oxidative stress, as shown in the graphic below, and these interactions tie into tau hyperphosphorylation, too:



Source: Luque-Contreras, D. (2014). Oxidative Stress and Metabolic Syndrome: Cause or Consequence of Alzheimers Disease? *Oxidative Medicine and Cellular Longevity, 2014,* 1-11.

However, some evidence suggests that mitochondrial dysfunction, including mitochondrial Aβ and ROS are detectable before Aβ plaques form. This information suggests that mitochondrial dysfunction happens before Aβ buildup in AD pathophysiology, again suggesting that amyloid beta is not the primary cause of AD. All in all, metabolic dysfunction and oxidative stress play a role in AD, but these hypotheses are inevitably tied back to the Aβ hypothesis, which is largely a failed therapeutic target. The pharmaceutical industry has been laser-focused on the Aβ theory for decades, and it is high time that other approaches are recognized, especially those with broader scopes.

Additional Pathology In Alzheimer's

Alzheimer's patients rarely only have only Aβ and tau aggregations in their brains. Typically, various vascular issues are comorbid with AD, including beta-amyloid deposits in brain arteries as well as atherosclerosis and the associated transient ischemic attacks or full-blown strokes. In fact, one study showed that at autopsy, ~80% of AD patients are shown to have vascular disease.

Vascular disease also in general reduces blood, nutrient, and oxygen flow to the brain, contributing to the aforementioned hypoxia, inducing BACE1 expression and inflammation. Lack of blood flow can also lead to blood-brain barrier (BBB) degradation, which allows unwanted material to flow into the brain. In Alzheimer's, a degraded blood-brain barrier has been linked to impaired glucose transport as well as diminished beta-amyloid and tau clearance.

Central Unifying Hypothesis: Inflammation

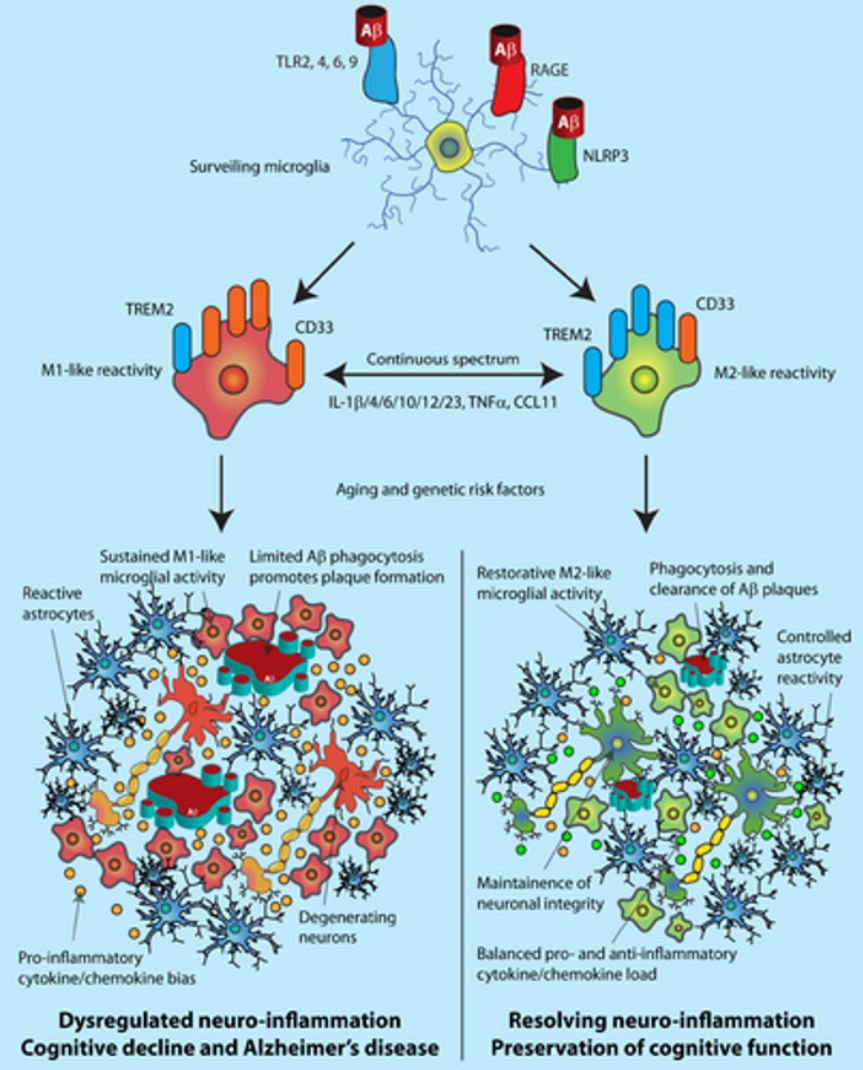
In our opinion, inflammation is an all-encompassing concept in Alzheimer's disease, affecting processes that affect the amyloid beta, tau, mitochondrial, oxidative stress, and vascular disease. In fact, some of the new amyloid beta targeted therapies are focused on the CNS immune system (microglia) removing amyloid beta damaged axons and Aβ plaques, suspecting that microglial efficiency in this process determines clinical outcome. But general chronic neuroinflammation, not just related to the microglial response or relating directly to plaques, might be a better focus:

> *"The presence of a sustained inflammatory response in the brain of patients with AD was, at one point, thought to be reactive to the neuronal loss occurring in the disorder. However, substantial body of research has now demonstrated that a persistent immune response in the brain is not only associated with neurodegeneration but it also facilitates and exacerbates both Aβ and NFT pathologies. Furthermore, it has been suggested that the inflammatory response may provide a link between the initial Aβ pathology and the later development of NFT"* (Kinney, J. W., et al. (2018). Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*, *575-590).*

Inflammation and Amyloid Beta

Mechanistically, inflammation plays into virtually all of the above hypotheses. There is evidence that inflammation plays a role in causing Aβ deposition, as it has been demonstrated that elevated IL-1 levels are responsible for increased APP production and subsequent Aβ load. There is also a TNF promoter on the APP gene. Backing up inflammation's translation to Aβ fibrils is the observation that cerebral Aβ deposits increase 1-3 weeks after head trauma, which is well known to cause a large inflammatory response. In addition, that Aβ deposition triggers more inflammation, as shown below. Certain players, as mentioned later in this report, in the AD space are aiming to polarize the microglial response to the "M2" phenotype—resolving inflammation and repairing tissue—to induce Aβ clearance

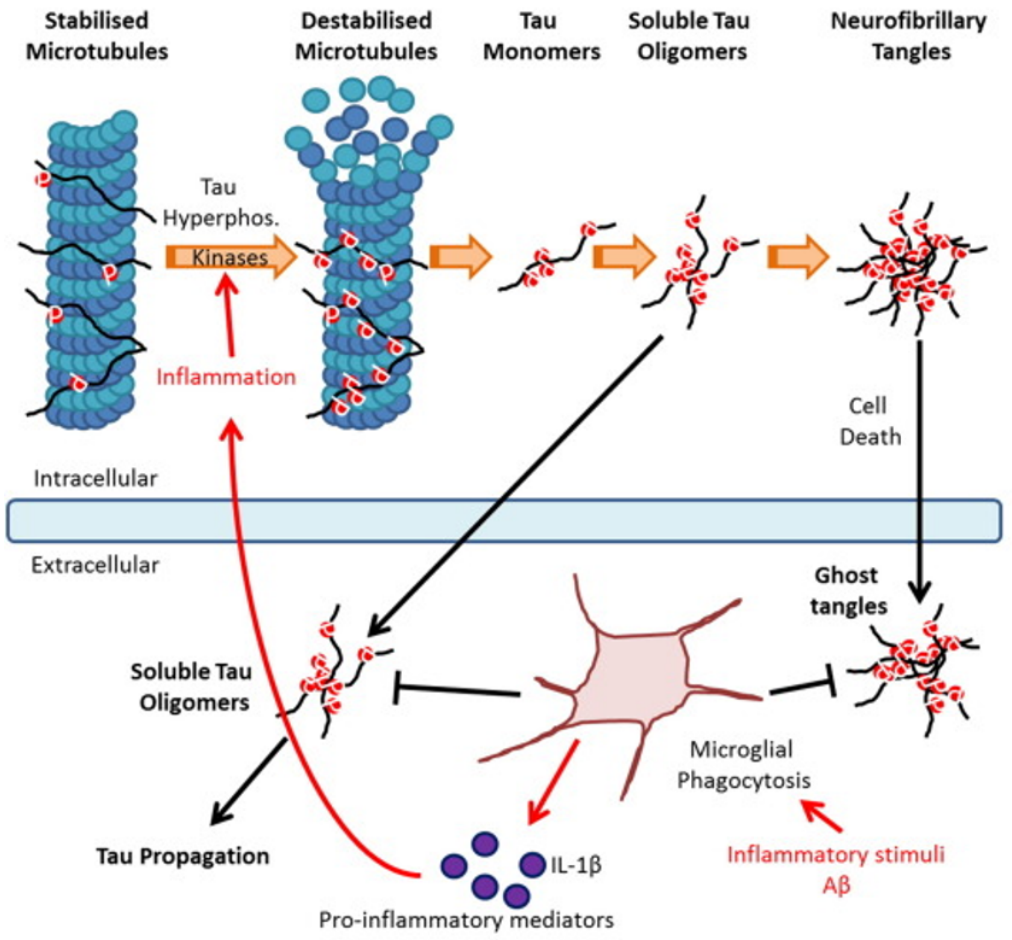
and decrease inflammation generally referred to as the "M1" phenotype). It should be noted that current research suggests that microglia specifically might not fit into those two categories as well as other peripheral immune cells such as macrophages. However, these therapies overall intend to change the phenotype of the microglia to curb inflammation. The microglial phenotype and its effect on the brain is depicted below.



Source: Minter, M. R et al. (2015). The contribution of neuroinflammation to amyloid toxicity in Alzheimers disease. *Journal of Neurochemistry, 136*(3), 457-474.

Inflammation and Tau

Inflammation also influences the processing of tau. There's evidence that misfolded and fibrilized tau is a result of activation of the NLRP3 inflammasome, which contributes to the hyperphosphorylation of tau. Of course, proinflammatory cytokine TNF-alpha promotes the activity of the NLRP3 inflammasome by priming it, although so do other inflammatory factors such as DAMPs (damage associated molecular patterns), PAMPs (pathogen associated molecular patterns), galectins, IL-1β, and Aβ. Other cytokines such as IL-1β have also been shown to stimulate kinases that hyperphosphorylate tau (through inducing IL-6). We have already reviewed how tau dysfunction, amyloid beta, and inflammation can propagate each other. The graphic below shows the feedforward loop of inflammatory mediators (such as IL-1β), how they affect kinase activity, and how those kinases affect tau. The tau pathology can cause cell death which can further influence inflammation.



Source: Barron, M. (2017). A state of delirium: Deciphering the effect of inflammation on tau pathology in Alzheimers disease. *Experimental Gerontology, 94*, 103-107.

Inflammation and Mitochondrial Dysfunction

Current evidence supports associations between inflammation and mitochondrial dysfunction as key mechanisms in neurological diseases. Basically, inflammation can cause mitochondrial dysfunction, and mitochondrial dysfunction can propagate inflammation. Inflammatory mediators such as cytokines produced by activated microglia, infiltrating immune cells, and potentially other native cells, can trigger transmembrane signaling that results in significant changes in mitochondrial metabolism. Key cytokines, specifically TNF-a, disrupt normal mitochondrial oxidative phosphorylation and the resulting ATP production. Additionally, inflammatory signaling induces ROS production, which results in disruption of the mitochondria's membrane, which further alters mitochondrial functioning, and can result in cell death. When injured mitochondria are not properly recycled via mitophagy, mitochondrial contents can be dumped into the cell's cytosol, eventually making their way to the extracellular space and propagating the inflammatory process. Inflammation and mitochondrial dysfunction seem to form a bidirectional cycle and propagate or sustain each other.

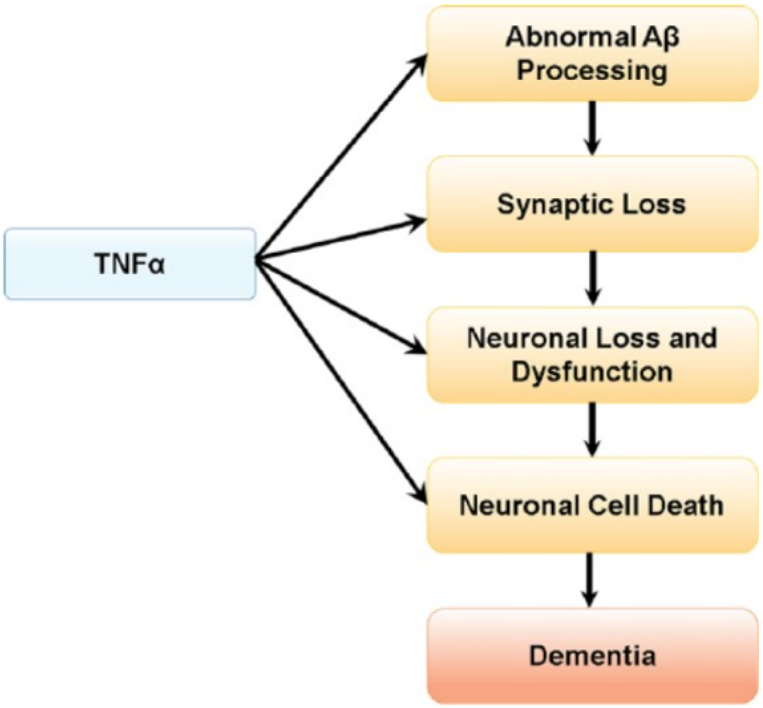
Inflammation and Vascular Disease

There is also considerable evidence connecting inflammation to compromising the blood-brain barrier (BBB). Inflammation results in the disruption of tight junction proteins (proteins that tightly connect blood vessel cells together, preventing unwanted substances from diffusing into the brain), which basically turns the brain from an immune-privileged organ into… just another organ, one that is sensitive to things it should not be exposed to. Specifi-

cally, certain inflammatory cytokines have been shown to alter the integrity of the BBB, such as TNF-alpha and IL-6. These inflammatory factors also contribute substantially to the other vascular diseases that accompany AD, such as atherosclerosis. Thus, we have speculated how inflammation might be a primary driver of AD and brings all the other hypotheses together.

INmune Bio and sTNF Inhibition

INmune Bio is breaking away from other pharmaceutical companies in its approach to Alzheimer's disease. The company is testing a soluble tumor necrosis factor alpha (sTNF) inhibitor, named XPro1595, for early and symptomatic Alzheimer's. Prior evidence suggests that TNF is already a validated target in AD, showing that rheumatoid arthritis (RA) patients on TNF-alpha inhibitors had a lower risk for AD compared to those on other RA treatments, and that TNF-a specifically is implicated in modulating APP cleavage. This is due to the damaging effects of inflammation, as well as TNF's effects on amyloid beta and tau, as shown below:



Source: Chang, R. (2017). Tumor necrosis factor α Inhibition for Alzheimer's Disease. *Journal of Central Nervous System Disease, 9*, 117957351770927.

However, commercialized TNF-a inhibitors—the ones used for rheumatoid arthritis and other autoimmune disease—have also been shown to be associated with demyelination in a clinical setting. In addition, TNF-deficient mice demyelinate like normal mice, but then fail to remyelinate. Animal studies replicate the clinical finding—etanercept exacerbates multiple sclerosis (MS) in animal models. This begs the question: how can TNF blocking be beneficial if it prevents remyelination? Myelin protects neurons' axons and therefore it would be critical to help restore myelin with a disease-modifying Alzheimer's treatment. Myelin is critical for a healthy brain. Why is INmune targeting TNF?

The Case For sTNF Inhibition

The first hint that TNF might be involved in AD came nearly three decades ago when plasma levels of TNF were found to be elevated in AD patients. Subsequent analyses have found increased TNF in the cerebral spinal fluid (CSF) of AD patients and histological analysis of post mortem AD brains have shown that TNF is co-localized with plaques. TNF levels have been shown to correlate with disease progression, and anti-TNF treatment, but not other immunosuppressive drugs, significantly reduced the risk of developing AD in patients with rheumatoid arthritis as mentioned before.

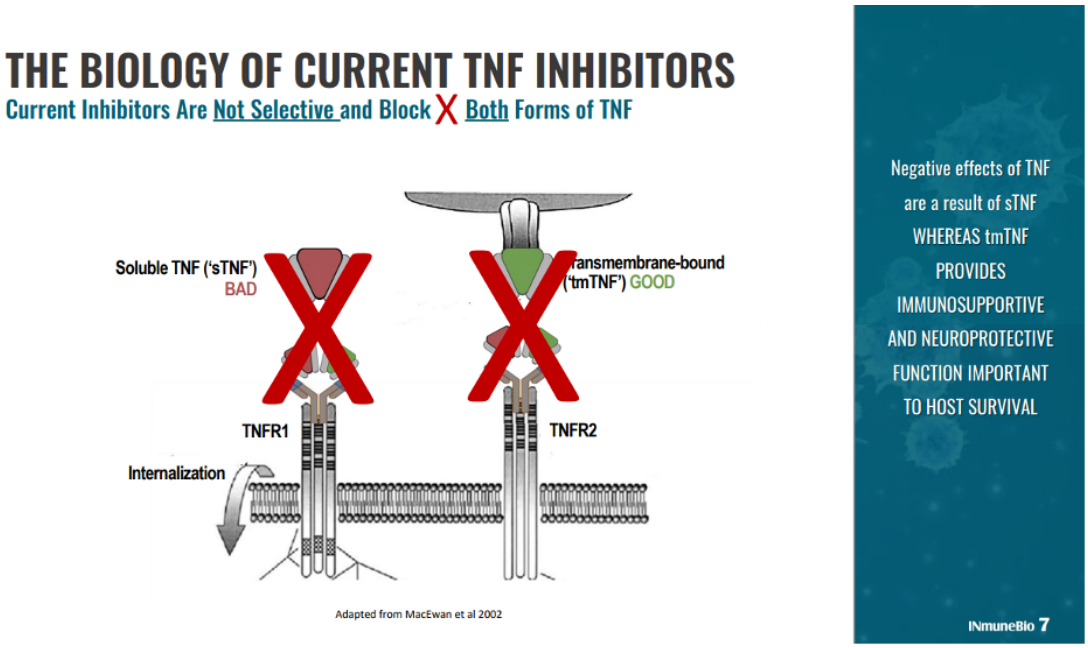
In animal models, TNF potently induces the expression and accumulation of amyloid beta via a number of mechanisms. Tumour necrosis factor can enhance the alternative processing of amyloid precursor protein by increasing the expression of β-secretase and activity of γ-secretase. Tumour necrosis factor also regulates gene transcription and translation of Aβ precursor protein. TNFR1 knockdown improved AD pathology demonstrating the differential role of TNF.

Tau has also been a target of TNF. Chronic TNF overexpression within the brains of triple transgenic mice led to early and exacerbated tau pathology and cell death. This has also been observed in vitro; TNF has been shown to increase tau hyperphosphorylation in SH-SY5Y cells. Subsequent studies reported that exogenous or endogenous TNF can induce intraneuronal accumulation of tau, primarily within the neurites, an effect blocked by the inhibition of TNF or TNFR1.

Both Aβ and tau act as damage associated molecular patterns (DAMPs). As such, they bind to toll-like receptors (TLRs) on immune cells that induce TNF and other pro-inflammatory cytokines, which perpetuates the cycle of Aβ and tau expression and accumulation, synaptic dysfunction, and cell death.

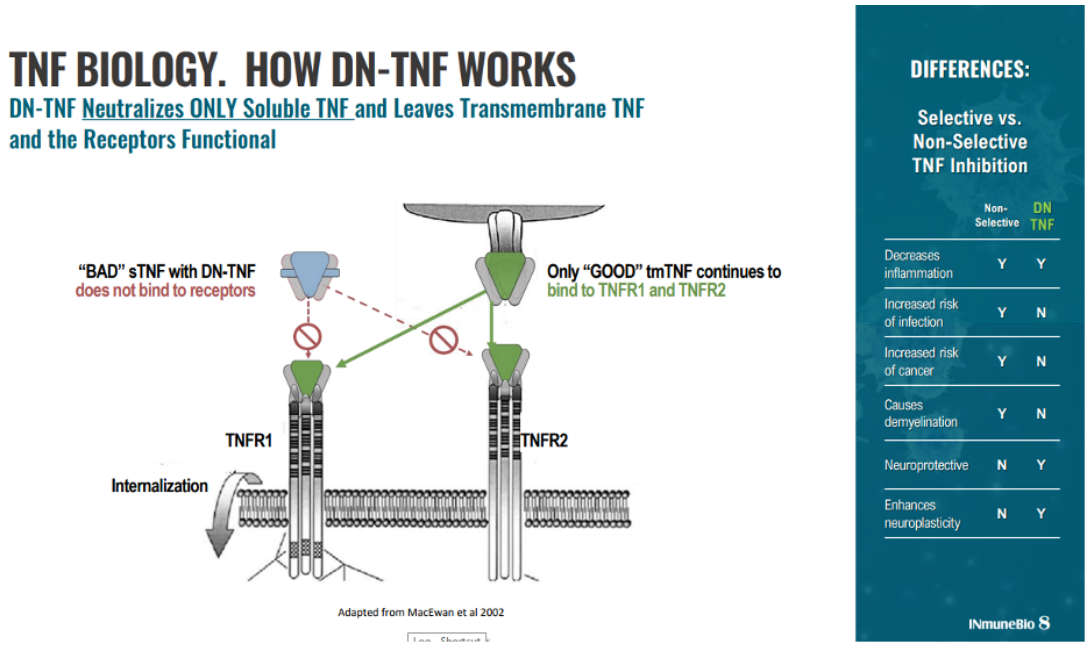
The key is that there are two forms of TNF-a, transmembrane TNF (tmTNF) and soluble TNF (sTNF). TNF is first expressed as a transmembrane protein on cells. Eventually, especially in the context of chronic inflammation, it is cleaved off of the cell's surface, where it subsequently floats around as a soluble trimer (three identical portions all connected into one piece) in the extracellular space. tmTNF and sTNF both activate TNF receptors 1 and 2, both of which have separate functions, but when tmTNF connects to either TNFR, signal transduction occurs in both the cell with the TNFR and the cell with tmTNF. Blocking tmTNF and the signaling that goes back into the tmTNF expressing cell (immune cell) is immunosuppressive, and this is why risks of cancer and infections are increased for those people on currently approved TNF inhibitors.

Within the CNS, the sTNF molecules interact primarily with TNFR1, which is responsible for inflammation and apoptosis. In AD, sTNF increases pathological processing and accumulation of both Aβ and tau, induces changes in synaptic function, and drives cell death. In contrast, tmTNF interacts with both TNFR1 and, primarily, TNFR2. In general, tmTNF/TNFR2 interactions promote cell survival and function, protein synthesis, immunocompetence, and remyelination. The most clinically relevant consequences of blocking tmTNF (with conventional TNF inhibitors) within the CNS is progressive multifocal leukoencephalopathy and demyelination. As a result, commercially available non-selective TNF inhibitors are contraindicated for neurologic disease. In patients with AD, sTNF can perpetuate AD pathology as TNF-induced Aβ and tau become TNF-inducing DAMPs. Below is a graphic of the blocked interactions of current TNF inhibitors:



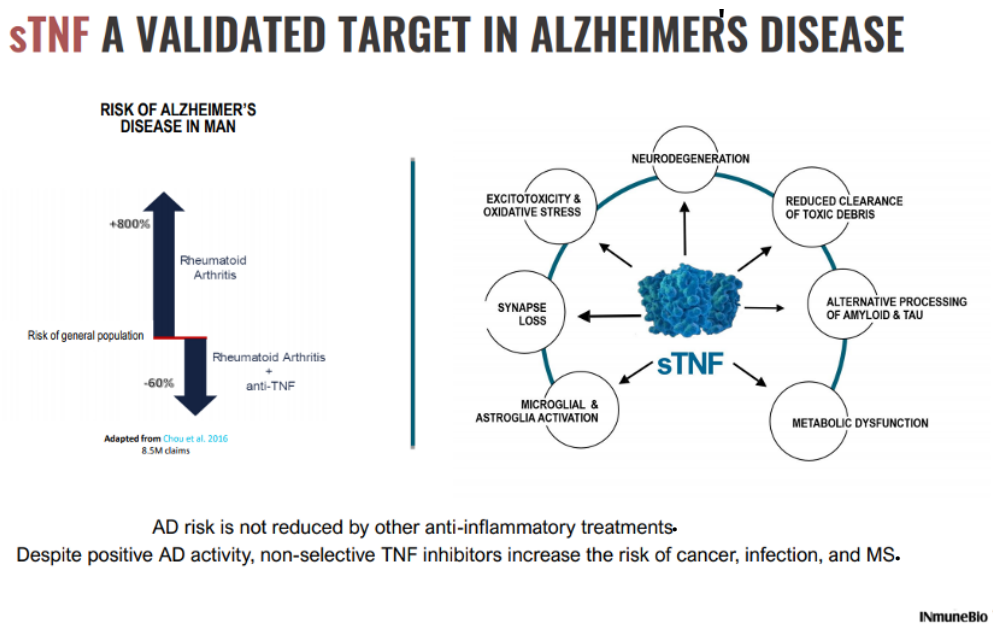
Source: INmune Bio Corporate Presentation, August 2020

In addition, current TNF inhibitors will block both sTNF and tmTNF from attaching to TNFR1 and TNFR2. The interaction of TNF with TNFR2 promotes remyelination, and sTNF has been demonstrated to prevent remyelination. Therefore, selective blocking of sTNF, rather than all TNF, can help remyelinate the brain and decrease inflammation just like current TNF inhibitors, all without increasing risk of infection and cancer:



Source: INmune Bio Corporate Presentation, August 2020

XPro1595 works by replacing one of the TNF monomers within the trimer with a modified TNF molecule that prevents the whole trimer from attaching to receptors. This "dominant negative" TNF cannot replace transmembrane TNF since the individual pieces connected to the cell's membrane will not dislodge. Thus, sTNF is blocked and tmTNF is not.



Source: *INmune Bio Corporate Presentation, August 2020*

As discussed above, inflammation (especially driven by TNF, a master inflammatory cytokine) has effects on various pathologies and hallmarks of AD. However, by targeting sTNF, beneficial effects can be facilitated by:

- Preventing inflammatory (M1) microglial and astroglial activation (promoting M2 phenotype),
- Preventing synaptic loss,
- Preventing excitotoxicity and oxidative stress,
- Preventing neurodegeneration (from inflammatory signaling),
- Increasing clearance of toxic debris (through the M2 phenotype, including clearance of tau and amyloid beta),
- Reducing pathological processing of tau and amyloid beta, and
- Reducing metabolic dysfunction, both mitochondrially and potentially reducing insulin resistance,
- Reducing APP and BACE1 expression in astrocytes

Through various studies, XPro1595 has decreased amyloid beta plaque load in mouse models, prevented synaptic deficits (loss of neuron communication that causes cognitive impairment) in mouse models, rescued neuron communication in older mice with AD pathology while simultaneously ameliorating the chronic inflammation (both adaptive and innate), and remyelinated neurons in a multiple sclerosis (MS) preclinical model. It is important to note that XPro1595 ameliorated pathology in a MS model, whereas prolonged use of currently approved TNF inhibitors are a known cause of MS.

Past Inflammation-Targeting Approaches Were Inherently Flawed

However, other anti-inflammatory drugs have shown promise in preclinical models but have mostly failed to show benefits in larger studies, both with cyclooxygenase inhibitors/NSAIDs (such as ibuprofen and aspirin) and currently approved TNF inhibitors, as well as steroids. However, it was found that etanercept did reduce incidence of AD in one study, but etanercept does not cross the BBB. This makes sense because TNFR2 signaling may not be blocked within the CNS, and therefore etanercept may have reduced inflammation peripherally without affecting myelination. In addi-

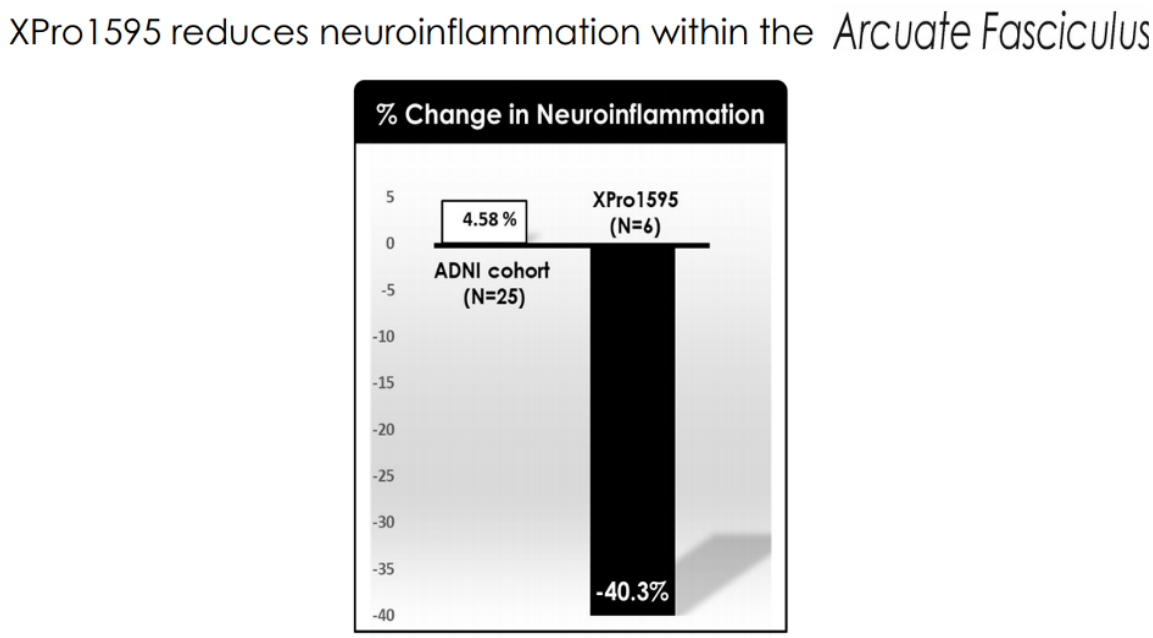
tion, the duration of treatment with TNF inhibitors probably plays a key difference, as chronic dosing leads to demyelination with etanercept, greatly increasing the risk for MS, and one dose of etanercept will likely not be enough to reduce chronic inflammation.

Another "inflammation" approach used IVIG, which doesn't necessarily translate to anything related to myelination and axon regrowth or protection, although it may help clear Aβ fibrils and induce a systemic anti-inflammatory phenotype of the immune system or microglia. However, a phase 3 trial of IVIG did not demonstrate any cognitive benefits in mild AD, although it is possible that the trial duration was not long enough. This approach is more similar to Aβ-targeting mABs that have failed in the past.

Additionally, regarding those tested cyclooxygenase (COX) inhibitors, COX-½ facilitates the production of various prostaglandins that have context-dependent inflammatory or anti-inflammatory actions, so blocking prostaglandin synthesis is not necessarily helpful long-term. Also, blocking the COX pathway only may increase the LOX-5 pathway, increasing the processing of arachidonic acid (AA) into inflammatory leukotrienes instead of prostaglandins. Thus, it appears that the NSAID and currently approved TNF approaches would have theoretical negative effects on AD and inflammation. What would be a better approach to inflammation in AD is an approach that has no potential negative immunomodulatory effects and no negative effects on various cells' phenotypes. We believe that XPro1595 appears to differentiate itself in this way from prior drugs in its attempt to treat AD.

XPro1595: Current Clinical Data

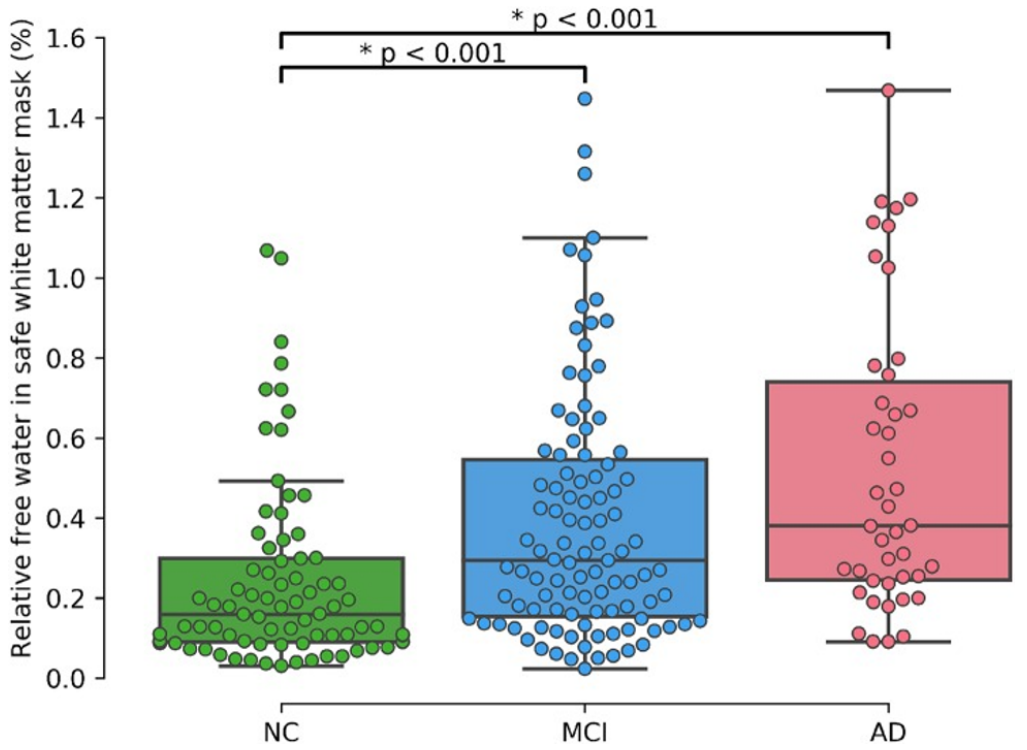
All of this theory is great, but what kind of clinical data does INmune Bio have at this time? A preliminary phase 1 readout showed a significant reduction in inflammation in the whole brain, as well as a very significant reduction in inflammation in the arcuate fasciculus, a key part of the brain involved in language processing. As Alzheimer's first symptoms may include changes in speech, these findings are particularly interesting and promising.



Source: INmune Bio Corporate Presentation, August 2020

These brain inflammation readings were measured using a new technique that measures "free water in white matter," which, simplified, means it measures the accumulation of fluid (free water) around the axons (white matter). This measurement measures the ability of fluid to diffuse around axons, and as more axons degenerate or more fluid accu-

mulates (edema), this measurement would increase in certain areas. Findings show that WMoFW may be a better indicator of early cognitive decline than other diffusion MRI methods, and it also correlates from control subjects to mild cognitive impairment (MCI), all the way to full-blown AD.



Source: Dumont, M. (2019). Free Water in White Matter Differentiates MCI and AD From Control Subjects. *Frontiers in Aging Neuroscience, 11.*

This reduction in inflammation is encouraging. More biomarker data that will support the FWoWM measurements are going to read out soon, perhaps in January 2021. However, how do these reductions in inflammation translate into clinical outcomes? INmune's interim readout in Alzheimer's this summer (2020) gives investors insight into the potential gravity of XPro1595.

In a video webinar, INmune's Phase 1 principal investigator described anecdotal stories of cognitive change for patients in the Phase 1 trial. The first patient described was a patient who was formerly larger-than-life socially, a movie buff, and part of the executive board of a football club. He had early-onset Alzheimer's and turned into a "shell of his former self," socially withdrawn and apathetic with limited language use, spent most of his days sleeping in his recliner. He would need help prompting with many daily tasks. After taking XPro1595, he gradually regained his personality and is back to his old self, asking interested, focused, and engaged in day-to-day life. He had started returning to watching movies and football (after 18 months of not watching). He held conversations with his family, "cracked one-liners like he used to," and brushed his teeth, shaved, and dressed independently. His family was willing to do anything they could to keep him on the drug after the trial ended, and this patient is on the extension phase of the trial.

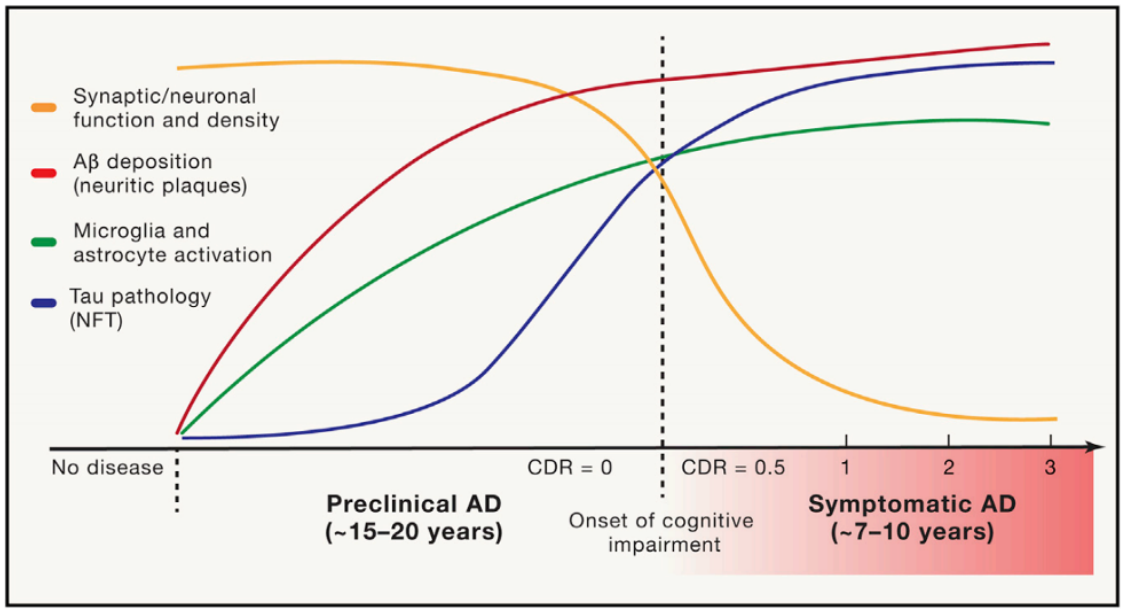
The second patient was a physics teacher on the milder end of the AD spectrum who quit teaching five years prior due to forgetting the formulae necessary to teach physics. The man was a retired deputy principal of a high school with a background in pharmacy and science. After participating in the trial, he has gone back to his usual life, is energized, has improved memory, and has taken on students to tutor, and has gone back to reading academic journals, able to recall later what he had read. He apparently is even considering writing a book. Needless to say, these drastic changes in behavior are highly valuable to the individuals, and while these changes cannot necessarily be statistically attributed to

XPro1595, it seems highly unlikely that any patients would improve so drastically, in a short amount of time, without a drug effect beyond placebo.

If these differential effects are replicated in phase 2 or 3 placebo controlled, blinded trials, the implication would be that XPro1595 is highly efficacious, impactful, and of immense value. Nonetheless, INmune's phase 1 trial was simply meant to show a reduction in neuroinflammation; major but anecdotal improvements in cognition are extremely exciting but just a hint of what the drug could prove, an "icing on the cake". Note that these incredible changes happened over the course of only 12 weeks.

The key with Xpro1595 is it appears to eliminate "bad" mechanisms without abrogating any "good" mechanisms. The main takeaway is: it's not that one targets inflammation, but *how* one targets inflammation. INmune appears to be taking an optimal approach to inflammation in the CNS, and this approach is potentially applicable to other forms of dementia such as Parkinson's.

The study focuses on those with mild Alzheimer's, as it is becoming more accepted that those with more severe diseases might have damage done to their brains that is relatively impossible from which to recover.



Source: Long, J. M., & Holtzman, D. M. (2019). *Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell,* 179(2), 312-339.

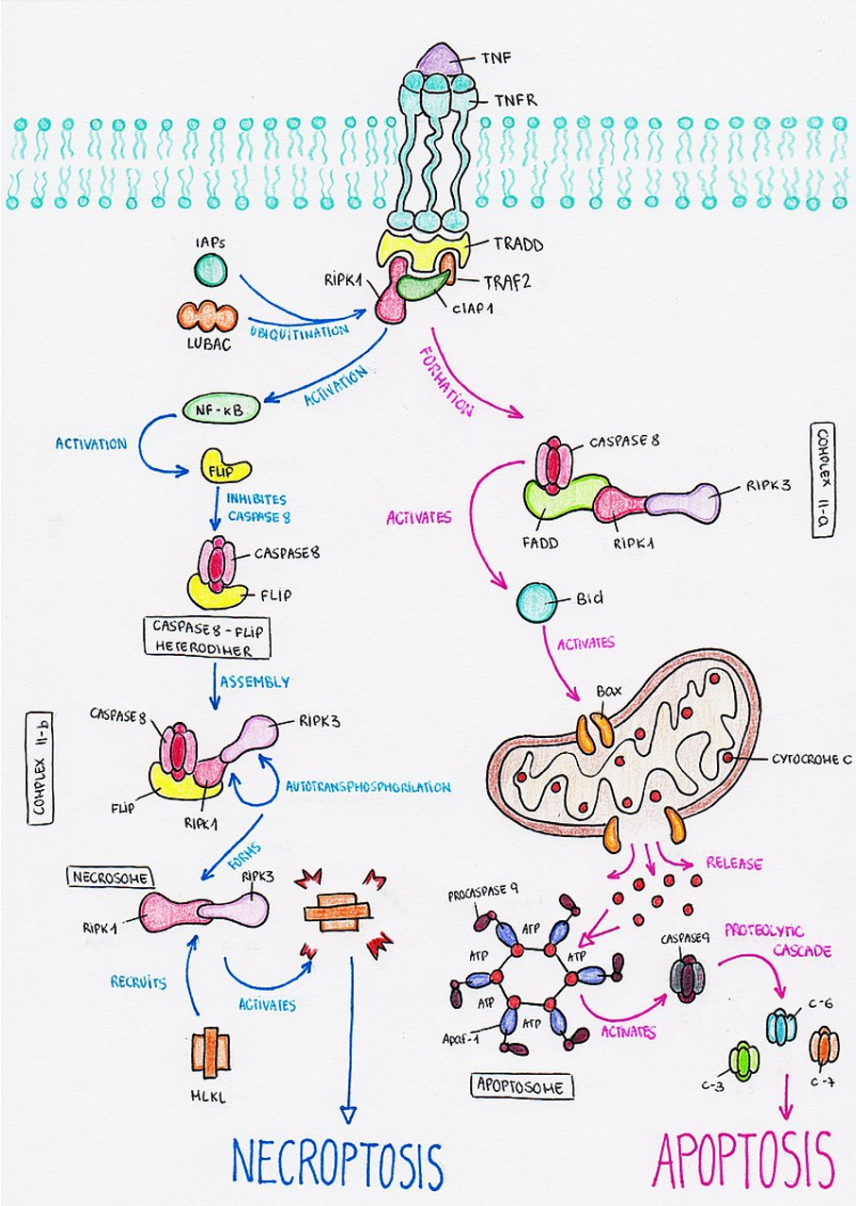
This graph above shows why it is important for this approach to catch people before they have such substantial loss in neuronal (and cognitive) function. Thus, one can see many mild-moderate and even very preliminary Alzheimer's-focused clinical trials, since it is crucial to catch the disease in its tracks before there is substantial neurodegeneration.

Other Inflammation Approaches and Competition

The Alzheimer's space has many competitors, but we will focus on those whom we believe have more similar approaches, those with immunomodulatory therapies. Three main competitors with inflammation-targeting therapies stand out: Alector, Cassava Sciences, and Denali Therapeutics. However, these companies are focused on specific immune-related targets that have been identified as related to the risk of developing AD, as opposed to what one might call a "pleiotropic" or "broad-effect" therapy on overall inflammation, influencing many downstream pathophysiological effects.

First, Denali Therapeutics' has two programs focused on AD. The first of which is a RIPK1 inhibitor, which blocks downstream signaling of TNFR1 (the inflammatory and cell-death related TNFR), which is a related approach to inhibiting sTNF—it's essentially mostly the same inflammatory signaling that can be targeted by sTNF. However, there's a *big* difference between the two approaches. As far as we know, sTNF is really only increased in chronic or overactive inflammation and does not serve any beneficial purpose, and can simply be labeled as pathogenic. TNFR1, on the other hand, while a lot of research suggests it is a promising target in chronic inflammation and neurodegenerative diseases, serves important functions in fighting infection as well as cell death regulation, and because of this, we were not surprised to see the program terminated due to the safety profile of the drug. After all, research suggests that:

> *"The gene-targeted deletion of TNFR1 compromises cellular responses to soluble TNF-α, including NF-κB translocation in fibroblasts and adhesion molecule expression on endothelial cells, and results in an inability to control bacterial infections"*



Source: RIPK1. Wikipedia.

Given that RIPK1 is a necessary downstream kinase crucial for proper TNFR1 signaling, it is not surprising that RIPK1 deficiency is associated with side effects such as IBD. Some studies attribute these side effects to off-target effects, and Denali's shelved RIPK1 inhibitor's safety issues in preclinical models was attributed to off-target effects. Denali and Sanofi are now pursuing the development of a different RIPK1 inhibitor, DNL788, as DNL747 development was suspended. Either way, we are skeptical of RIPK1 inhibitors in general and think targeting sTNF will result in a superior safety profile while having the same beneficial downstream effects. In addition, in the periphery, sTNF may preferentially drive "bad" inflammation via TNFR2 whereas tmTNF likely exerts its "good" effects by binding to TNFR1 – therefore; RIPK1 inhibitors, which are downstream of TNFR1 may have peripheral inflammatory effects or "opposite" effects in the periphery, compared to in the CNS.

We think that INmune's sTNF inhibitor as a platform is a superior approach to neurological indications and systemic inflammatory indications given the currently observed and theoretical safety profile of XPro1595. Basically, instead of messing with the cell's inner machinery, why not block the pathological source of the signaling in the first place, and allow necessary signaling in the case of a beneficial immune response to infection. Thus, Denali's agreement with Sanofi might serve as a benchmark for valuing the dnTNF platform. We note that there were over $1 billion in milestone payments, over $100 million in upfront payments, and a 50/50 profit split between the two companies. Thus, XPro1595 might command a high royalty percentage in a commercial partnership agreement.

Denali's other interesting candidate is its ATV platform-enabled TREM2 modulator (from Takeda). TREM2 is a receptor on subsets of many types of immune cells including microglia. When TREM 2 is activated, it signals phagocytosis (of various elements including amyloid beta), and a reduced inflammatory response. Studies have linked TREM2 variants and loss of function to AD, TREM2 upregulation on microglia surrounding amyloid beta deposits, and a correlation of TREM2 signaling and amyloid clearance - thus the focus on TREM2. However, we think that, while TREM2 functioning is critical in AD and TREM2 modulation might be beneficial in those that have TREM2 variation and loss of function, TREM2 is already activated by amyloid beta itself, and microglia are not the only cells in the brain that can propagate inflammation.

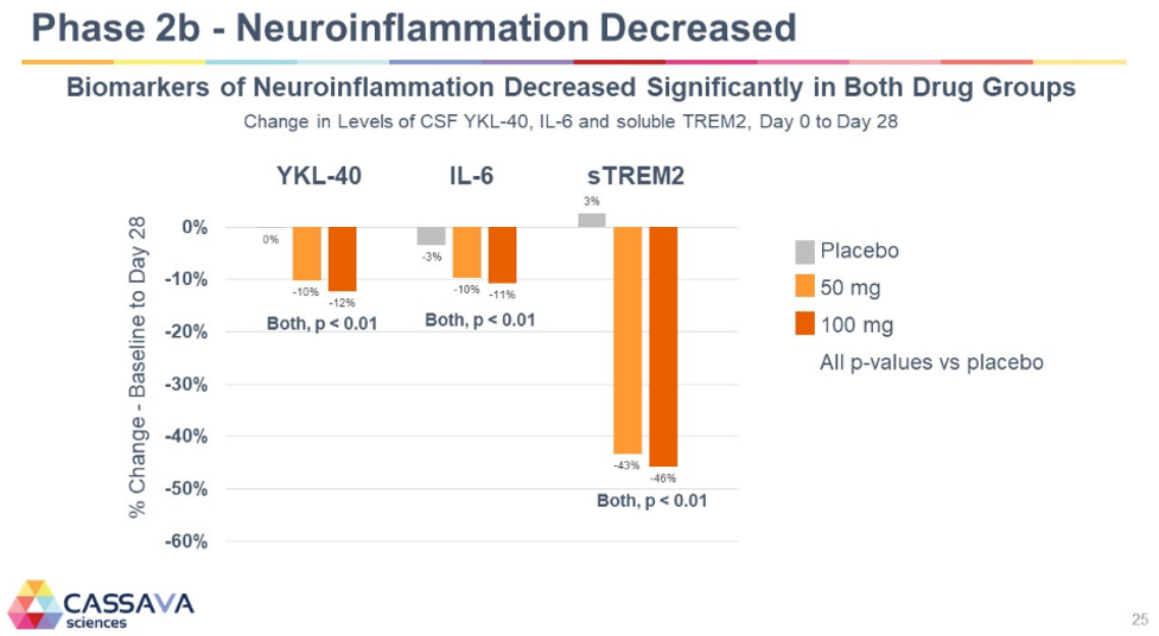
However, there is evidence that might temper one's expectations for TREM2 as a target in AD. First, amyloid beta has been shown to activate TREM2 directly, which explains microglia migration to amyloid beta. Second, while most studies agree on TREM2 signaling reducing inflammation, certain studies suggest that TREM2 signaling illicits both a pro and anti-inflammatory response, and that TREM2 signaling is potentially involved in neuropathic pain and an allodynia:

> *"Dap12 deficiency also suppressed nerve injury-induced mechanical allodynia and TREM2 activation induced allodynia [...], suggesting that microglial TREM2/DAP12-mediated signaling contributes to the development and persistence of neuropathic pain."*

If this effect is consistent in clinical studies, TREM2 agonists or modulators may be doomed in the marketplace, if ever approved. There are also unclear conclusions surrounding TREM2's effects at different stages in AD, as well as its effects on tau hyperphosphorylation. Overall, TREM2 is a promising target but there appear to be some potential issues that may invalidate it as a practical or attractive therapeutic target. Alector also has a TREM2 targeting AD mAB (agonist).

Alector's other promising AD candidate, AL003, targets siglec-3, also known as CD33. Siglec-3 is an inhibitory receptor on microglia that recognizes sialic acid. Its signaling inhibits phagocytosis, and variants of the receptor and their associated activity are associated with differential AD risk, like TREM2. Thus, it is the "checkpoint inhibitor" of a microglial response against amyloid; to compare to cancer therapies, perhaps OX40 would be analogous to TREM2, and PD-1 would be analogous to siglec-3. Although there seems to be limited preclinical or clinical efficacy data on siglec-3/CD33 inhibitors for Alzheimer's, the approach remains promising. AbbVie seems to agree, as Alector and AbbVie agreed to share costs and profits 50/50, globally, for AL003. All in all, this approach is also somewhat confined to microglia and sTNF represents a broader approach to AD treatment.

Another anti-inflammatory drug competing with INmune's XPro1595 is being developed at Cassava Sciences. PTI-125 targets protein filamin A, (FLNA), which aims to block inflammatory signaling of amyloid beta. FLNA is altered in the AD brain and allows inflammatory signaling of amyloid beta through the alpha 7 nicotinic acetylcholine receptor, which promotes hyperphosphorylation of tau, and through TLR4, which also increases inflammation. FLNA interacts with various receptors as it cross links in cells' cytoskeletons. Targeting the altered version of FLNA allows for amelioration of this inflammatory signaling induced by amyloid beta. However, we view this approach as somewhat confined to effects of amyloid beta, although current post-hoc clinical data is relatively promising, as the drug was able to reduce inflammatory biomarkers. PTI-125 already completed a phase 2b study.



Source: Cassava Sciences Corporate Presentation, September 2020

The drug also appeared to improve cognition, with data showing that PTI-125 (sumifilam) induced a 23-37% improvement in episodic memory versus placebo and a 17-46% improvement in spatial working memory compared with placebo. We think Cassava's data bodes well for INmune as improvements in memory correlated with tau pathology (consistent with prior research), and cerebral spinal fluid inflammatory biomarkers were reduced in tandem.

There is substantial competition for INmune in anti-inflammatory AD treatments, but XPro1595 represents a unique approach.

Valuation

We estimate that XPro1595 may become a very high-value drug with minimal-to-no negative effects or side effects, which along with a robust efficacy profile and high pricing and reimbursement could warrant a strong royalty structure. However, we temper this effect on share price value by using a conservative market penetration, given the number of competing companies in AD, even if said competition has inferior drugs or never reaches commercialization.

Assumptions:

- 23 million fully diluted shares outstanding (accounts for additional dilution) [5,6]
- Hypothetical 25% gross royalty agreement signed.
- Payments to Xencor of a 5% royalty, resulting in net 20% royalty
- All inflammatory AD patients (40%), not just mild
- MCI to Moderate (44.9% of AD population) eligible for treatment
- 6% peak market penetration
- LME in 2043 (various pending patents)
- 5.5 million Americans with AD, growing at ~3.5% annually
- $40,000/year initial treatment cost, increasing with projected inflation
- Commercialization in 2026
- 18% discount rate

USA																		
Year	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043
Revenues																		
Estimated AD Population (K)	6761	6998	7242	7496	7758	8030	8311	8602	8903	9214	9537	9871	10216	10574	10944	11327	11723	12134
MCI, Mild-Moderate AD	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%
Addressable Trauma Patients (K)	3035.6	3141.9	3251.9	3365.7	3483.5	3605.4	3731.6	3862.2	3997.4	4137.3	4282.1	4432.0	4587.1	4747.6	4913.8	5085.8	5263.8	5448.0
Market Penetration (cumulative)	0.8%	1.5%	2.3%	3.0%	3.8%	4.5%	5.3%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%	6.0%
AD Patients Treated (K)	22.8	47.1	73.2	101.0	130.6	162.2	195.9	231.7	239.8	248.2	256.9	265.9	275.2	284.9	294.8	305.1	315.8	326.9
Price per Treatment	$40,000	$40,800	$41,616	$42,448	$43,297	$44,163	$45,046	$45,947	$46,866	$47,804	$48,760	$49,735	$50,730	$51,744	$52,779	$53,835	$54,911	$56,010
Revenue (M)	**$910.7**	**$1,922.8**	**$3,044.9**	**$4,286.0**	**$5,655.9**	**$7,165.2**	**$8,825.0**	**$10,647.5**	**$11,240.5**	**$11,866.6**	**$12,527.6**	**$13,225.4**	**$13,962.0**	**$14,739.7**	**$15,560.7**	**$16,427.5**	**$17,342.5**	**$18,308.4**
EBIT (M) (20% Net Royalty)	$182.1	$384.6	$609.0	$857.2	$1,131.2	$1,433.0	$1,765.0	$2,129.5	$2,248.1	$2,373.3	$2,505.5	$2,645.1	$2,792.4	$2,947.9	$3,112.1	$3,285.5	$3,468.5	$3,661.7
Discount Rate	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%
Discounted EBIT (M)	$182.1	$325.9	$437.4	$521.7	$583.5	$626.4	$653.8	$668.5	$598.1	$535.1	$478.7	$428.3	$383.2	$342.8	$306.7	$274.4	$245.5	$219.6
NPV (M)	$2,894																	
NPV Terminal Value (M)	$0																	
Risk Factor (Clinical & Regulatory)	16%																	
Risk Adjusted Value (M)	$469																	
Shares Oustanding, Fully Diluted (M)	18.8																	
OS (Accounting for Future Dilution)	23																	
Price per Share (XPro1595, AD, USA)	**$20.38**																	

This valuation is for Alzheimer's disease in the USA, using a hypothetical royalty structure. It does not take into account for markets in different countries or continents such as Europe, a (in our opinion) likely translation of efficacy into other dementias such as Parkinson's, (in our opinion) off-label use where patients do not tolerate existing TNF-a inhibitors or other pipeline programs of the company's. Considering additional markets and neurodegenerative disorders, one might use a multiple of this valuation if the company executes a partnership agreement that incorporates other indications or global markets. Additionally, as the drug is successfully derisked in various diseases through positive clinical trial readouts, the calculated risk-adjusted value would theoretically go up. We think there could be immense off-label demand for a sTNF blocker that exerts comparable therapeutic efficacy as conventional TNF inhibitors, while avoiding some or all of the side effects of conventional TNF inhibitors.

Ultimately, we expect that XPro1595 will augment the effectiveness of drugs that target more specific aspects of AD, and therefore will be a key drug in combination therapy against AD. For instance, microglia that phagocytose amyloid in AD are thought to become futile in their responses against amyloid. Thus, XPro administration with questionably effective drugs like adacanumab, which is intended to help the body clear amyloid beta, may enable anti-amyloid drugs to have a much more robust effect. Another possibility is that XPro1595 could offer a source of antiinflammatory response in various cells while a TREM2 agonist upregulates the adaptive immune response (while the potential proinflammatory effects of TREM2 are counteracted by XPro1595) for increased clearance of amyloid and other unwanted debris without increased inflammation. If scenarios like these play out as we speculate, XPro1595 could be a backbone and a monotherapy for AD, and our 6% penetration rate might be significantly underestimating the opportunity for INmune. As we estimate Xpro1595 will be more successful than we are projecting, penetrating more of the AD market, succeeding in other dementia markets, and generating immense off-label demand by replacing prescriptions for existing TNF inhibitors, we think our calculated price target is likely an underestimation.

Management Highlights

First and foremost, it is notable that management has participated in financings and currently owns about 6 million shares, or almost half the company's outstanding stock.

INmune's management team is experienced. CEO and acting CMO Raymond J. Tesi, MD has over a decade of experience in CEO and CMO positions in developmental stage biotechnology companies, and has been a licensed physician since 1982. CFO David Moss has founded, funded, and taken public numerous companies in various industries since 1995, and has experience in corporate finance, strategy, business development, management, and as an investor. Mark Lowdell, PhD, INmune's CSO and CMO (manufacturing) has expertise in immunology, as he is also Professor of Cell and Tissue Therapy at University College London. Christopher J. Barnum, PhD is an expert in neuroimmunology and has experience both in academia and industry (startups and big pharma), and his research (a decade of working on XPro1595) has been supported by the NIH, the Michael J. Fox Foundation, and the Alzheimer's Association.

Financials

INmune had $24.3 million in cash as of September 30th, 2020, with a quarterly cash burn of $4.7 million and a TTM loss of $11.3 million. INmune has over a year's worth of cash at the current burn rate, and will likely require more cash as it launches clinical trials in cancer and NASH in the coming quarters. Regardless, the company is currently well-funded, in our opinion.

Risks

There are risks associated with INmune that are common to the typical developmental stage biotechnology company. INmune's clinical studies could fail to show benefit for its drugs in development. The company is not cash flow positive and will likely require cash through financings in the future. The FDA or other regulatory agencies may not approve INmune's drugs. Commercial uptake could be less than projected due to numerous variables, and/or insurance may decide not to cover INmune's drugs.

Conclusion

INmune Bio potentially has a best-in-class disease-modifying Alzheimer's drug. Success in AD and related indications would, in our opinion, result in great value realization for the company and its shares, and as such, the shares appear significantly undervalued considering the potential success of the drug. Additionally, the shares appear undervalued on a risk-adjusted basis. Lastly, the dnTNF XPro1595 is a platform drug for inflammation in general (particularly chronic inflammation) that improves upon prior mega-blockbuster TNF-a inhibitor platform drugs, and as such the implications and opportunity for INmune in this regard could be just as massive, if not more, than the commercial successes already shown by prior TNF-a inhibitors. TNF inhibitor platforms, including Remicade (infliximab - J&J), Enbrel (etanercept - Amgen), Humira (adalimumab - AbbVie), all of which have generated peak sales ranging from $4-20 billion despite the associated serious side effects. INMB shares appear significantly undervalued when only considering the company's promising candidate in Alzheimer's and its commercial potential in the USA.

Disclosure

Analyst Certification
I, Karl Egeland, certify that the views expressed, including (but not limited to) price target, rating (if any) and financial estimates, herein accurately reflect my personal views on the security and company (or companies) mentioned in this report.

Valuation: Our price target of $20.38 is solely based upon the market potential for Xpro1595 to treat Alzheimer's diseases in the United States, and does not take into account other geographical areas or other medical conditions.
Risks: Risks to our $20.38 price target include, but are not limited to:

- Clinical trial failure risks. Xpro1595 might not reduce neuroinflammation, might not improve cognition, or may fail to ultimately be approved due to an adverse safety profile.
- Sales risks. INmune is a small company and might need an established pharmaceutical partner to commercialize Xpro1595. Sales might not meet expectations.
- Financing risks. INmune is a developmental stage biotechnology company and may need to raise money from time to time, which may dilute existing shareholders' ownership.

About the Research Analyst:
Karl Egeland holds a bachelors of science in mechanical engineering as well as a masters in business administration.

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