Zacks Small-Cap Research
Sponsored – Impartial - Comprehensive

June 10, 2019
David Bautz, PhD
(312) 265-9471
dbautz@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

INmune Bio, Inc. (INMB-NASDAQ)

INMB: TNF-α Inhibition Associated with Decreased Risk of Developing Alzheimer's Disease…

Based on our probability adjusted DCF model that takes into account potential future revenues of INB03, XPro1595, and INKmune, INMB is valued at $19/share. This model is highly dependent upon continued clinical success of those compounds and will be adjusted accordingly based upon future clinical results.

Current Price (06/10/19)	$10.27
Valuation	**$19.00**

INITIATION

On June 4, 2019, the Washington Post published a story describing how scientists at Pfizer discovered that the use of the tumor necrosis factor (TNF)-alpha inhibitor Enbrel® was associated with a 64% decreased risk of developing Alzheimer's disease (AD). Pfizer opted not to follow up this discovery because it deemed the chance for a successful clinical trial to be low. INmune Bio, Inc. (INMB) is developing an inhibitor of soluble TNF-α for which it has received a $1 million grant from the Alzheimer's Association to conduct a Phase 1 clinical trial in Alzheimer's patients with mild to moderate disease. Targeting amyloid beta to treat AD has been a complete failure, and the results seen by Pfizer add additional evidence to support the idea that targeting inflammation may be important in treating and preventing the disease.

SUMMARY DATA

52-Week High	**$11.00**
52-Week Low	**$7.08**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**15,817**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$105**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**

Risk Level	**High**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	0 A	0 A	0 A	0 A	0 A
2019	0 A	0 E	0 E	0 E	0 E
2020					0 E
2021					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	0 A	0 A	0 A	0 A	-$1.43 A
2019	-$0.20 A	-$0.18 E	-$0.19 E	-$0.19 E	-$0.75 E
2020					-$0.75 E
2021					-$0.63 E

WHAT'S NEW

TNF-α Inhibition Decreases Risk of Alzheimer's Disease

On June 4, 2019, the Washington Post published a story describing how researchers at Pfizer made an interesting observation about the arthritis drug Enbrel® in 2015 showing that the drug reduced the risk of developing Alzheimer's disease (AD) by 64%. Enbrel® is a soluble tumor necrosis factor (TNF)-alpha receptor that is designed to bind TNF-α and block its interaction with cell surface TNF receptors. It is currently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, and plaque psoriasis. It 2018 it generated worldwide revenues of $7.4 billion (EvaluatePharma), however its patents outside of the U.S. expired in Aug. 2015. Its patent protection in the U.S. is scheduled to expire in the U.S. in Apr. 2029, but that is subject to change pending the outcome of ongoing litigation.

The results showing a decreased risk of AD in patients taking Enbrel® was based on an analysis by Pfizer statisticians of 254,000 insurance claims involving individuals with rheumatoid arthritis (RA) and other inflammatory diseases. The cohort was divided into two groups: those who received an Alzheimer's diagnosis and those that did not. There were 302 individuals treated with Enbrel® in the group that did not receive an Alzheimer's diagnosis compared to only 110 treated with Enbrel® in the group with an Alzheimer's diagnosis. Interestingly, the same effect was seen in another insurance database when examined by Pfizer and similar results were seen with Humira®, an anti-TNF-α monoclonal antibody.

Pfizer's results are also similar to what was seen in a 2016 analysis of 8.5 million insured adults in the Verisk Health claims database (Chou *et al*., 2016). The results from that study showed that AD was more prevalent among RA patients (0.79%) than those without RA (0.11%) and exposure to anti-TNF agents as a class, but not other immunosuppressive drugs, was associated with a lower risk of AD among RA patients (P=0.02). However, a subgroup analysis showed that only Enbrel®, but not other anti-TNF agents, was associated with a decreased risk of AD in RA patients (P=0.02).

The association between inflammation and AD has been known for a number of years (Akiyama *et al*., 2000), however it has been overlooked as a potential means of treating and preventing AD due to the focus on amyloid beta. A multitude of inflammatory markers are found in AD patients' brains and a number of studies have shown a link between chronic inflammation and an increased risk of developing AD (Walker *et al*., 2017; Tao *et al*., 2018). Neuroinflammation is mediated by microglia cells, resident phagocytes of the central nervous system (CNS), which are the major source of cytokines in AD, particularly TNF.

A number of preclinical studies have shown an association between inflammation and AD pathology in several animal models of AD, including APPV717F mice (Qiao *et al*., 2001), APPSwe Tg2576 mice (Sheng *et al*., 2003), and 3xTgAD mice (Kitazawa *et al*., 2005). An elevation in TNF mRNA is seen in 3xTgAD mice prior to the appearance of AD pathology (Janelsins *et al*., 2005) and is correlated with cognitive deficits (Billings *et al*., 2005). Those results led to a number of experiments that examined the inhibition of TNF in preventing AD pathology. In 3xTgAD mice, inhibition of sTNF with XPro1595 (INmune Bio's TNF-α inhibitor, discussed below) prevented inflammation-induced accumulation of C-terminal amyloid beta protein (McAlpine *et al*., 2009). In TgCRND3 amyloid transgenic mice, treatment with XPro1595 for four weeks starting at age 1 month prevented synaptic deficits at age 6 months (Cavanagh *et al*., 2016).

An association between TNF and AD is also seen in the clinic. Elevated levels of TNF are found in the serum of AD patients (Fillit *et al*., 1991), a TNF promoter polymorphism was found to be associated with AD (Ma *et al*., 2004), elevated TNF serum levels are associated with an increased risk of conversion from mild cognitive impairment (MCI) to AD (Tarkowski *et al*., 2003), and a small, open label pilot study of Enbrel® in patients with mild-to-severe AD showed improvement in a number of AD outcomes (Tobinick *et al*., 2006). Additional studies involving Enbrel® in AD patients includes a small study showing an improvement in cognition in AD patients with RA (Chen *et al*., 2010) and a more recent study that in 41 patients with mild to moderate AD that showed some interesting trends, however no statistically significant changes in cognition, behavior, or global function (Butchart *et al*., 2015). In total, we believe there is ample rationale for investigating therapeutics that target TNF for the treatment of AD.

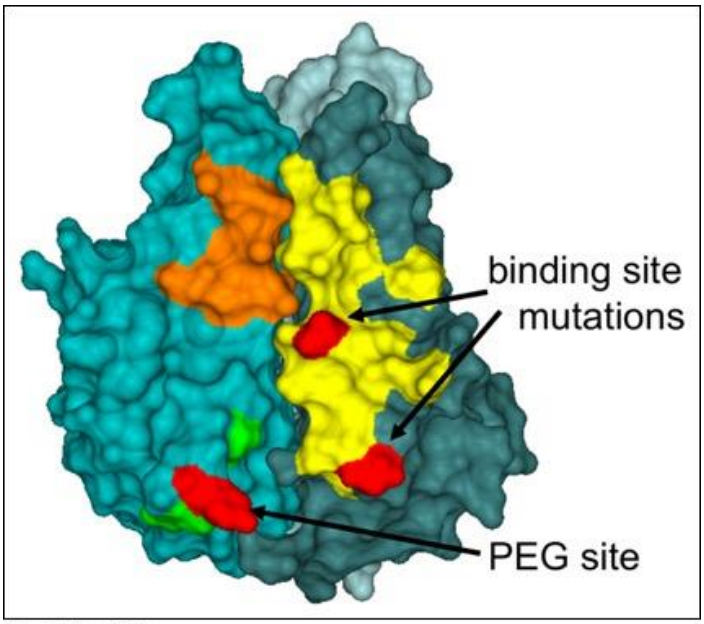
TNF Overview

TNF is an inflammatory cytokine that is known to play an important role in inflammation and immunity (Aggarwal, 2003). It is a 26 kDa transmembrane protein that is expressed on the cell surface (known as transmembrane TNF, tmTNF) and can be cleaved by TNFα-converting enzyme to produce a 17 kDa trimeric soluble TNF (sTNF), which is found circulating in the bloodstream.

Both tmTNF and sTNF bind to two transmembrane receptor molecules, TNFR1 and TNFR2 (Tartaglia *et al*., 1991). While most cells express TNFR1, TNFR2 is predominantly expressed on cells of the immune system. TNF exists as a trimer in its active form, in which it is capable of binding to its receptors and exerting a number of broad-spectrum effects including cell proliferation, differentiation, and apoptosis (Baud *et al*., 2001). sTNF has also been implicated in a number of indications including inflammation, infections, and cancer. Studies with knockout mice have shown that the pro-inflammatory actions of sTNF are mostly mediated through binding of TNFR1 (Bradley, 2008). In contrast, tmTNF exerts most of its biological activities through binding to TNFR2, including T cell activation, proliferation, growth factor production, and the host defense to infections (Grell *et al*., 1995). In summary, sTNF is predominantly responsible for inflammatory responses while tmTNF is predominantly responsible for immune-mediated responses.

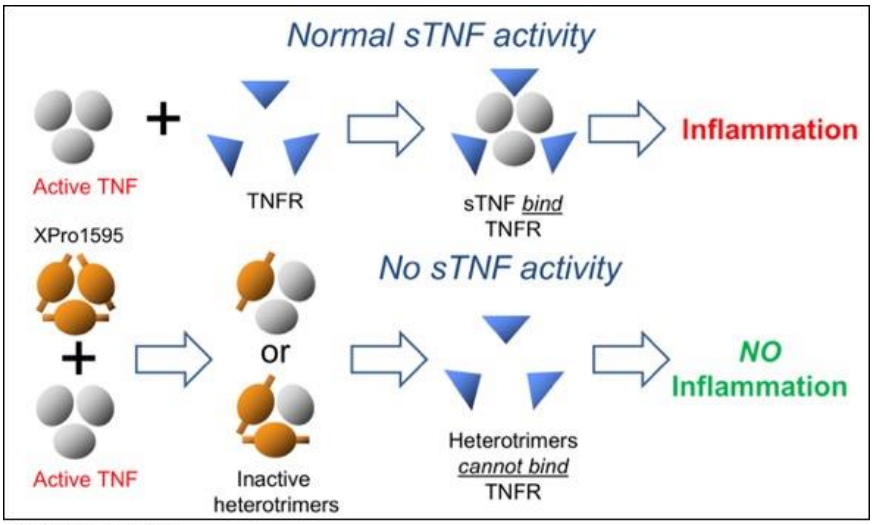
XPro1595

XPro1595 is designed to inhibit sTNF signaling while not impacting tmTNF signaling. It is an engineered protein that is nearly identical to sTNF except for two point mutations in the coding sequence and the addition of polyethylene glycol (PEG) to increase its half-life in circulation (Steed *et al*., 2003). The following figure shows the crystal structure of XPro1595, the location of the two altered amino acids, and the PEG site.



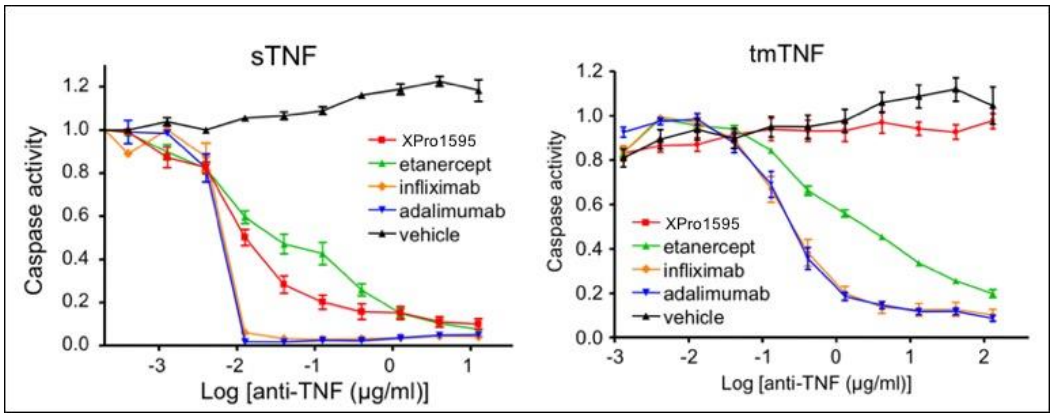
Source: INmune Bio, Inc.

The mechanism of action for XPro1595 is predicated on the fact that sTNF forms homotrimers in order to bind to its receptors. XPro1595 is capable of forming heterotrimers with sTNF (a combination of 1 sTNF + 2 XPro1595 or 2 sTNF + 1 XPro1595), and the heterotrimers that form are incapable of binding to TNFR1 or TNFR2. This is depicted in the cartoon below. The end result is that sTNF is sequestered and prevented from binding to TNFR, thus decreasing pro-inflammatory signals.

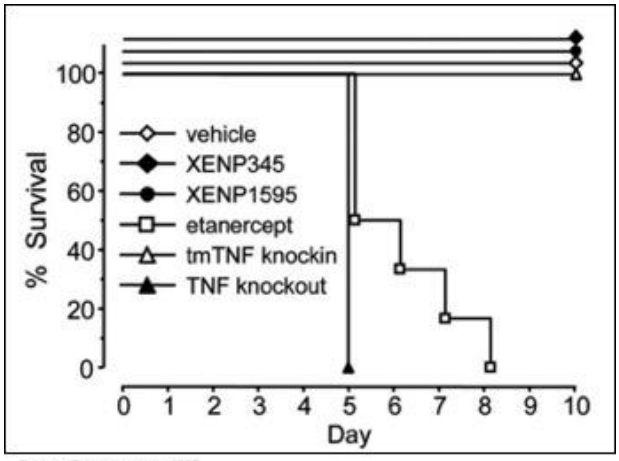


Source: INmune Bio, Inc.

Importantly, studies show that XPro1595 inhibits sTNF signaling without interfering with tmTNF signaling (Zalevsky *et al*., 2007). The following figures show the effect of increasing concentration of anti-TNF molecules on TNF-induced caspase activity for both sTNF (lower left) and tmTNF (lower right). XPro1595 failed to inhibit tmTNF even at >100 μg/ml, which is approximately 10,000-fold higher than the dose that inhibits sTNF.



As discussed previously, the use of anti-TNF therapy can lead to immunosuppression and an increased risk of infection. The following graph shows that in contrast to Enbrel® (etanercept), XPro1595 (labeled as XENP1595) did not increase susceptibility to *Listeria* in a mouse model of infection. All mice treated with Enbrel® succumbed to *Listeria* within eight days, while no mice treated with XPro1595 died. Thus, XPro1595 affects sTNF signaling but does not affect tmTNF signaling, and thus does not alter the TNF-induced response to infection.



Source: Zalevsky et al., 2007

$1 Million Grant to Support Phase 1 Trial

In order to advance XPro1595 in the treatment of AD, INmune was recently awarded a $1 million grant from the Alzheimer's Association. The award derives from the Part the Cloud grant, which is intended to accelerate novel preclinical research findings into clinical testing. The grant will support a biomarker-directed Phase 1 clinical trial in 18 patients with mild-to-moderate AD. XPro1595 will be administered subcutaneously once a week for three months and biomarkers of inflammation will be assessed at 0, 6, and 12 weeks. The primary endpoints for the trial are safety and a decrease in inflammation as measured in the blood, cerebrospinal fluid (CSF), the brain and the breath. Secondary endpoints include measures of cognition, psychiatric symptoms, and quality of life, however since the trial is only 12 weeks it is doubtful cognitive benefits will be seen. We anticipate this trial initiating in the summer of 2019.

Conclusion

While the Washington Post article tried to paint the executives at Pfizer as irresponsible for not following up on the potential for Enbrel® to be used in AD, we believe the more salient point of the article is that another research group saw an association between inhibiting TNF-α and a decreased risk of AD, adding to what we believe is already ample evidence to support investigating the effect of inhibiting TNF in treating and/or preventing the disease. While current TNF-α inhibitors are likely not the best candidates for treating AD, given the increased risk of infection and other potentially serious adverse side effects, XPro1595 could potentially mitigate the inflammatory effects of TNF-α while leaving the response to infection intact. We look forward to the upcoming Phase 1 clinical trial of XPro1595 in patients with mild-to-moderate AD and the potential for a new paradigm in AD research. Our current valuation for INmune remains at $19 per share.

PROJECTED FINANCIALS

INmune Bio, Inc.
Income Statement

INMune Bio, Inc.	2018 A	Q1 A	Q2 E	Q3 E	Q4 E	2019 E	2020 E	2021 E
INB03	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
INKmune	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Other Income	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$1.1	$0.1	$0.3	$0.3	$0.3	$1.0	$2.0	$2.5
General & Administrative	$11.3	$1.8	$1.5	$1.6	$1.6	$6.5	$7.0	$7.0
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($12.4)	($1.9)	($1.8)	($1.9)	($1.9)	($7.5)	($9.0)	($9.5)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($12.4)	($1.9)	($1.8)	($1.9)	($1.9)	($7.5)	($9.0)	($9.5)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($12.4)**	**($1.9)**	**($1.8)**	**($1.9)**	**($1.9)**	**($7.5)**	**($9.0)**	**($9.5)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.43)**	**($0.20)**	**($0.18)**	**($0.18)**	**($0.18)**	**($0.75)**	**($0.75)**	**($0.63)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	8.7	9.4	10.0	10.3	10.4	10.0	12.0	15.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

HISTORICAL STOCK PRICE

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, David Bautz, PhD, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESTMENT BANKING AND FEES FOR SERVICES

Zacks SCR does not provide investment banking services nor has it received compensation for investment banking services from the issuers of the securities covered in this report or article.
Zacks SCR has received compensation from the issuer directly or from an investor relations consulting firm engaged by the issuer for providing non-investment banking services to this issuer and expects to receive additional compensation for such non-investment banking services provided to this issuer. The non-investment banking services provided to the issuer includes the preparation of this report, investor relations services, investment software, financial database analysis, organization of non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per-client basis and are subject to the number and types of services contracted. Fees typically range between ten thousand and fifty thousand dollars per annum. Details of fees paid by this issuer are available upon request.

POLICY DISCLOSURES

This report provides an objective valuation of the issuer today and expected valuations of the issuer at various future dates based on applying standard investment valuation methodologies to the revenue and EPS forecasts made by the SCR Analyst of the issuer's business.
SCR Analysts are restricted from holding or trading securities in the issuers that they cover. ZIR and Zacks SCR do not make a market in any security followed by SCR nor do they act as dealers in these securities. Each Zacks SCR Analyst has full discretion over the valuation of the issuer included in this report based on his or her own due diligence. SCR Analysts are paid based on the number of companies they cover. SCR Analyst compensation is not, was not, nor will be, directly or indirectly, related to the specific valuations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports and articles are based on data obtained from sources that it believes to be reliable, but are not guaranteed to be accurate nor do they purport to be complete. Because of individual financial or investment objectives and/or financial circumstances, this report or article should not be construed as advice designed to meet the particular investment needs of any investor. Investing involves risk. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports or articles or tweets are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.