Memorandum from Executive Chairman Eugene Williams

At ProMIS we have tried to communicate frequently and clearly about the status of our programs and the strategy of the company through press releases, white papers, recorded presentations from management, and conference presentations. Many recent discussions with shareholders and investors have made us aware that it would be useful to synthesize those updates into a single Chairman’s letter. The audience we are trying to communicate to includes people who have recently started following ProMIS, some who have been following our progress for years, and some who were involved in the predecessor company to ProMIS.

Over the last year there have been dramatic changes both in the external market and at ProMIS. There have been numerous failures of competitive Alzheimer’s programs, and one erroneous report of a failure that was corrected this week (Biogen’s aducanumab). This has led to concern and skepticism in the investment community. The media coverage of this space has generally thrown everything into a single “amyloid” bucket, due to the complexity of the science, even though it is critical to understand that all the failures can be attributed to the fact that those programs targeted the wrong forms of amyloid. At the same time there has been tremendous progress at ProMIS, expanding our portfolio into new program areas and validating our unique drug discovery platform. We hope you find this note useful in putting all that into context and explaining the status and path forward for ProMIS.

When we created ProMIS four years ago, from the shell of a predecessor public TSX company called Amorfix, we saw two important aspects to the opportunity, both of which have played out positively. First, ProMIS has a unique discovery platform technology for therapeutic antibodies. We have the ability to develop multiple distinct product families that can be monetized in partnering deals with large pharma. It is a scalable model for rapid value creation and capital formation. Secondly, we are convinced that our lead program could be breakthrough therapy in Alzheimer’s disease. Until recently ProMIS sole focus was our lead program in Alzheimer’s, PMN310, which we believe has the characteristics to be “best in class”. In the last year our portfolio has expanded dramatically, as we have refined and applied our highly efficient discovery engine.

Recent positive news about Biogen’s aducanumab came out this week and is given detailed attention in CMO Jim Kupiec’s white paper analysis on or website. The rationale for ProMIS initial focus was based on Biogen’s aducanumab – which announced positive clinical data in December 2014, the first ever positive data for a disease modifying Alzheimer’s drug. Extensive diligence at that time led us to conclude that those positive results were right in line with the latest scientific understanding of Alzheimer’s, but also left a lot of room for improvement. This scientific rationale will be familiar to many of you, but in summary: aducanumab was more selective for the form of amyloid that needs to be targeted by a drug, the toxic, mis-folded oligomers of amyloid, not the other forms of amyloid, monomer or plaque. In contrast to all the other programs that had failed, (and those that have failed subsequently) aducanumab did not bind the monomeric form of amyloid. But since it did bind plaque, which caused a side effect and lowered the dose available for the toxic oligomers, it left
room for improvement. ProMIS PMN310 was designed to be extremely selective for the toxic oligomer and was chosen as the best of 300 candidates at doing that. Our data, including comparative data with aducanumab was recently published in Scientific Reports (available on our website).

Our expectation has always been that aducanumab would work and be approvable, but not overwhelmingly so. That was an expectation supported not only by the science but also by the three years of follow up data Biogen shared as patients continued to be treated with aducanumab in the early smaller trial.

We were among those quite surprised in March this year, when Biogen announced a “failure” of aducanumab, but this week we learned that the source of our surprise was the fact that the announcement was premature and wrong. In Biogen’s view, and we agree, aducanumab’s data in the highest dose arm are approvable given the tremendous unmet need in Alzheimer’s. After discussions with the FDA, Biogen has decided to file for approval in 2020.

The communication in March from Biogen probably could have been better, particularly since we know now that Biogen data existed, not yet analyzed, that obviously could lead to a more positive result. Biogen used a pre-defined method to predict the final outcome based on an incomplete data set, and the prediction was wrong. Coming on the heels of an unintentional announcement about adding 500 subjects in Feb 2018, and the confusion about the Eisai product BAN2401 in July 2018, the Biogen announcement in March 2019 put a significant damper on the availability of investment capital, in Alzheimer’s generally, and particularly in amyloid. It slowed progress for many companies, including ProMIS. Hopefully as the investment community better understands the final data, it will lead to a search for opportunities that build on aducanumab, but incorporate science driven improvements, like our lead program PMN310. As we have discussed before, the three biggest products in industry history were not first in class but best in class. Biogen’s aducanumab appears to be first in class, which is to their great credit. We will try to show in the clinic that ProMIS PMN310 is ‘best in class”.

In the near and medium term we will pursue the following value drivers, in rough chronological order. More detail for those of you interested can be found below:

- Partnering deals in one or more of our three active program areas, alpha-synuclein, TDP43, tau
- NASDAQ listing enabled by the catalyst of a partnering deal
- Additional partnering deals potentially with novel mis-folded protein targets addressed by ProMIS unique technology engine
- Expectations for progress in Alzheimer’s driven by the growing understanding of aducanumab and the latest science, which may reflect favorably on PMN310 and ProMIS
- Clinical data, in proof of concept trials using biomarkers, from ProMIS programs
ProMIS unique advantage rests on our discovery platform. Discovery platforms provide several major advantages, including 1) risk diversification, multiple shots on goal, 2) the ability to monetize some assets through partnering, supporting capital formation that enables taking other assets further into development, creating more value, and 3) in any M&A exit, which is the usual end game for a biotech company, you get value for not only the existing portfolio of products and IP but also the expectation that there could be a great deal more to come.

ProMIS has a unique antibody discovery capability focused on mis-folded protein diseases. A little background science, hopefully not too technical, or too much. Proteins are strings of amino acids – there are 20 common amino acids. Proteins need to fold into the correct 3-dimensional shape to perform their biologic function. Sometimes they mis-fold, usually resulting in an inert molecule, but sometimes resulting in a toxic mis-folded protein. In many cases those toxic mis-folded proteins copy themselves and spread like the infectious prions that cause mad cow disease, CJD, etc. That is the case in neurodegenerative diseases like Alzheimer’s, Parkinson’s and ALS.

Monoclonal antibodies are a large established class of therapies. The typical approach to creating monoclonal antibodies is not very effective for mis-folded proteins. The typical approach picks a segment of the protein defined by a series of several amino acids (called an epitope) and creates antibodies that seek out and bind to that epitope. The problem is that mis-folded proteins and properly folded versions of the same protein have the same amino acid sequence. ProMIS has a unique approach – we can identify amino acid sequences in a particular shape that only appears on the mis-folded version, and as a result create highly selective antibodies that neutralize only the toxic mis-folded proteins, leaving alone the other normal or inert versions of the same protein.

This unique capability is attracting the interest of large pharma. Over the last 12 months we have generated a lot of scientific data with antibodies in three areas – all are proteins that can mis-fold and cause disease: alpha synuclein (Parkinson’s, some dementias), TDP43 (ALS, some dementias), and tau (Alzheimer’s, other). We have multiple very active partnering discussions ongoing in these three areas, several getting into terms as we announced at a conference presentation in September. While partnering efforts can be unpredictable in terms of timing and can be derailed by issues unrelated to the substance of the programs, our ongoing discussions give us confidence in at least one if not two or three partnering deals in a ~3-12 month timeframe. We have an additional 3 targets (other mis-folded proteins) in discovery stage that are looking very good, and the potential to create antibody therapies in dozens of additional mis-folded protein areas.

Equally important is the efficiency of our antibody discovery process – in both time and capital. We now, after a couple years of refinement and experience, can go from a cold start to data that can attract partnering interest for our preclinical assets in ~12 months for less than $500k incremental cost. The market value of those programs in a partnering deal, based on comparables from competitor deals in the neurodegenerative field, could be in the single digit
or low double digit millions in up-front payments, followed by potentially hundreds of millions of dollars in at-risk, downstream milestone payments over the next ~2-10 years.

ProMIS has a scalable, highly efficient machine for value creation. Over the next 3-4 years we plan to apply this to multiple areas, building a valuable portfolio and giving us the potential for multiple partnering deals, plus the ability to be in the capital position to take more of our programs forward ourselves into the clinic. Some investors we meet have adroitly described this as a “land grab”. There are only so many ways to selectively attack mis-folded proteins that drive disease, and over the coming 2-3 years we will develop IP coverage for a growing percentage of those.

Now let’s turn to our potentially most significant value driver, our lead program in Alzheimer’s which we call PMN310. It is a highly selective antibody for the mis-folded toxic oligomers that kill neurons in Alzheimer’s. As you may know, there have been many recent failures in the “amyloid” field generally. All these programs were designed 10-15 years ago and developed by large pharma companies. We believe that two recent advances in science, combined with our unique platform, give us prospects for a dramatically better outcome. We believe that we are targeting the right, toxic form of amyloid, unlike all the programs that failed. There is a large and growing body of scientific literature supporting the finding that the low molecular mis-folded toxic oligomers of amyloid are the disease “culprit”. Also, we are using recent improvements in clinical measures (biomarkers) that can give us a reliable and hopefully positive answer much earlier and with significantly less capital than was the case in those failed programs.

In recent years, scientists have developed the ability to culture human neurons in the lab. This has enabled testing to see which forms of amyloid or other proteins are toxic, and which are not. The results have been very consistent and clear, the mis-folded forms of amyloid and other neurodegenerative disease proteins we are targeting are toxic, other forms like the simple monomer form that is produced all life long are not toxic, and in fact play an important role in brain health. All the failed programs targeted forms of amyloid (monomer, plaque) that are not the toxic target. PMN310 selectively targets the mis-folded, toxic oligomer form of amyloid.

Secondly, none of the failed programs relied on early clinical data for go/no go decisions since the large pharma sponsors felt that only trials with thousands of patients were large enough to obtain a reliable read as to whether a drug was working. That was a function of the metrics used, clinical endpoints that looked at a variety of things like counting backward from 100 by 7. All of the programs that failed had negative early trials, but proceeded nonetheless into expensive late stage trials, which meant that they spent 8-10 years and ~$500MM + before getting a negative answer. Today there are ways to measure the impact of a drug in blood or spinal fluid, using biomarkers. There are biomarkers that can indicate a drug is slowing the rate of loss of brain neurons, or the synaptic connections between neurons. These are direct measures of a positive impact on disease that should result in clinical benefit, like lowering
HBA1C in diabetes, or lowering LDL in cardiac disease. Large pharma is investing a lot in developing and refining these measures, and finds them compelling.

We will be using these measures in our first clinical trials. That means that in a trial costing ~$5MM-$10MM, in roughly ~12 months, we might see compelling evidence of a positive treatment effect. We plan to look at Alzheimer’s in Down Syndrome (where Alzheimer’s is now the #1 health issue, is rapidly progressive, and starts much earlier, usually by age 40). It is biologically the same disease as elderly or sporadic Alzheimer’s. We will include both symptomatic and pre-symptomatic patients in this study, which means we could see evidence of efficacy in both treatment and prevention. We could have these results in 2-2.5 years (since we need to do work before starting a clinical trial, including drug manufacturing), after that a larger Phase 2 study would be conducted, and then after that, in roughly a 5 year timeframe, the final stage Phase 3 trials could be underway, perhaps for both treatment and prevention.

It is very likely that Alzheimer’s will ultimately be treated by a portfolio of complementary therapies, like cancer and cardiovascular disease. There will not be a magic bullet. One area that has received positive attention lately is neuro-inflammation, which we agree will be an important aspect of treating Alzheimer’s. Inflammation exacerbates pathology in a lot of diseases, but it is always “sparked” by a root cause of disease. The scientific evidence is strong that the ‘sparks’ for neuro-inflammation are the mis-folded proteins that our therapies are designed to neutralize.

We have financed ProMIS all along with individual investor capital. We took over a TSX public company with a $1MM enterprise value to start ProMIS, which focused our capital formation strategy largely on Canadian individual investors. The initial sole focus on our lead program in Alzheimer’s, which was a decision driven primarily by the science and the unmet need, but also was a good fit with the interests of our investor group. Everyone we know has family members, often parents affected by Alzheimer’s. By age 80, 30% of the population has symptomatic Alzheimer’s. It takes 15-20 years of disease progression (brain neurons being lost) before you have symptoms. Most of us at ProMIS are all now in the neighborhood of 60 years old, as are many of our friends. The odds are that 3 of 10 of us will begin developing Alzheimer’s in the next five years. In five years our lead program PMN310 (probably at that point in the hands of a large pharma acquirer) could be entering the last stages of development before approval (Phase 3) with positive early clinical data showing we can treat symptomatic disease and slow the progression toward symptoms.

It was clear at the beginning that institutional capital was not likely to be available for that program in the short run, in part because of recent shifts in the life sciences industry structure. Large pharma no longer even tries to invent new drugs, but systematically looks to buy from biotech. When the life sciences VC market came back from the 2008 meltdown, it came back with a model in line with that. VCs and crossover investors in life sciences are very attuned to what is “hot” in the eyes of large pharma. That is a very effective model for them. It can lead to some arguable excesses (there are 3900 immuno-oncology programs, perhaps too many rare disease and gene therapy start-ups), and it also leaves some untapped opportunity. Our
strategy was to bring in individual investor capital to advance our lead program but also to refine our discovery platform and validate it with partnering deals.

Right now we are in the stage of “crossing over” to having an investment thesis that should appeal to institutional investors and allow for greater capital formation. Numerous discussions over the years with equity analysts, bankers, and US institutional investors have been very consistent in saying that when we get a partnering deal, it will enable institutional capital raising. The headline will become “large pharma supported unique technology platform”, instead of primarily “Alzheimer’s/amyloid”. The capital and catalyst of a partnering deal will enable us to become NASDAQ listed and attract more high tier analysts and potentially both retail and institutional investors to narrow the valuation gap we believe exists.

In addition, we believe that over the coming months there will be a greater recognition of the likelihood that Biogen’s aducanumab will be the first ever approved disease modifying therapy in Alzheimer’s, although with a modest clinical benefit. It will change the thinking about amyloid generally, and more people will understand the growing body of scientific literature showing that the toxic oligomer of amyloid is the critical target. Selectivity for the toxic oligomer will be increasingly recognized as a critical differentiator, the basis of “best in class”. Those expectations could be very positive for ProMIS, and we will do what we can to move rapidly into the clinic and conduct trails with biomarkers that hopefully will show compelling positive data.

Thanks for your interest in ProMIS.

Eugene Williams, Executive Chairman

References
1) William Klein, Journal of Alzheimer’s Disease, 2018;
2) Staney Prusiner, JAMA Neurology, May 2019;
3) Mattsson, JAMA Neurology April 2019
4) Gibbs, Scientific Reports, July 2019 (direct link: https://rdcu.be/bJeLB)
Supportive figures

High selectivity for the toxic oligomer is the key to effective therapy

- Toxic oligomers are the least abundant form of amyloid-beta in the brain...
- Both aducanumab and BAN2401 had a strong dose response curve...higher dose enables greater efficacy
- Both had ARIA-E which limited dosing...due to plaque binding
- Binding other forms of amyloid reduces drug available for the toxic oligomer.....and likely reduces efficacy

The problem.... ....selectivity is critical....lack of selectivity lay behind the failure of crenezumab and  moderate efficacy of aducanumab in Alzheimer’s...
Alzheimer’s Disease: Soluble toxic Aβ oligomers, not plaque, not monomers, are the most neuropathogenic Aβ species

- Synapse abnormalities and memory impairment correlate poorly with plaque burden in human and mouse AD.1-2
- Aβ monomers and Aβ insoluble fibrils (plaque) have little or no demonstrable toxicity in vitro or in vivo.3-5
- Soluble Aβ oligomers show the highest degree of neurotoxicity6
  - Toxicity in primary neuron cultures and brain slices6,7,9
  - Induction of cognitive impairment in rodents3,4,10

Synaptotoxicity of human Aβ oligomers on hippocampal neurons in vitro7

In vivo impairment of recognition memory by Aβ oligomers, not monomers and not fibrils10

Binding the right form of amyloid beta is critical: the toxic oligomer is the target and PMN310 is the first oligomer selective antibody therapeutic

Bapineuzumab
- Phase 2 failure
- Phase 3 failure
- ARIA-E side effect

Solanezumab
- Phase 2 failure
- Phase 3 failure

Aducanumab
- Phase 2 success
- ARIA-E side effect
- Phase 3 failure

PMN310
- Selective binding to oligomers
- Expected improvement in efficacy & safety

* Synthetic oligomers