



## Chairman's Memorandum, December 16, 2021

### *A breakthrough year, and looking forward to 2022*

ProMIS has never been in a better substantive position than we find ourselves now at the end of 2021. We started the company with the mission to apply our unique technology to developing breakthrough therapies for patients and families affected by Alzheimer's disease, ALS (amyotrophic lateral sclerosis), and other devastating diseases caused by mis-folded proteins. We are now making significant progress toward that goal.

2021 was a very successful year for us in terms of capital formation. We raised over \$27MM US, with the support of prestigious investors, and are well capitalized for the foreseeable future. Shareholder support was very strong for a resolution enabling the Board to consolidate shares, in a manner that could qualify us for listing on a major North American exchange, where very deep pools of capital are available to support a cutting-edge science story like ours.

Over the last several years perhaps our greatest progress has been in refining and improving our unique discovery engine, based on the ability to use computational methods to predict portions of mis-folded proteins (conformational epitopes) which has given us a consistently successful track record creating highly selective antibody therapies. Google's publication of the Alpha Fold protein database, with normal conformations of many thousands of proteins, has accelerated our progress toward new targets since it provides the starting point for our unique computational approaches. That database is analogous to the publication of the human genome 20 years ago, which ushered in an age of tremendous progress and value creation in gene-based therapies. ProMIS is very well positioned to be a leader in the new area of therapies targeting protein misfolding. We are pursuing several new targets in diseases like schizophrenia and expect tremendous progress in expanding our portfolio in 2022.

Our existing portfolio of highly selective antibodies targeting pathogenic mis-folded alpha synuclein, TDP-43 (TAR DNA Binding Protein-43), RACK1 (Receptor for Activated C Kinase 1), and tau is moving forward at an accelerated pace given our capital position. In many of these protein areas, failures or disappointments in the clinic have come from antibodies that were not adequately selective for the mis-folded form, very similar to what has been seen in the amyloid area. We are well on our way to generating in vitro and in vivo data throughout 2022, confirming lead therapeutic candidates that are ready to enter IND enabling work and head to the clinic.

Finally, our lead program PMN310 is moving full speed ahead through the IND enabling work necessary to initiate our first in human clinical trial. The clinical readouts in the amyloid field continue to strongly support our scientific hypothesis, that selectively targeting the neurotoxic amyloid oligomer will be key to optimum safety and efficacy. Three amyloid antibody programs that have shown clinical benefit, from Eisai, Biogen, and Lilly, all target neurotoxic oligomers, which drives efficacy; but they also bind plaque, which leads to the ARIA-E side effect (edema/brain swelling). At CTAD in 2021, Biogen reported similar findings during a treatment gap with aducanumab that Eisai reported with BAN2401 at CTAD in 2019, confirming the likelihood that targeting **neurotoxic oligomers** was the likely mechanism of efficacy. In both programs, during a treatment gap of approximately one and a half years, the decline in cognition, which had been slowed by active treatment, returned to the same rate as placebo, despite plaque staying at a reduced, low level. Eisai in 2019 noted that these findings suggested that continued treatment

against the soluble oligomer may be necessary to maintain clinical benefit. The same phenomenon was seen in the Lilly trial of donanemab, where patients stopped treatment after achieving a pre-determined level of amyloid plaque reduction. The clinical benefit was greater in the middle of the trial, when the majority of patients were still on treatment, than it was at the end when the majority had stopped treatment. (See below for more detail.)

More information on all these topics is available on our updated website at [www.promisneurosciences.com](http://www.promisneurosciences.com)

We are very bullish about the prospects for ProMIS in 2022 and beyond and continue to believe as we have discussed before that the neurodegenerative disease field has turned a corner. Our unique, selective antibodies could be valuable contributors to making real progress against these devastating diseases, and we remain committed to making that happen. Thank you for your ongoing interest in ProMIS.

ProMIS Neurosciences: Chairman's Memorandum. August 4, 2021; **Updated December 16 with notes from CTAD, November 2021**

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We are in a new era in the fight against Alzheimer's, ALS, and other neurodegenerative diseases. ProMIS and many others have predicted this development. We believe that the Alzheimer's community will look back on 2021 as a turning point, just as 2010 was a turning point in immuno-oncology and the fight against cancer. There were many signs of that recognition at the AAIC 2021 meeting, **and at the CTAD meeting in November 2021.**

#### **Key Points: Alzheimer's**

- 1) Alzheimer's is seeing a dramatic increase in interest and investment, it has become an area that large pharma companies cannot afford to be left out of, akin to immuno-oncology in the last decade.
- 2) The FDA's decision to approve Biogen's Aduhelm confirmed the regulatory feasibility of Alzheimer's disease therapies, contributing to the accelerated interest and investment. ***The EMA (European Medicines Agency) decided to deny Aduhelm approval, as was announced in November. However, "regulatory feasibility" has led to both Lilly and Eisai filing for accelerated approval of their therapies.***
- 3) The door has been opened for improved next generation therapies, that selectively target the pathogenic form of proteins like amyloid-beta.
- 4) Therapies that target aggregated amyloid-beta (neurotoxic oligomers and plaque) in Alzheimer's have all shown clinical benefit; therapies that target monomer or are non-selective, targeting all forms of amyloid-beta, have failed in every clinical trial.
- 5) Successful clinical outcomes from the three therapies targeting aggregated amyloid, Biogen's Aduhelm, Eisai's BAN2401 (lecanumab) and Lilly's donanemab, support the concept that the neurotoxic oligomer is the key target for therapy, and clinical benefit comes from neutralizing the oligomer. The simplest explanation (Occam's Razor), fitting all the clinical and scientific data, is that the oligomer needs to be the target for therapy.
- 6) ProMIS' PMN310 is well positioned to be the best of the next generation therapies in Alzheimer's, with a high

degree of selectivity for the toxic oligomer, effector function with the potential for efficacy at a low dose, and the possibility of both IV and subcutaneous delivery.

Amyloid targeted therapies: PMN310 as potentially the best “next generation” therapy

- Therapies targeting aggregated amyloid (neurotoxic oligomers and plaque) show benefit
- Clinical data suggest that oligomer targeting is actually the cause of benefit (not plaque)
- “Next generation” therapies will more selectively target only neurotoxic oligomers
- PMN310 appears to have the desired profile for a “best” next generation therapy

1) The evidence suggests that Aduhelm, BAN2401, and donanemab all target both plaque and neurotoxic oligomers, (but not monomer)

- Biogen’s Aduhelm has demonstrated this in publications, and in the FDA Advisory Committee briefing package.
- Eisai’s BAN2401 was selected by BioArctic to target toxic oligomers but has some plaque binding.
- Lilly’s donanemab was designed to target plaque, but targets pyroglutamate amyloid, which has long been associated with toxic oligomer formation. Indeed, in our hands, testing of donanemab side-by-side with other antibodies known to bind amyloid oligomers (all antibodies sourced from Creative Biolabs) showed that donanemab binds both synthetic oligomers and soluble oligomers from human brain homogenate at a similar level as Aduhelm and other antibodies.

2) Clinical results obtained during treatment gaps, support the view that neurotoxic oligomers, not plaque, are the driver of disease progression, and that continued dosing to sustain clearance of toxic oligomers is required to maintain benefit after plaque clearance.

Eisai presented data on BAN2401 at CTAD in December 2019 and drew exactly this conclusion.

Patients who had been in the Phase 2 trial stopped treatment and were evaluated for an open label extension study. Patients in high dose treatment arms had experienced both a slowing of disease progression (measured on the clinical endpoint CDR-SB, the endpoint used in both the Aduhelm and the ongoing BAN2401 pivotal trials), and a reduction of amyloid plaque, often down to normal levels.

-Plaque remained low and did not increase after stopping treatment. If plaque was the disease driver, then disease progression would be expected to stay stably reduced. In fact, the opposite happened. After treatment was stopped, plaque stayed low, but disease progression resumed **at the same rate as placebo**.

- Eisai concluded that: “Continued clinical progression with persistent amyloid [plaque] reduction during Gap Period suggests: a potential role for soluble amyloid aggregate species in clinical decline; continued treatment may be necessary even after amyloid [plaque] is removed.”

**At CTAD in November, Biogen presented data from their “gap period”. The results were almost exactly as reported by Eisai two years earlier. After treatment was stopped, plaque stayed low, but disease progression resumed at the same rate as placebo.**

The Lilly donanemab Phase 2 study was designed in a way that provided some information on the same issue. The study was “treat to target”, i.e., after amyloid plaque was reduced to a target level, treatment was stopped. By week 28 of the 76-week study, 27.4% of the patients in the treatment arm were switched to placebo and had a 48-week treatment gap; by week 56 of the study, 54.7% of the patients in the treatment arm were switched

to placebo and had a 20-week treatment gap.

Based on the hypothesis that oligomer binding and neutralization may have contributed to the positive outcome of donanemab, one would expect that the clinical benefit in the middle of the study might be better than at the end of the study, since by the end a majority of patients were in a treatment gap that might allow disease progression to resume. This is exactly what happened. Measured by CDR-SB, the treatment benefit vs placebo was greater at week 36 than at week 76.

### 3) Biomarkers results further support the oligomer hypothesis

Both Aduhelm and donanemab reduced levels of the biomarker p-tau in a dose-dependent fashion. P-tau (for phosphorylated-tau) is toxic tau. How does an amyloid targeted therapy lower toxic tau?

Steven Strittmatter and others have published on the interaction of amyloid and tau in disease. Amyloid toxic oligomers, which are extra-cellular and can move around the brain, trigger “hyperphosphorylation” of tau, which in its normal healthy form is usually intracellular, or inside the neuron. Toxic, or p-tau, then propagates or spreads in a prion-like fashion and contributes to disease progression. The most likely explanation for the observed lowering of p-tau is a lowering of causative amyloid oligomers.

### 4) Next generation therapies will selectively target only amyloid oligomers, yielding greater efficacy and avoiding the side effect of ARIA-E (brain swelling)

- Current therapies targeting both forms of aggregated amyloid all have a side effect, ARIA-E, which requires complicated and expensive clinical management, including dose titration, MRI assessments, and, occasionally, gaps in treatment.
- ARIA-E has only occurred with antibodies that bind plaque.
- Acumen recently entered the clinic, after a successful NASDAQ IPO, with a single asset, the first selective antibody for amyloid oligomers, ACU193. It is an antibody with no effector function, and a relatively short half-life, that may require high dosing (the initial clinical trial is testing 10mg/kg/month – the same as Aduhelm, but also 60mg/kg/month and 60mg/kg twice a month), but the market reception has been very positive and we believe deservedly so. A recent Stifel analyst report on Acumen described “next generation” therapies as those that selectively target the pathogenic form of proteins like amyloid – we agree.

### 5) PMN310 could be the “best of the next generation” anti-amyloid, AD therapies

- PMN310 is extremely selective for toxic oligomers, most importantly those in human brain homogenate (the “real thing”) with high affinity binding.
- That selectivity can improve efficacy over first generation therapies like Aduhelm by not wasting dose on the wrong target, plaque.
- That selectivity will likely result in little or no ARIA-E side effect which has only been seen in therapies that bind amyloid plaque.
- PMN310 has been updated with effector function, an isotype of antibody that promotes microglial clearance, and will likely enhance efficacy at a lower dose. An antibody with this isotype (IgG1) that did not bind plaque
- Lilly’s solanezumab – had little or no ARIA-E.
- PMN310 has shown stability at high concentrations, which along with high affinity binding and possible efficacy at a low dose has the potential to support development of a subcutaneous delivery form of PMN310 for maintenance therapy to avoid recurrent infusions after an initial course of IV therapy to “knock down” disease.
- These combined features could give PMN310 safety, efficacy, cost, and convenience advantages over other amyloid directed therapies for Alzheimer’s disease.