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INmune Bio, Inc. (INMB-NASDAQ)

INMB: Two Additional Clinical Trials Set to Initiate in 2019…

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 (05/21/19)	$9.49
Valuation	**$19.00**

INITIATION

INmune Bio, Inc. (INMB) is developing novel immunotherapies that target the innate immune system to potentially treat a wide variety of cancers. In addition, the company 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. Following an IPO in February 2019, the company will be initiating two additional Phase 1 clinical trials over the next couple of months, with early data readouts in late 2019 or early 2020. There are few treatments in development that target the innate immune system and we are excited by the early clinical data INmune has complied thus far and believe that the innate immune system is a currently untapped resource for extending the lives of cancer patients.

SUMMARY DATA

52-Week High	**$11.50**
52-Week Low	**$7.08**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**17,599**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$97**
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

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WHAT'S NEW

We recently initiated coverage of INmune Bio, Inc. (INMB) with a $19 valuation. INmune is a biopharmaceutical company developing therapies that target the innate immune system to treat cancer. In contrast to the adaptive immune system, which relies upon a highly targeted response to specific antigens, the innate immune system is designed to deliver a non-specific response to abnormal cells or foreign antigens. The company targets myeloid derived suppressor cells (MDSC) and natural killer (NK) cells through its lead development products, INB03 and INKmune. INB03 is designed to inhibit soluble tumor necrosis factor (sTNF), a key signaling molecule for MDSC activation while INKmune provides the necessary priming signal to convert NK cells from a 'resting' to an 'active' state. In addition to the two cancer therapies, INmune is also developing XPro1595 (which has a similar MOA as INB03) as a treatment for mild to moderate Alzheimer's Disease.

Upcoming catalysts for the company include:

INB03 – A Phase 1 monotherapy trial is currently underway. This trial will transition to a combination therapy clinical trial in the summer of 2019. A Phase 2 clinical trial testing INB03 with checkpoint inhibitors in patients who are resistant to checkpoint inhibitor therapy will initiate in 2020.

XPro1595 – We anticipate a Phase 1 clinical trial in patients with Alzheimer's disease will initiate in the summer of 2019. This study is supported by a $1 million grant from the Alzheimer's Association.

INKmune – A Phase 1/2 clinical trial will initiate later in 2019 in patients with relapsed/refractory ovarian cancer.

Financial Update

On May 15, 2019, INmune announced financial results for the first quarter of 2019. As expected, the company did not report any revenues. Net R&D expenses for the first quarters of both 2019 and 2018 were $0.1 million, however in 2019 gross R&D expenses totaled $0.4 million and were partially offset by a grant from the Alzheimer's Association of which $0.3 million was recorded as an offset to R&D expenses. G&A expenses in the first quarter of 2019 were $1.8 million compared to $2.7 million in the first quarter of 2018. The decrease was attributable to lower stock-based compensation expense partially offset by higher professional fees and payroll expenses. Net loss for the first quarter of 2019 was $1.9 million compared to a net loss of $2.8 million in the first quarter of 2018.

As of March 31, 2019, INmune had approximately $6.0 million in cash and cash equivalents, which was due in part to the completion of an IPO in February 2019 that resulted in net proceeds to the company of $7.3 million. In May 2019, the company completed a private placement with existing investors (including the CEO and CFO, who purchased 11,100 and 5,000 shares, respectively) that resulted in gross proceeds of approximately $4.7 million. In addition, the company entered into a stock purchase agreement with Lincoln Park Capital Fund, whereby the company will have the option, but not obligation, to sell to Lincoln Park up to $20 million in common stock. Lincoln Park made an initial investment of $300,000 as part of that deal. We believe this financing will be sufficient to help advance the company's development products into Phase 2 testing.

As of May 10, 2019, INmune had approximately 10.3 million shares of common stock outstanding and when factoring in stock options and warrants a fully diluted share count of approximately 13.3 million.

Business Update

INB03 for Checkpoint Inhibitor Resistance

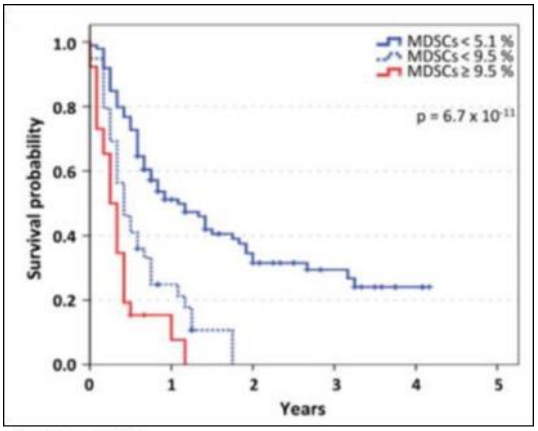
Checkpoint Inhibitor Therapy

Cancer immunotherapy, inciting the immune system to eliminate cancer cells, has improved dramatically with the development of checkpoint inhibitor (CPI) agents targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Yervoy® (ipilimumab), an anti-CTLA-4 monoclonal antibody, was first approved in 2011 for the treatment of metastatic melanoma. A pooled meta-analysis of 1861 advanced melanoma patients treated with anti-CTLA-4 therapy showed an estimated 3-year survival rate of 22% (Schadendorf *et al*., 2015), which is a dramatic improvement over the 3-year survival rates for advanced melanoma patients treated with dacarbazine of 12.2% (Robert *et al*., 2011). Opdivo® (nivolumab), an anti-

PD-1 monoclonal antibody, was first approved in 2014 for the treatment of patients with unresectable or metastatic melanoma whose cancers had progressed following ipilimumab therapy based on results of the CheckMate 037 clinical trial (Weber *et al*., 2015). Since that time a number of anti-PD-1 antibodies have been approved for a wide range of indications, including non-small cell lung cancer, advanced renal cell carcinoma, and recurrent squamous-cell carcinoma of the head and neck.

CPI therapy has led to exceptional improvements in overall survival, time to progression, and objective response rates in a number of different cancers, however there is still room for improvement. Response rates to ipilimumab usually peak at approximately 20% while for anti-PD-1 therapy it rarely exceeds 40% (Pitt *et al*., 2016). Identifying why response rates to CPI therapy are limited to only a subset of patients is currently a very active area of study.

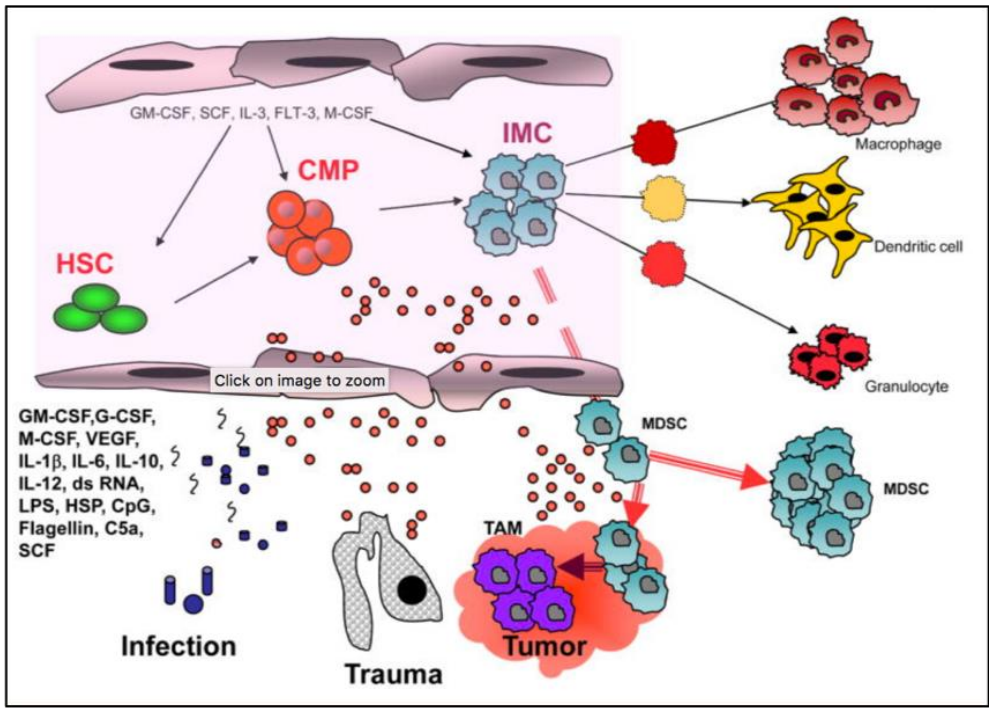
Thus far, a number of immunological factors that correlate with response to CPI treatment have been identified, with one of the most promising being the presence of myeloid derived suppressor cells (MDSCs) (Weide *et al*., 2014; Meyer *et al*., 2014; Gebhardt *et al*., 2015). A study of 209 melanoma patients treated with ipilimumab identified MDSCs as the strongest stand-alone factor that correlated with long-term survival (Martens *et al*., 2016). The following figure shows how patients with <5.1% MDSCs have the highest survival probability (including a number of long-term survivors >4 years) while those with higher levels of MDSCs have much lower survival rates (and no long-term survivors). Based upon this data, we believe that a treatment strategy targeting MDSCs is clearly warranted and could help to improve response rates to CPI therapy.



Source: Martens *et al*., 2016

Myeloid Derived Suppressor Cells

Myeloid derived suppressor cells (MDSCs), which were first formally labeled in 2007 (Gabrilovich *et al*., 2007), are a heterogeneous population of immature myeloid cells (IMCs) that are prevented from fully differentiating into mature cells (granulocytes, macrophages, dendritic cells) due to the presence of various growth factors and cytokines associated with pathological conditions (e.g., cancer) (Youn *et al*., 2008). The following figure shows the process of hematopoietic stem cells (HSCs) differentiating into common myeloid progenitor (CMP) cells and then into IMCs, with IMCs typically migrating to peripheral tissues and differentiating into dendritic cells, macrophages, and/or granulocytes. However, factors expressed in the tumor microenvironment cause accumulation of IMCs, prevent their differentiation, and induce their activation. Following activation, MDSCs express various immunological suppressive factors such as arginase, inducible nitric oxide synthase, and reactive oxygen species. The end result is a population of cells that possess immunosuppressive functions to act as a 'shield' around the tumor and prevent its eradication by the immune system.



Source: Gabrilovich and Nagaraj, 2009

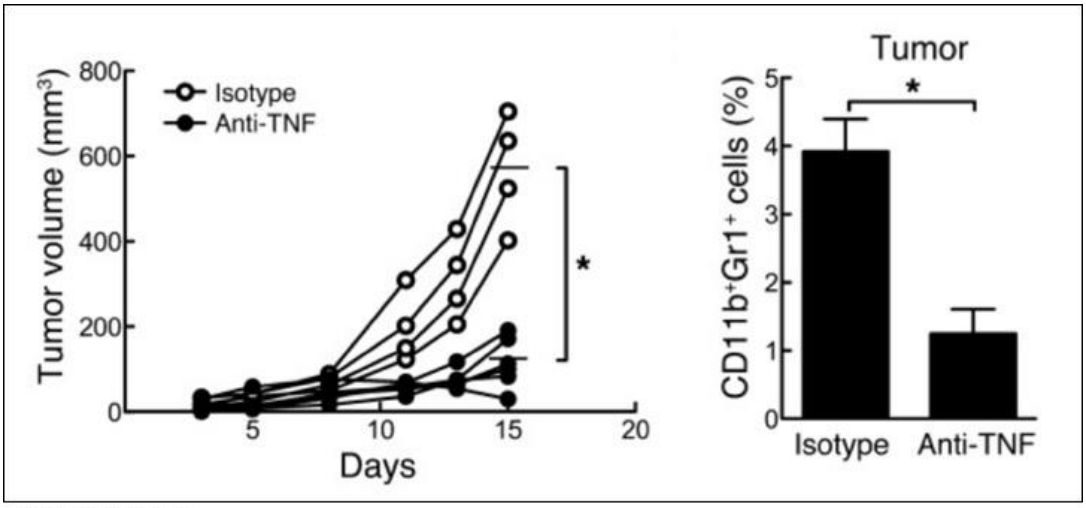
As mentioned previously, MDSCs are correlated with survival in patients treated with CPI therapy and their presence is correlated with disease stage in the blood of cancer patients (Diaz-Montero *et al*., 2009). The fact that these cells accumulate in tumor-bearing patients implies that they are somehow protected from apoptosis, with tumor necrosis factor (TNF) shown to be important in maintaining their survival.

Tumor Necrosis Factor and MDSCs

Tumor necrosis factor (TNF) is an inflammatory cytokine that is known to play an important role in the tumor microenvironment (Mantovani *et al*., 2008). It is a 26 kDa transmembrane protein that is expressed by activated macrophages, NK cells, T cells, and a wide variety of non-immune cells such as endothelial cells. TNF 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.

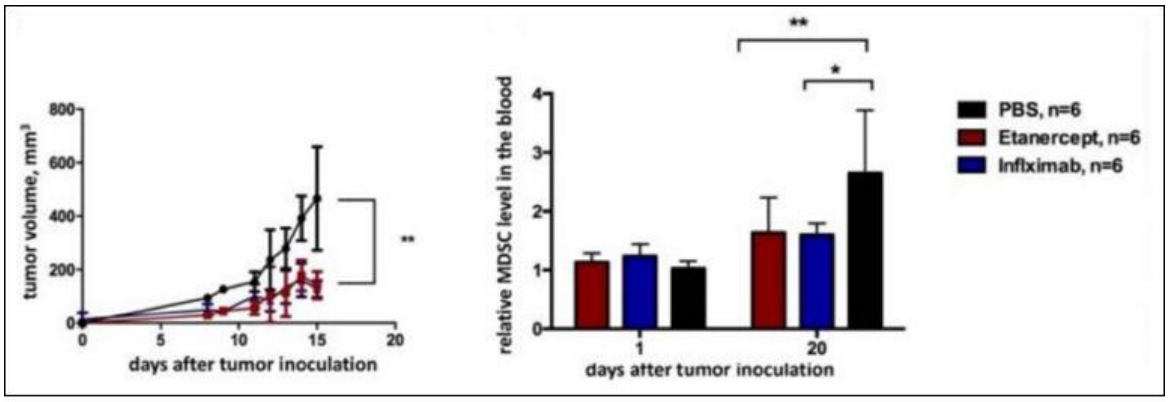
Both tmTNF and sTNF bind to two transmembrane receptor molecules, TNFR1 and TNFR2 (Tartaglia *et al*., 1991). While most cells express TNFR1, TNFR2 is predominantly expressed on cells of the immune system. TNF exists as a trimer in its active form, in which it is capable of binding to its receptors and 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.

TNF is implicated in the differentiation of MDSCs due to its role in the induction and maturation of macrophages and dendritic cells. Studies in mice where both TNFRs were knocked out (*Tnfr*$^{-/-}$) showed that MDSCs are reliant upon TNF signaling to avoid apoptosis (Zhao *et al*., 2010). The following figures show how tumor growth is delayed in mice treated with a TNF inhibitor antibody (lower left) that is accompanied by a concomitant reduction in CD11b^{+}Gr1^{+} (markers of MDSCs in mice) cells. This response was due to the increased apoptosis of MDSCs brought about by the lack of TNF signaling.



Source: Zhao *et al.*, 2010

Similar results were seen in a humanized knock-in mouse model, in which the mice produce human TNF (Atretkhany *et al.*, 2016). The following figure shows decreased tumor growth and lower levels of MDSCs in the blood of mice treated with either etanercept or infliximab. TNF ablation also led to a decrease in nitric oxide, indicating that TNF is involved in supporting the immunosuppressive function of MDSCs.

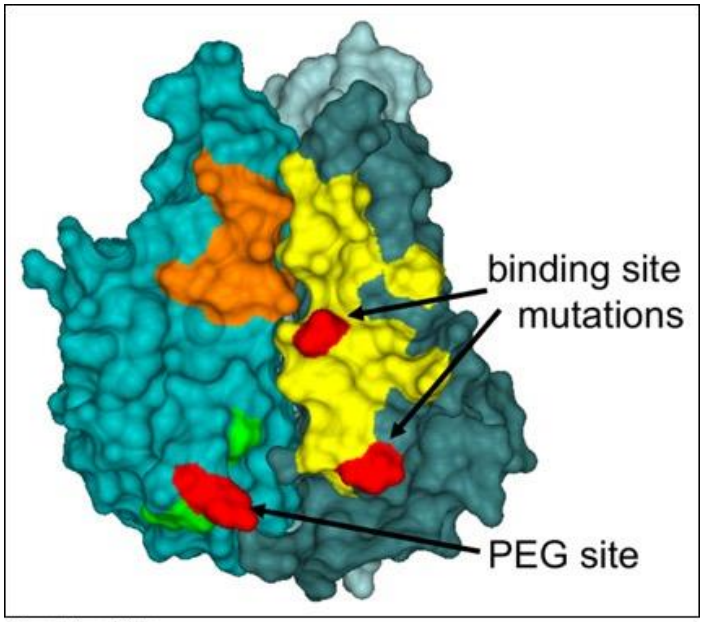


Source: Atretkhany *et al.*, 2016

TNF inhibition would appear to be an exciting potential cancer therapy, and a number of TNF inhibitors have been on the market for a long time, including Humira® (adalimumab), Remicade® (infliximab), and Enbrel® (etanercept). These compounds are approved for the treatment of various inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Unfortunately, while effective for combating the effect of TNF in inflammation, chronic inhibition of TNF is associated with a number of potentially serious side effects, including immunosuppression, increased risk of infection, hematological malignancies, and demyelinating events and neuropathies. The side effect profile, particularly the immunosuppression, is likely the result of indiscriminate binding of TNF inhibitors to both sTNF and tmTNF. Thus, what would be ideal is a therapy that could block TNF-induced activation of MDSC while allowing for proper TNF-induced immune responses.

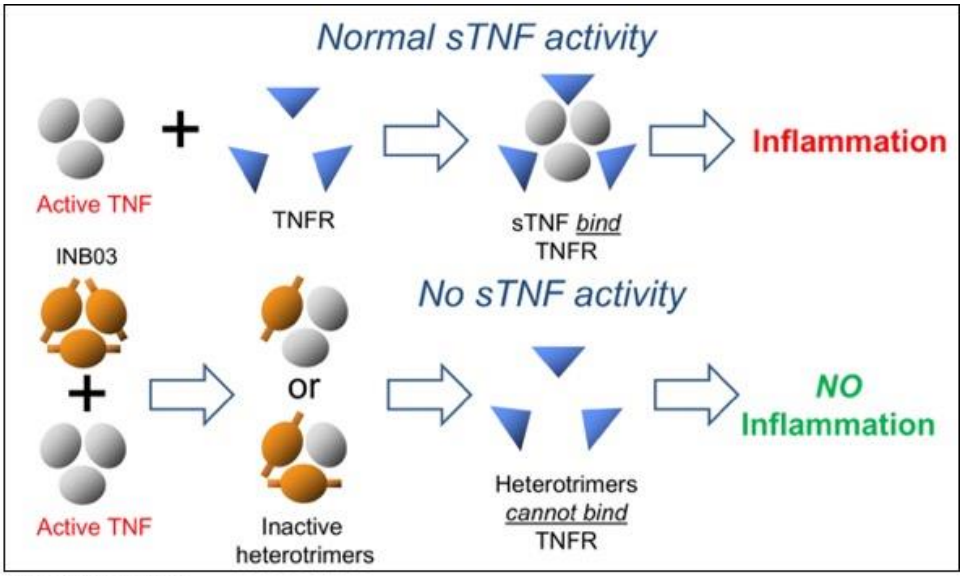
INB03

INB03 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 INB03, the location of the two altered amino acids, and the PEG site.



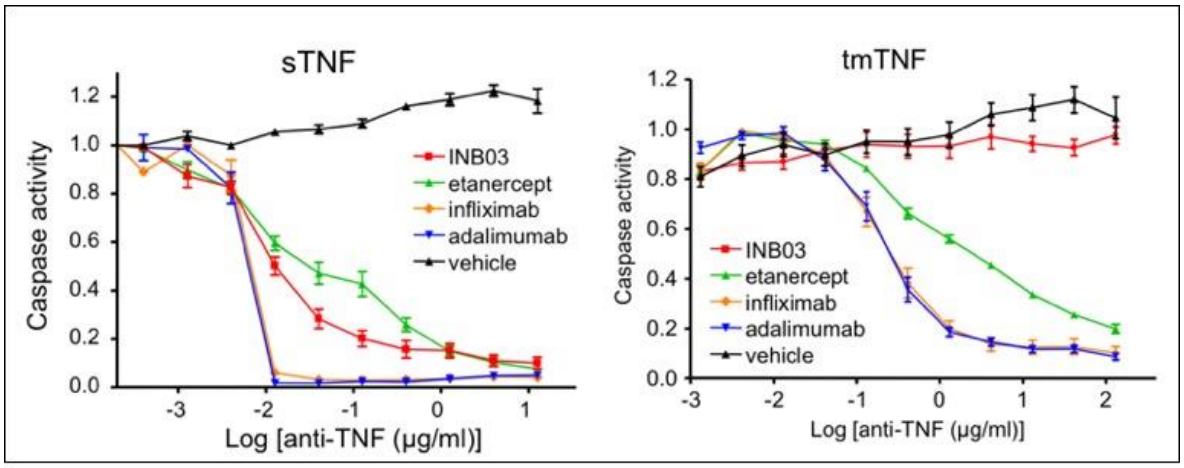
Source: INmune Bio, Inc.

The mechanism of action for INB03 is predicated on the fact that sTNF forms homotrimers in order to bind to its receptors. INB03 is capable of forming heterotrimers with sTNF (a combination of 1 sTNF + 2 INB03 or 2 sTNF + 1 INB03), 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.



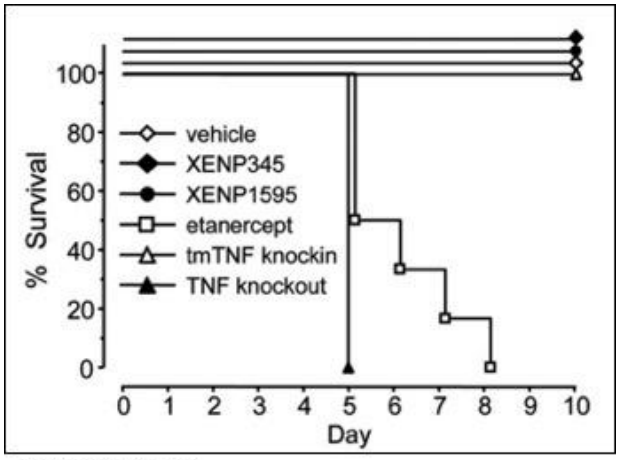
Source: INmune Bio, Inc.

Importantly, studies show that INB03 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). INB03 failed to inhibit tmTNF even at >100 μg/ml, which is approximately 10,000-fold higher than the dose that inhibits sTNF.



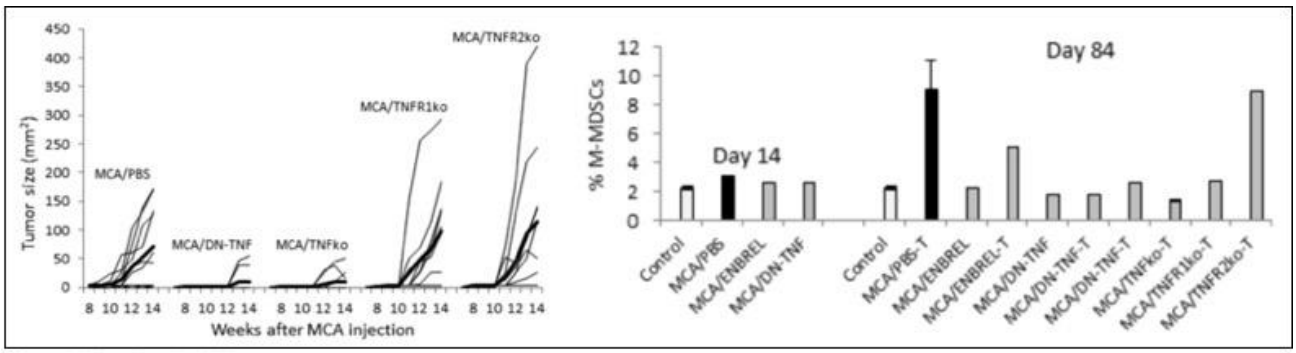
Source: INmune Bio, Inc.

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 etanercept, INB03 (labeled as XENP1595) did not increase susceptibility to *Listeria* in a mouse model of infection. All mice treated with etanercept succumbed to *Listeria* within eight days, while no mice treated with INB03 died. Thus, INB03 affects sTNF signaling but does not affect tmTNF signaling, and thus does not alter the TNF-induced response to infection.



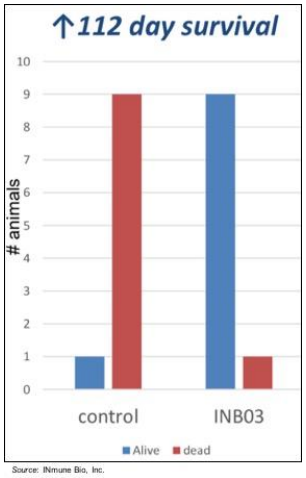
Source: Zalevsky *et al.*, 2007

In a mouse model of chemically induced carcinogenesis that utilized 3-methylcholanthrene (MCA) to induce tumor formation, INB03 decreased both the incidence and size of tumors as well the accumulation of MDSCs. The following figure on the left shows that there are fewer tumors that form in mice treated with INB03 (denoted as DN-TNF) and the tumors that do form are smaller than those in mice treated with phosphate buffered saline (PBS). Interestingly, both the number and size of tumors are larger in mice lacking either TNFR1 or TNFR2. The following figure on the right shows that there is also a decrease in MDSCs in mice treated with INB03 compared to mice treated with PBS.



Source: Vujanovic *et al.*, 2016

The end result is a much higher rate of survival in mice treated with INB03 compared to control. The following chart shows that 90% of INB03 mice were alive at Day 112 compared to only 10% of control mice.



In summary, sTNF is involved in tumor growth and progression along with the establishment and activity of MDSCs. Treatment with INB03 leads to sequestration of TNF that both impairs tumor growth and formation along with decreasing the number of MDSCs and their immunosuppressive activity.

Clinical Trial Plan for INB03

INmune is developing INB03 as an adjunct treatment to CPI therapy (i.e., it is a checkpoint inhibitor potentiator) and we believe that since it is an immune system modulator it could potentially be used to treat a wide range of solid and hematological malignancies. The clinical trial plan is predicated on the use of biomarkers, specifically the presence of MDSCs, to identify those patients most likely to respond to treatment, as MDSCs are rarely present in patients without cancer or chronic inflammation and the level of MDSCs are correlated with disease stage.

The company has initiated a Phase 1 study in Australia in 12 patients with advanced solid tumors and biomarkers of chronic inflammation, including a high level of MDSCs. All of these patients have failed or progressed after several lines of therapy. Patients are being treated once a week with a subcutaneous injection of INB03 at 0.3 mg/kg, 1.0 mg/kg, or 3.0 mg/kg. The primary endpoints of the study are safety and a decrease in the number of MDSCs. No dose-limiting toxicity was noted in animal studies; thus, we don't anticipate any safety issues. Initial data from this study is expected in the second quarter of 2019.

Following the Phase 1 study, the company is planning to move into a Phase 2 study in combination with an approved CPI. That study will also take place in Australia, however it may expand to include clinical sites in the U.S. While the final details of the study won't be known until the conclusion of the Phase 1 study, we anticipate the trial enrolling patients with lung cancer or melanoma who have failed previous therapy (including CPI therapy) and have increased markers of inflammation (including elevated levels of MDSCs in their blood). Treatment is likely to consist of weekly injections of INB03 along with the CPI for at least six months. The primary endpoint would likely be progression free survival based on imaging of tumor size along with determining changes in MDSC level.

Checkpoint Inhibitor Potentiator Deals

Developing checkpoint inhibitor potentiators, which INmune is doing with INB03, is a validated development pathway based on a number of previous partnering deals.

- In June 2016, Merck (MRK) announced a collaboration with Moderna Therapeutics (MRNA) for the development of mRNA-based cancer vaccines to be tested with Keytruda®. The deal included an upfront payment of $200 million.

- In August 2017, Bristol-Myers announced the acquisition of IFM Therapeutics for $300 million upfront and the potential for up to $1.0 billion in milestones for each of the first two products from the lead development programs. IFM was developing two preclinical assets: a stimulator of interferon genes (STING) agonist and a NLRP3 agonist. Both compounds are designed to stimulate the innate immune system and could be used in conjunction with CPI therapy.

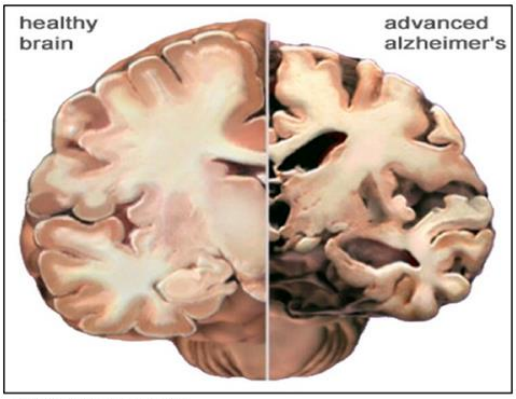
- In February 2018, Bristol-Myers Squibb (BMY) announced a collaboration with Nektar Therapeutics (NKTR) for the development of NKTR-214 in multiple tumor types that included a $1.0 billion upfront payment in cash and an $850 million equity investment by BMY. NKTR-214 (bempegaldesleukin) is a CD122 agonist that is designed to expand a patient's T cell and NK cell populations. Data from a Phase 1/2 clinical trial of NKTR-214 in combination with Opdivo® reported objective response rates of 46% to 75% in a range of advanced tumor types.

XPro1595 for the Treatment of Alzheimer's Disease

INmune is developing XPro1595 for the treatment of Alzheimer's Disease (AD). XPro1595 has the same mechanism of action as INB03. As discussed below, there is a plethora of data showing an association between inflammation and AD as well as preclinical data supporting the use of XPro1595 in preventing Alzheimer's pathology in mouse models of AD.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia in older adults. The disease is named after Dr. Alois Alzheimer, who identified the first case in a 50-year-old woman named Auguste Deter in 1902. Dr. Alzheimer followed her case until her death in 1906, at which point he first publicly reported on it (Alzheimer, 1907).



Source: thebrightdirection.com

After Ms. Deter's death, Dr. Alzheimer examined her brain and found many abnormal clumps (now known as amyloid plaques) and tangled bundles of fibers (now known as neurofibrillary tangles). Over the next five years, 11 similar cases were reported in the medical literature, with some of them already using the term Alzheimer's disease (Berchtold *et al*., 1998).

The most common early symptom of AD is a gradually worsening ability to remember new information. This is due to neurons associated with forming new memories dying off first. As neurons in other parts of the brain die, individuals experience different symptoms, which include:

- ✓ Memory loss that disrupts daily life
- ✓ Inability to plan or solve problems
- ✓ Difficulty completing familiar tasks
- ✓ Confusion with location and time
- ✓ Difficulty with visual images and spatial relationships
- ✓ Problems with words in speaking or writing
- ✓ Withdrawal from social activities
- ✓ Changes in mood, including apathy and depression

Each person progresses through AD at a different rate, and little is known about how or why there is such a marked variation, thus predicting how it will affect someone is quite difficult. One thing that is common to everyone diagnosed with AD is that his or her cognitive and functional abilities will gradually decline. As the disease progresses symptoms can include confusion, irritability, aggression, mood swings, and long-term memory loss. In the final advanced stage of the disease, people need help with the basic activities of living (e.g., bathing, dressing, eating, and using the restroom), they lose the ability to communicate, fail to recognize loved ones, and eventually become bed bound and reliant on round-the-clock care (Förstl *et al*., 1999). The inability to move makes them more prone to infections, including pneumonia, which are often a contributing factor to the death of those with AD.

Competing theories for the cause of Alzheimer's

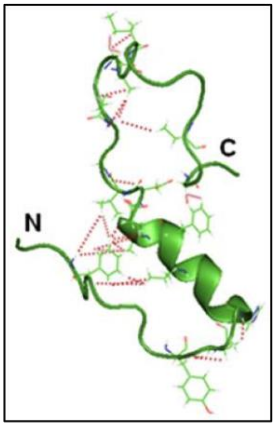
The root cause of Alzheimer's is still unknown; however, it is likely to involve a number of different factors as opposed to being due to one single cause. These factors are likely a combination of genetic, environmental, and lifestyle. There are a number of hypotheses that exist to explain the cause of the disease:

- ➢ Genetic: A rare form of the disease, known as Familial Alzheimer's Disease (FAD), typically strikes early in life,

before the age of 65, and is inherited in an autosomal dominant fashion. This form of the disease is the only one for which there is a clear understanding of the cause. FAD is caused by mutations in one of at least three genes: presenilin 1, presenilin 2, and amyloid precursor protein (Bertram *et al*., 2008). However, the vast majority of Alzheimer's cases do not exhibit autosomal-dominant inheritance and instead are termed sporadic AD. Even so, there are known genetic risk factors, the best studied of which is the inheritance of the ε4 allele of the apolipoprotein E (APOE) gene (Mahley *et al*., 2006). The APOEε4 allele increases the risk of the disease by three times in heterozygotes (having one copy of the allele) and by 15 times in homozygotes (having two copies of the allele; Blennow *et al*., 2006). In addition, mutations in the TREM2 gene are associated with a three to five times higher risk of developing AD (Jonsson *et al*., 2012).

- Cholinergic hypothesis: This is the oldest theory, and the one for which most of the current AD treatments are based on. It proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. A number of studies from the mid-1970s showed substantial deficits in the enzyme responsible for the synthesis of acetylcholine in the brains of patients with AD (Davies *et al*., 1976). However, this theory has fallen out of favor since it was originally proposed, as medications to treat acetylcholine deficiency have not shown strong efficacy in treating AD patients.

- Amyloid hypothesis: This hypothesis proposes that extracellular beta-amyloid deposits are the fundamental cause of the disease (Hardy *et al*., 1991). Beta-amyloid is a fragment of the larger protein amyloid precursor protein (APP), mutations of which are known to cause FAD. Several lines of evidence support the amyloid hypothesis: 1) the location of APP is on chromosome 21, while those with Down Syndrome (trisomy 21) almost all show signs of AD by 40 years of age (Lott *et al*., 2005); 2) APOEε4 is a major genetic risk factor for AD, and while apolipoproteins enhance the breakdown of beta-amyloid, some isoforms are less capable of performing this task than others, leading to more beta-amyloid buildup on the brain (Polvikoski *et al*., 1995); 3) mice that harbor a mutant form of APP develop amyloid plaques and Alzheimer's-like pathology (Games *et al*., 1995). Lastly, amyloid plaques are readily identifiable by microscopy in the brains of AD patients (Tiraboschi *et al*., 2004). While the brains of many older individuals develop some plaques, the brains of AD patients show severe pathological changes specifically within the temporal neocortex (Bouras *et al*., 1994).



Beta-amyloid
Source: Vivekanandan *et al*., 2011

- Tau hypothesis: Tau is a protein located mainly within the axonal compartment of neurons and is an important element in microtubule stabilization and neurite outgrowth. In AD, a proportion of tau protein becomes abnormally phosphorylated, dissociates from axonal microtubules, and accumulates in paired helical filaments inside the neuron (Goedert *et al*., 1991). When this occurs, the microtubules disintegrate causing the collapse of the neuron's transport system (Igbal *et al*., 2005). Just as with beta-amyloid plaques, tau tangles are readily observable in the brains of those affected by AD.

The exact mechanism for how production and aggregation of beta-amyloid peptide results in the pathology of AD is still unclear. It is also unknown how all the other factors conspire to impair neuronal function and survival or what the ultimate initiating factor is for the disease.

Diagnosis of AD

A patient's primary care physician generally diagnoses AD. A diagnosis is based on a medical and family history, including a history of cognitive and behavioral changes. Imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) can be utilized to exclude other brain abnormalities or different dementias. Memory testing and other assessments of intellectual functionality can help with further characterization.

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised guidelines for diagnosing AD (McKhann *et al*., 2011). The criteria and guidelines were an updated version of the diagnostic criteria and guidelines published in 1984 by the Alzheimer's Association and the National Institute of Neurological Disorders and Stroke (McKann *et al*., 1984). In 2012, the NIA and Alzheimer's Association also proposed new guidelines to help pathologists characterize the brain changes due to AD and other dementias (Hyman *et al*., 2012).

The 1984 guidelines were based chiefly on a primary care physician's judgment about the cause of the individual symptoms, results of cognitive tests, and general neurological assessment. The updated guidelines incorporated two noteworthy changes:

1. They identify Alzheimer's as a three-stage disease, with the first stage of Alzheimer's occurring before there are any symptoms such as memory loss. The 1984 guidelines stated that memory loss and a decline in thinking abilities had to already have occurred;
2. They incorporate biomarker tests. A biomarker is a biological factor that can be measured and utilized to indicate the presence or absence of a disease.

The three stages of AD proposed by the 2011 guidelines are: Preclinical AD, Mild Cognitive Impairment (MCI) due to AD, and Dementia due to AD.

- Preclinical AD: At this stage individuals have changes in brain, cerebrospinal fluid, and/or blood biomarkers that indicate the earliest signs of disease, but they have not yet developed clinical symptoms. This preclinical stage reflects the current understanding of Alzheimer's disease that brain changes may occur up to 20 years before symptoms occur (Villemagne *et al*., 2013). An important note about this stage of the disease is that there are no diagnostic criteria available at this point, but rather the guidelines state that additional research is necessary before this stage of Alzheimer's can be identified. The biomarker test(s) will need to be validated to determine the most effective test to diagnose the disease with a high degree of accuracy.

- MCI due to AD: Individuals with MCI have mild but noticeable changes in thinking abilities, but are still able to function on a day-to-day basis. It is thought that as many as 10 to 20% of people ages 65 and older have MCI (Lopez *et al*., 2003). After reliable and accurate biomarker tests are available, the 2011 guidelines recommend biomarker testing for people with MCI to learn whether they have biological changes that put them at risk of developing AD and other dementias. If biomarker testing shows changes that are similar to the changes in AD, the 2011 criteria and guidelines recommend a diagnosis of MCI due to AD. However, just as a diagnosis of preclinical AD cannot currently be made, neither can a diagnosis of MCI due to AD be made as additional research is necessary to validate the 2011 criteria before they can be used in a clinical setting.

- Dementia due to AD: The 2011 criteria and guidelines describe this stage as including quite noticeable memory, thinking, and behavioral symptoms that, unlike MCI, limit the person's ability to function in daily life.

Multiple clinical trial failures point to a flawed AD drug development modality

The development of new and novel AD therapeutics has proven to be quite difficult. No new medications have been approved by the FDA for the treatment of AD since 2003. To examine the AD drug development process, a recent study examined all AD clinical trials since 2002 along with all currently ongoing trials and active compounds (Cummings *et al*., 2014). The results of this study are quite discouraging, with the authors noting the overall success rate for approval from trials conducted from 2002 to 2012 being 0.4%.

A recent study of all active Phase 1, 2, and 3 clinical trials in AD showed that there are a total of 112 agents in active trials, with 26 of them in Phase 3 trials (Cummings *et al*., 2018). Fifty-seven percent of compounds are disease modifying therapies, with 30% of those being anti-amyloid agents. In comparison to 2017, a total of eight agents failed Phase 3 clinical trials.

Some notable trial failures involving anti-beta-amyloid therapeutics include:

- Solanezumab (Eli Lilly): This compound is a humanized monoclonal antibody that preferentially binds to soluble forms of amyloid and in preclinical studies was shown to clear amyloid from the brain. Two Phase 3, randomized, double-blind, placebo controlled trials were performed where patients with mild to moderate AD received either placebo or solanezumab every 4 weeks for 18 months (Doody *et al*., 2014). Results showed no statistically significant difference between groups in the Alzheimers's Disease Assessment Scale (ADAS) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL). A third Phase 3 clinical trial involving patients with mild dementia due to AD also failed to reach significance (Honig *et al*., 2018) and Eli Lily has since ceased development of the drug.

- Bapineuzumab (Pfizer): This compound is a humanized anti-beta-amyloid monoclonal antibody that was shown in preclinical mouse models to reduce the amount of beta-amyloid in the brain and improve memory. Two double-blind, randomized, placebo controlled Phase 3 trials were conducted in patients with mild to moderate AD (Salloway *et al*., 2014). Results showed no significant difference between groups in the ADAS or the Disability Assessment for Dementia.

- Crenezumab (Genentech): This compound is a humanized monoclonal antibody that targets beta-amyloid. This drug was selected in 2012 to be tested in a five-year trial in patients with early-onset AD, in a partnership

between Genentech, Banner Alzheimer's Institute, and the National Institutes of Health. In January 2019, Roche announced the discontinuation of the CREAD 1 and 2 clinical trials based on the results of a pre-planned interim analysis.

- Aducanumab (Biogen/Eisai): This compound is a fully human monoclonal antibody directed against aggregated forms of beta amyloid. It was being studied in two Phase 3 trials, ENGAGE and EMERGE, in patients with mild cognitive impairment due to AD and mild AD demetia. The trials were halted in March 2019 following a futility analysis conducted by an independent monitoring committee.

Developing therapeutics targeted to beta-amyloid was an intense area of research over the past decade. However, targeting beta-amyloid has not proven to be a successful approach to treating AD based on the multiple clinical trial failures. Thus, a new paradigm in treating the disease is necessary through identification of novel treatment targets and medications, as the current AD drug development platform has proven ineffective.

Targeting TNF to Treat AD

Inflammation has been an underappreciated and often overlooked mediator in patients with AD (Akiyama *et al*., 2000). 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 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 MCI to AD (Tarkowski *et al*., 2003), and a small, open label pilot study of etanercept in patients with mild-to-severe AD showed improvement in a number of AD outcomes (Tobinick *et al*., 2006). Thus, there is ample rationale for investigating therapeutics that target TNF for the treatment of AD.

$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.

INKmune for the Treatment of Minimal Residual Diseas

Innate Immune System

The immune system is classified according to its two branches: innate or adaptive (acquired) immunity. Much of the focus of immune system research over the past 100 years has focused on the adaptive immune response, particularly how it can be augmented to reach a particular goal (i.e., vaccine's against infectious diseases). However, interest in the innate immune system has increased in recent years as scientists gain a better understanding of its involvement in inflammatory diseases as well as cancer.

The cells of the innate immune system are derived from both hematopoietic and non-hematopoietic origin and include macrophages, dendritic cells, neutrophils, eosinophils, and NK cells. Non-hematopoietic cells of the innate

immune system include epithelial cells of the respiratory, gastrointestinal, and genitourinary tracts.

In contrast to the adaptive immune response, which can target an essentially unlimited number of potential antigens, the innate immune response is limited to a select group of receptors that detect invading pathogens. However, while an adaptive immune response can take days to weeks, the innate immune response typically begins within minutes of pathogen exposure. There are three basic mechanisms by which the innate immune system recognizes pathogens or damaged cells:

- Pathogen-associated molecular patterns (PAMPs) – these are conserved molecular structures that are expressed by a wide variety of microorganisms.
- Damage-associated molecular patterns (DAMPs) – these are proteins and metabolic markers of infection and inflammation that help to mark cells to be cleared
- 'Missing self' – proteins expressed by normal, healthy cells but not expressed by infected or foreign cells.

NK cells express a number of receptors, most of which are specific for major histocompatibility (MHC) class I proteins, that help to differentiate cells that are 'self' from those that are 'non-self'. Cancer cells typically down-regulate MHC class I proteins as a means of evading cytotoxic T cell recognition (Garcia-Lora *et al*., 2003), thus NK cells play a prominent role in removing those cells from the body.

Natural Killer Cells

NK cells are a crucial component of the innate immune system as they represent 10% of the total peripheral mononuclear cells of circulating human lymphocytes and are the third largest population of lymphocytes following B and T cells (Mandal *et al*., 2015).

A multitude of inhibitory and activating signals are integrated by NK cells in order to rapidly respond to target cells (e.g., cancer or infected cells). In the case of cancer cells, naïve NK cells must go through a two-stage activation process (Bryceson *et al*., 2006):

- In the first stage, NK cells are converted from a 'resting' state to an 'active' state
- In the second stage, NK cells are triggered to kill the target cell

These two signals can be thought of as "priming" and "triggering" events. The priming signal is provided by either an activating cytokine (e.g., IL-2) or by binding to a tumor cell expressing an appropriate number and type of ligands for priming receptors on NK cells (North *et al*., 2007). Tumor cells are able to evade detection by naïve NK cells by not expressing the priming and/or triggering ligands, however research shows that it is typically the priming signal that is downregulated on cancer cells. Thus, a treatment that supplied the priming signal to resting NK cells could convert them to an active state to initiate cancer killing.

Previous research from Professor Mark Lowdell's (INmune's Chief Scientific Officer) lab showed that tumor-primed NK cells are able to lyse NK-resistant cell lines (North *et al*., 2007). Following incubation with the irradiated tumor cell line CTV-1, normal donor NK cells are capable of lysing NK-resistant RAJI and Daudi cells, primary acute myeloid leukemia (AML) cells, and that cell-cell interaction is required for CTV-1-activation. Tumor-mediated priming results in the NK cells maintaining a primed state even in the absence of tumor, and this was maintained even after cryopreservation (Sabry *et al*., 2011). This is in contrast to cytokine (e.g., IL-2) primed NK cells, which do not maintain the primed state when the cytokine is removed.

Minimal Residual Disease

A complete remission (CR) in cancer treatment, which is defined as the absence of tumor using a radiographic technique (e.g., PET or MRI scans), is achieved through a reduction in tumor burden of >99%. However, if a patient had 10^{10} tumor cells in their body, a >99% reduction would only lower that number to $<10^{8}$, thus cancer cells would continue to exist. These remaining cancer cells that survive chemotherapy or other targeted treatments are referred to as minimal residual disease (MRD).

MRD is a key driver of cancer relapse. For example, in hematologic cancers such as leukemias and lymphomas a single intense cycle of chemotherapy can typically result in a CR, however almost no patient is cured without additional therapy due to the presence of MRD. While the presence of MRD, whether through detection by flow cytometry or polymerase chain reaction (PCR), does not guarantee relapse, it does correlate quite well (Ossenkoppele *et al*., 2016).

As mentioned above, NK cells play a crucial role in eliminating tumor cells in the body, which includes MRD following cancer therapy. However, NK cells are typically in a 'resting' state following cancer therapy due to residual cancer cells downregulating the priming signal necessary for their activation. Thus, what is required is a treatment that delivers the priming signal to those resting NK cells such that they can activate and eliminate MRD.

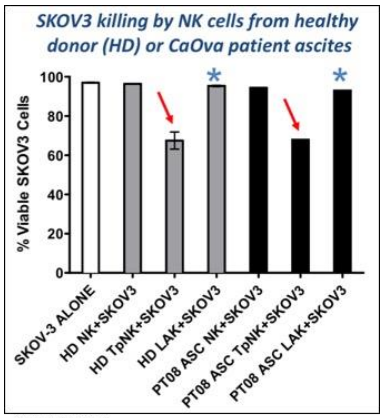
INKmune

INKmune is a proprietary, replication deficient cell line that supplies the priming signal to NK cells *in vivo* to convert them from a 'resting' to an 'active' state. The main advantage of INKmune is that in comparison to cytokine- or monoclonal antibody (mAb)-primed NK cells, which require the presence of the cytokine or mAb to maintain the NK cells in a primed state, once activated by INKmune the NK cells maintain their primed state.

A first-generation therapy utilizing tumor primed NK (TpNK) cells was tested in two Phase 1 clinical trials in patients with acute myelogenous leukemia (AML) (Kottaridis *et al*., 2015; Fehniger *et al*., 2018). In both trials, haplo-identical NK cells from a first degree relative were primed *ex vivo* using a lysate of a tumor cell line (CTV-1). Following infusion of the TpNK cells, prolonged (>1 yr) relapse-free survivals (RFS) were noted in four patients, with three patients having RFS >33 months and two patients with continuing CRs >48 months.

The primary conclusions from the Phase 1 studies were that activated NK cells were clinically active, a majority of the patients relapse (thus multiple treatments are necessary), and a personalized therapy is cumbersome, thus an "off-the-shelf" treatment is ideal.

A Phase 1/2 study with INKmune is planned to initiate in the second quarter of 2019. The study will enroll patients with relapsed or refractory ovarian cancer who have a low burden of residual disease and peripheral or ascites NK cells that respond to INKmune in a laboratory test. The following graph shows killing of SKOV3 cells (an ovarian cancer cell line) by NK cells, from either healthy donors or ovarian cancer patients, primed with INKmune. Interestingly, NK cells primed with IL-2 do not kill SKOV3 cells (depicted by the blue star).



In the Phase 1 portion of the study, INKmune will be administered through intraperitoneal delivery to determine safety and the optimal dose to advance to the Phase 2 portion of the trial. We anticipate six patients being treated in the Phase 1 portion of the study (which may be increased up to 18 patients) and approximately 30 patients (20 active, 10 control) in the Phase 2 portion. The primary endpoint of the Phase 2 trial will be improved RFS in INKmune patients compared to control patients. Secondary endpoints will be evidence of improved immunologic function, improved NK mediated cell killing in an in vitro assay, a decrease in tumor burden, and change in CA125 levels. CA125 is a blood biomarker that is elevated in most patients with ovarian cancer (Scholler *et al*., 2007). Decreasing levels of CA125 in the blood are generally indicative of a positive response to therapy. We anticipate the first patient being enrolled into the Phase 1 portion of the study later in 2019 and the Phase 2 portion of the study to initiate in the second half of 2020.

NK Cell Activation Partnership

While there are few NK cell activators in development, interest in their development was shown through a collaboration between Dragonfly Therapeutics and Merck that is worth up to $695 million in upfront and milestone payments. Dragonfly is developing the TriNKET platform that is designed to bind proteins found on the surface of

tumor cells and NK cells in an effort to stimulate the NK cells to eliminate the tumors.

Intellectual Property

INKmune is protected by a family of patents that are currently pending in the United State Patent and Trademark Office (USPTO) and the International Bureau of the World Intellectual Property Organization (WIPO) under the Patent Cooperation Treaty (PCT). The patent family consists of the following:

"IN VIVO PRIMING OF NATURAL KILLER CELLS"
- U.S. Patent Application 15/268,399

"IN VIVO PRIMING OF NATURAL KILLER CELLS"
- PCT/US2016/061835

"IN VIVO PRIMING OF NATURAL KILLER CELLS"
- PCT/US2018/022722

The patent family covering INB03 includes patents related to DN-TNF technology and XPro1595. In addition to patents that have been issued, additional patents concerning the use of INB03 in cancer and neurological disorders are in active prosecution.

"PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF TNF-ALPHA RELATED DISORDERS"
- US Patent #7662367 – Expires 12/26/2026

"PROTEIN BASED TNF-ALPHA VARIANTS FOR THE TREATMENT OF TNF-ALPHA RELATED DISORDERS"
- US Patent #7446174 – Expires 8/9/2026

"PROTEIN BASED TNF-ALPHA VARIANTS FOR THE TREATMENT OF TNF-ALPHA RELATED DISORDERS"
- EP Patent #1578988 – Expires 4/14/2025

"PROTEIN BASED TNF-ALPHA VARIANTS FOR THE TREATMENT OF TNF-ALPHA RELATED DISORDERS"
- JP Patent #4353802 – Expires 4/14/2025

"TREATMENT OF TNF-ALPHA RELATED DISORDERS WITH TNF-ALPHA VARIANT PROTEINS"
- US Patent #7687461 – Expires 11/17/2026

"TNF-ALPHA VARIANTS PROTEINS FOR THE TREATMENT OF TNF-ALPHA RELATED DISORDERS"
- US Patent #7244823 – Expires 3/31/2024

"NOVEL TNF-a VARIANTS"
- US Patent #7056695 – Expires 3/2/2021

"CANCER PREVENTION AND THERAPY BY INHIBITING SOLUBLE TUMOR NECROSIS FACTOR"
- WO2017106278A1

"METHODS OF TREATING NEUROLOGICAL DISEASES"
- US 2015/0239951 A1

"METHODS OF TREATING NEUROLOGICAL DISEASES"
- EP2892547

"TREATMENT OF COMPLICATIONS RELATED TO ACUTE OR CHRONIC HYPERGLYCEMIA"
- US Patent Application 62/564,232

"COMPOSITION AND METHOD FOR CANCER THERAPY"
- US Patent Application 62/633,030

"METHODS FOR TREATING NEURODEGENERATIVE DISEASES USING A COMBINATION OF A SELECTIVE INHIBITOR OF SOLUBLE TNF WITH A CB2 AGONIST"
- US Patent Application 62/520,514

Risks to Consider

Clinical Risk: There is a limited amount of available clinical data for the use of INB03, XPro1595, and INKmune in each of their targeted indications. While there is pre-clinical data that supports the use of those products in their respective indications, there is no guarantee that the clinical results will match those seen in pre-clinical studies. Negative results from one or more of the clinical trials, or if any of their development products cause unforeseen adverse side effects, would have a negative impact on the company's share price.

Development Risk: The biopharmaceutical industry is highly competitive and there are a number of other larger companies developing treatments for cancer and Alzheimer's disease. INmune is planning to rely on orphan drug designation (ODD), which provides a number of incentives to advance development of treatments for orphan diseases, to advance development of INKmune. However, ODD has not been granted and may not be granted. INmue currently only has two employees and will rely on third party contractors to manufacture drug supplies and

conduct clinical trials. Failure by these third parties to meet their obligations could cause a delay in development timelines and adversely affect the company's business plan.

Financing Risk: INmune is not profitable and will require substantial additional capital in order to advance its development products through clinical testing and to approval. The company raised approximately $7.3 million in gross proceeds from the initial public offering (IPO) in February 2019. We believe that combined with the expected tax credits from UK and Australian clinical trials along with the proceeds from the Alzheimer's Association grant, this will be sufficient to fund operations for at least the next 12 months and allow the completion of the Phase 1/2 ovarian cancer trial and the Phase 1 trial of INB03. However, additional capital will be required to finance advanced clinical trials, which will likely result in significant shareholder dilution.

Stock Risk: Insiders own approximately 85% of the outstanding common stock and thus shareholders will have no effective voice in the management of the company. The company's shares are traded on the NASDAQ, but trading volume thus far is very light and there is limited liquidity, thus it may be difficult to buy or sell a significant number of shares without affecting the share price.

Raymond J. Tess, MD – President and Chief Executive Officer

Dr. Tesi has been INmune's President, Chief Executive Officer, and acting Chief Medical Officer since the formation of the company in September 2015. From November 2011 to May 2015, Dr. Tesi was CEO, President, and acting Chief Medical Officer of FPRT Bio Inc., a development-stage biotech company formed to develop XPro1595 for the treatment of neurodegenerative disease and other inflammatory diseases. From November 2010 to October 2011, Dr. Tesi was Chief Medical Officer of Adienne SRL, an emerging biotech company in Bergamo, Italy focused on products to treat patients with hematologic malignancy. From June 2007 to September 2010, Dr. Tesi was CEO and President of Coronado Biosciences, a company he founded. Dr. Tesi received his MD degree from Washington University School of Medicine in 1982, has been a licensed physician since 1982, and a Fellow of the American College of Surgery.

David J. Moss – Chief Financial Officer

Mr. Moss has been CFO since the formation of the company in September 2015. Mr. Moss has founded, funded, and taken public various companies in a variety of industries since 1995, most recently Tonix Pharmaceuticals (NASDAQ: TNXP). Mr. Moss was a founding investor in Reliant Service Group LLC, which was acquired in 2015 by a leading private equity firm. Mr. Moss previously served as Managing Director, Corporate Finance for a New York-based securities firm, where he advised companies on corporate strategy, financings, and business development. Prior to that, he served as Managing Partner at a Seattle-based venture capital firm. Mr. Moss holds an MBA from Rice University and a BA in Economics from the University of California, San Diego.

Professor Mark Lowdell, PhD – Chief Scientific Officer and Chief Manufacturing Officer

Professor Lowdell has been Chief Scientific Officer and Chief Manufacturing Officer since the formation of the company in September 2015. Prof. Lowdell is Professor of Cell and Tissue Therapy at University College London, where he has led a translational immunotherapy group since 1994. Since February 2009, Prof. Lowdell has also been Director of Cellular Therapy at the Royal Free London NHS Foundation Trust. He received his PhD in clinical immunology from London Hospital Medical College, University of London in 1992 and is a qualified immunopathologist.

VALUATION

We are initiating coverage of INmune Bio, Inc. (INMB) with a valuation of $19. INmune is a biopharmaceutical company focused on treatments that target the innate immune system. As opposed to the adaptive arm of the immune system, which targets highly specific antigens and can take days to weeks to mount an efficient response, the innate immune system is designed to rapidly attack any and all harmful cells in the body in a non-specific manner. The company has three lead development products: INB03 – which targets soluble tumor necrosis factor (TNF) to down regulate myeloid derived suppressor cells (MDSCs), key immunosuppressive cells in the tumor microenvironment; XPro1595 – for use in patients with mild to moderate Alzheimer's Disease (AD); and INKmune – which targets the activation of senescent natural killer cells to eliminate residual cancer cells.

INB03

INB03 is an engineered protein that is nearly identical to soluble tumor necrosis factor (sTNF) except for two point mutations in the coding sequence along with the addition of polyethylene glycol to increase its half-life in circulation. It is designed to inhibit sTNF signaling (which mainly controls inflammation) while not impacting transmembrane TNF (tmTNF) signaling (which mainly controls the immune response). The mechanism of action for INB03 is predicated on the fact that sTNF forms homotrimers in order to bind to its receptors. INB03 is capable of forming heterotrimers with sTNF (a combination of 1 sTNF + 2 INB03 or 2 sTNF + 1 INB03), and the heterotrimers that form are incapable of binding to either TNF receptor (TNFR1 or TNFR2). The end result is that sTNF is sequestered and prevented from binding to TNFR, thus decreasing pro-inflammatory signals.

sTNF is implicated in the survival of myeloid derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells (IMCs) that are prevented from fully differentiating into mature cells (granulocytes, macrophages, dendritic cells) due to the presence of various growth factors and cytokines associated with pathological conditions (e.g., cancer). Following activation, MDSCs express various immunological suppressive factors such as arginase, inducible nitric oxide synthase, and reactive oxygen species. This results in a population of cells in the tumor microenvironment that possess immunosuppressive functions to act as a 'shield' around the tumor and prevent its eradication by the immune system.

INmune has initiate a Phase 1 clinical trial in 12 patients with advanced solid tumors and biomarkers of chronic inflammation, including a high level of MDSCs. All of these patients have failed or progressed after several lines of therapy. The primary endpoints of the study are safety and a decrease in the number of MDSCs. No dose-limiting toxicity was noted in animal studies; thus, we don't anticipate any safety issues. Initial data from this study is expected in the second quarter of 2019.

XPro1595

The recent clinical trial failure of aducanumab has again spotlighted the fact that targeting beta-amyloid to treat patients with AD is not leading to any advancement in the field. We believe it is time to start focusing on alternative treatment strategies, and XPro1595 has substantial preclinical data to justify it as a therapeutic candidate. XPro1595 has the same mechanism of action as INB03, and TNF-activated inflammation has been an underappreciated mediator in AD for a number of years. In addition, multiple preclinical studies show that TNF is elevated in mouse models of AD and that inhibiting TNF can prevent synaptic death. INmune was recently awarded a $1 million grant from the Alzheimer's Association to conduct a Phase 1 study in patients with mild-to-moderate AD to examine various inflammatory factors upon treatment with XPro1595.

INKmune

The innate immune system has been underutilized as an asset in the treatment of cancer patients. Normally, natural killer (NK) cells rid the body of diseased cells, including cancer cells that are still present following standard chemotherapy and radiation treatment, which is referred to as minimal residual disease (MRD). Unfortunately, NK cells are typically in a 'resting' state following cancer therapy due to residual cancer cells downregulating the priming signal necessary for their activation. INKmune is a proprietary, replication deficient cell line that supplies the priming signal to NK cells *in vivo* to convert them from a 'resting' to an 'active' state. The main advantage of INKmune is that in comparison to cytokine- or monoclonal antibody (mAb)-primed NK cells, which require the presence of the cytokine or mAb to maintain the NK cells in a primed state, once activated by INKmune the NK cells

maintain their primed state. A Phase 1/2 study with INKmune is planned to initiate in the second quarter of 2019. The study will enroll patients with relapsed or refractory ovarian cancer who have a low burden of residual disease and peripheral or ascites NK cells that respond to INKmune in a laboratory test. We anticipate data from the Phase 1 portion of the study in late 2019 or early 2020 and the Phase 2 portion of the study to initiate in the second half of 2020.

Valuation

We value INmune using a probability adjusted discounted cash flow model that takes into account potential future revenues for INB03, XPro1595, and INKmune. We model for INmune to partner each of the assets and to receive a 15% royalty on net sales.

For INB03, we model for its use in non-small cell lung cancer (NSCLC), which is where checkpoint inhibitors have shown great promise, but only in approximately 25% of treated patients. Following initiation of a Phase 1 study this year, we estimate a Phase 3 trial initiates in 2022, an NDA filing in 2024, and approval in 2025. Based on approximately 225,000 lung cancer cases a year, with 80% of those being NSCLC and 75% resistant to checkpoint inhibitors, we model for a potential market size of approximately 70,000 patients, which would lead to we estimate peak revenues in excess of $1.5 billion in both the U.S. and E.U. Applying a 15% discount rate and a 25% probability of approval leads to a net present value of $145 million for INB03.

For XPro1595, we anticipate a Phase 1 study initiating in 2019, a Phase 3 trial starting in 2023, an NDA filing in 2026, and approval in 2027. There are currently approximately 5 million Americans suffering from AD, and that number will only increase with the aging population. We believe a successful Alzheimer's treatment would be a definite blockbuster with peak sales of $3 billion. However, with all the clinical trial failures in AD we only assign a probability of 10% at this point. Using a 15% discount rate leads to a net present value for XPro1595 of $31 million.

For INKmune, we model for approval in ovarian cancer, however we realize that there are many other types of cancers for which the treatment could be beneficial. There are approximately 60,000 cases of ovarian cancer worldwide. We model for a Phase 1 study initiating in 2019, a Phase 3 study initiating in 2023, an NDA filing in 2025, and approval in 2026. We believe peak worldwide sales in ovarian cancer could be $1 billion, and we assign a 25% probability of approval. Using a 15% discount rate leads to a net present value for INKmune of $31 million.

Combining the net present values for each of the company's assets along with the current cash balance and potential money from exercised warrants leads to a net present value for the company of $239 million. There are approximately 10.3 million common shares currently outstanding and when factoring in stock options and warrants a fully diluted share count of 13.3 million. Dividing the company's net present value by the fully diluted share count leads to a valuation of approximately $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*

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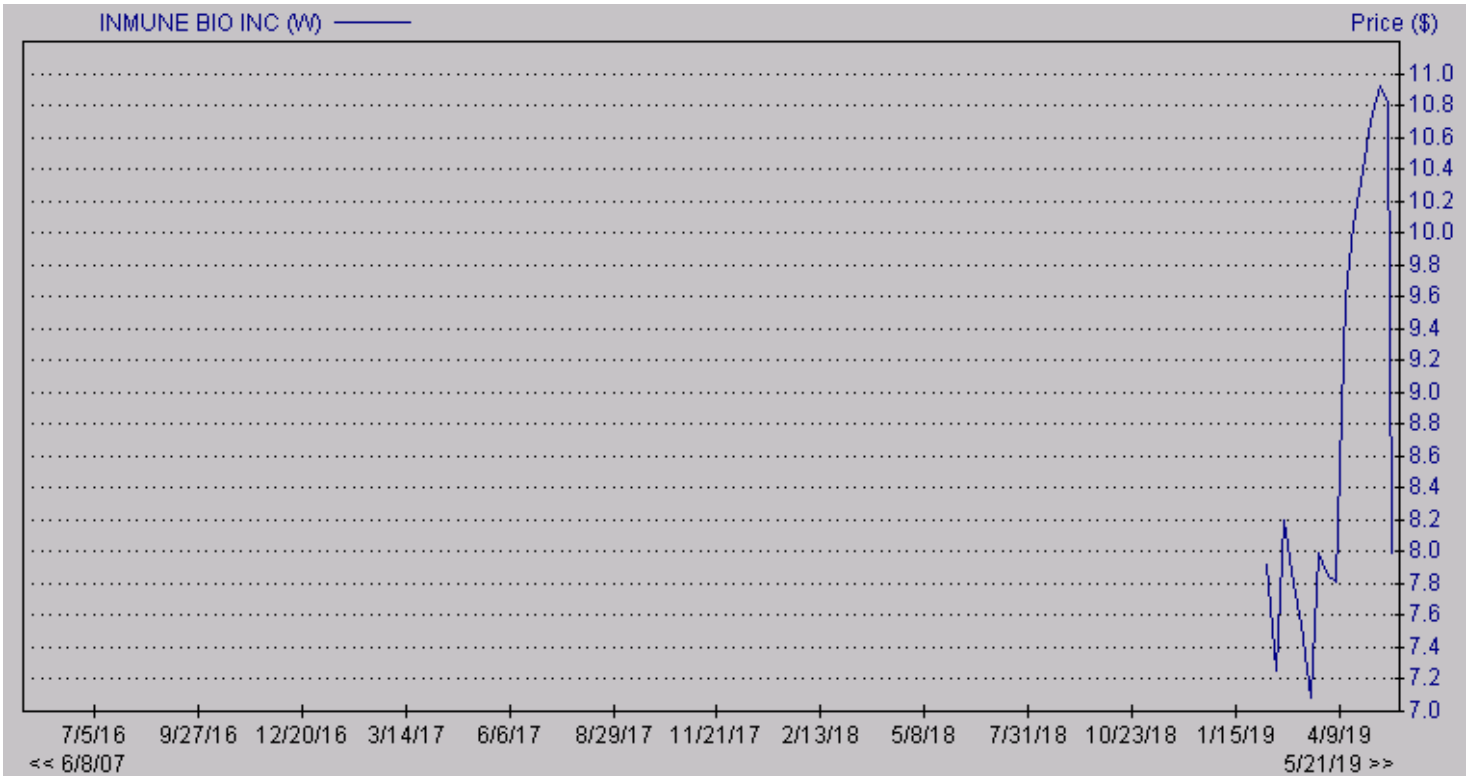
HISTORICAL STOCK PRICE



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