zēlosDx

# WINDOW INTO THE BRAIN™

## TOOLS TO ENABLE BREAKTHROUGH DISCOVERIES IN BRAIN DISEASE

# TECHNOLOGY OVERVIEW

**ZelosDx** is a Tucson-based company that is commercializing blood testing products to help researchers make breakthrough discoveries in brain health and disease. **Our WINDOW INTO THE BRAIN™ technology is based on the concept that phagocytic cells in peripheral blood present a novel tool for a rapid and low-cost diagnostics of brain health.** It is our business goal to provide such a tool to the clinical research community to enable breakthrough discoveries in disease onset and progression, drug development and patient care. It is well known that phagocytic cells are recruited to inflamed brain tissue where they engulf debris resulting from disease or trauma[1-3]. More recently it has been shown that such debris is also generated in cognitively normal brains[4,5]. ZelosDx was the first to demonstrate that phagocytic cells carrying brain biomarkers can reenter the blood stream, presenting **a novel and hitherto unrecognized source of molecular biomarkers for neurodegeneration in the aging, diseased, or traumatized brain**.

Neuronal biomarkers can be useful for the diagnosis of brain trauma [6-9], dementia[10,11] or disease[11-17], presenting the potential for early detection of neurodegeneration. But harmful metabolites are also generated in the healthy brain and are cleared through the glymphatic pathway[18]. Glymphatic dysfunction may result in the accumulation of toxic proteins such as A-beta and Tau, leading to the invasion of phagocytes and subsequent neuroinflammation[19], thereby generating conditions prodromal for neurodegenerative diseases[18,20]. Typically these molecules cannot spill directly into the blood stream due to the action of the blood-brain barrier (BBB), but even when the BBB breaks down as a result of trauma or disease, their concentration in serum or plasma is near or below detection limits for standard enzyme-linked immunosorbent assays (ELISA). While this limitation can be partially overcome by either testing cerebrospinal fluid (CSF), which is invasive, risky and costly, or through the use of very sophisticated and expensive equipment solutions[21], those approaches do not lend themselves to routine clinical applications.

**ZelosDx,** with its patented ELISA technology termed '**Window into the Brain' (WIB™),** was the first to produce evidence that **phagocytic cells carrying brain biomarkers can be detected in peripheral blood**[22], not only in patients with neurologic disease, but even in healthy donors (unpublished)**.** Building on its ELISA data obtained using human as well as animal blood, ZelosDx's product development plan includes the use of single cell analysis to test for various brain-specific biomarkers in phagocytic cells, the determination of the cell type most useful for this analysis, and the development of a method for their isolation from small amounts of peripheral blood. In collaboration with physicists at the University of Wisconsin-Milwaukee, ZelosDx is working on a path for automated rapid and low-cost biomarker

quantitation for applications in clinical research and diagnostics. Other ongoing and planned collaborative efforts include the application of ZelosDx technologies to the analysis of blood samples from human donors with various neurological conditions, as well as animal studies of deep tissue and transcranial electro-stimulation.

Neurologic disease and trauma affect over 100 million patients in the US alone and is on the increase[23], with associated healthcare costs of $1.3 trillion annually. Except for a single FDA-cleared biomarker-based diagnostic for TBI[8,24], low-cost blood testing products that are sufficiently sensitive for detection in early-stage disease are unavailable and sorely needed for clinical research and drug development. Especially with the aging demographics in the US and other developed countries the monitoring of brain health with a simple blood test would be of tremendous health and financial benefit to the patient as well as the society at large.

The global biomarker market is estimated to reach $53 billion by 2021[25], with **neurological biomarkers** comprising 10%, but growing at a 14.5% compound annual growth rate (CAGR) due to the rising prevalence of neurological diseases and increasing emphasis on early diagnosis & treatment[26]. ZelosDx will address this market opportunity by making the novel **WIB™** novel blood-testing tool widely available in the form of easy-to-use reagent kits and assay systems to investigate neurological processes at the cellular level. The diverse interests of our current collaborators and potential customers that we have interviewed may serve as evidence for the potentially wide applicability of phagocytes as a source for biomarkers. The most efficient approach to reach this research market is to license to manufacturers the patented ZelosDx technology for incorporation into their blood testing assay systems.

If you are interested in learning more about the ZelosDx technology you can reach Uwe Muller, PhD, VP Product Development at umuller@zelosdx.com or Marie Wesselhoft, President, at mwesselhoft@zelosdx.com.


1. Gjelstrup, M.C. *et al.* Subsets of activated monocytes and markers of inflammation in incipient and progressed multiple sclerosis. *Immunol Cell Biol* **96**, 160-174 (2018).
2. Ziegler-Heitbrock, L. The CD14+ CD16+ blood monocytes: their role in infection and inflammation. *J Leukoc Biol* **81**, 584-92 (2007).
3. van den Bossche, W.B.L. *et al.* Monocytes carrying GFAP detect glioma, brain metastasis and ischaemic stroke, and predict glioblastoma survival. *Brain Commun* **3**, fcaa215 (2021).
4. Yeung, L.K. *et al.* Cerebrospinal fluid amyloid levels are associated with delayed memory retention in cognitively normal biomarker-negative older adults. *Neurobiol Aging* **84**, 90-97 (2019).

5. Tort-Merino, A. *et al.* Tau Protein is Associated with Longitudinal Memory Decline in Cognitively Healthy Subjects with Normal Alzheimer's Disease Cerebrospinal Fluid Biomarker Levels. *J Alzheimers Dis* **70**, 211-225 (2019).
6. Czeiter, E. *et al.* Blood biomarkers on admission in acute traumatic brain injury: Relations to severity, CT findings and care path in the CENTER-TBI study. *EBioMedicine* **56**, 102785 (2020).
7. Ren, C. *et al.* Assessment of Serum UCH-L1 and GFAP in Acute Stroke Patients. *Sci Rep* **6**, 24588 (2016).
8. Bazarian, J.J. *et al.* Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. *Lancet Neurol* **17**, 782-789 (2018).
9. Bryden, D.W., Tilghman, J.I. & Hinds, S.R., 2nd. Blast-Related Traumatic Brain Injury: Current Concepts and Research Considerations. *J Exp Neurosci* **13**, 1179069519872213 (2019).
10. Lewczuk, P. *et al.* Cerebrospinal fluid and blood biomarkers for neurodegenerative dementias: An update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry. *World J Biol Psychiatry* **19**, 244-328 (2018).
11. Lo, R.Y. *et al.* Longitudinal change of biomarkers in cognitive decline. *Arch Neurol* **68**, 1257-66 (2011).
12. Lashley, T. *et al.* Molecular biomarkers of Alzheimer's disease: progress and prospects. *Dis Model Mech* **11**(2018).
13. Janelidze, S. *et al.* Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. *Nat Commun* **11**, 1683 (2020).
14. Feneberg, E., Gray, E., Ansorge, O., Talbot, K. & Turner, M.R. Towards a TDP-43-Based Biomarker for ALS and FTLD. *Mol Neurobiol* **55**, 7789-7801 (2018).
15. Körtvelyessy, P. *et al.* Biomarkers of Neurodegeneration in Autoimmune-Mediated Encephalitis. *Front Neurol* **9**, 668 (2018).
16. Majbour, N.K. *et al.* Oligomeric and phosphorylated alpha-synuclein as potential CSF biomarkers for Parkinson's disease. *Mol Neurodegener* **11**, 7 (2016).
17. Abdelhak, A. *et al.* Glial Activation Markers in CSF and Serum From Patients With Primary Progressive Multiple Sclerosis: Potential of Serum GFAP as Disease Severity Marker? *Front Neurol* **10**, 280 (2019).
18. Rasmussen, M.K., Mestre, H. & Nedergaard, M. The glymphatic pathway in neurological disorders. *Lancet Neurol* **17**, 1016-1024 (2018).
19. Emmert, A.S. *et al.* Impaired neural differentiation and glymphatic CSF flow in the Ccdc39 rat model of neonatal hydrocephalus: genetic interaction with L1cam. *Dis Model Mech* **12**(2019).
20. Benedict, C., Blennow, K., Zetterberg, H. & Cedernaes, J. Effects of acute sleep loss on diurnal plasma dynamics of CNS health biomarkers in young men. *Neurology* **94**, e1181-e1189 (2020).
21. Song, L. *et al.* A digital enzyme-linked immunosorbent assay for ultrasensitive measurement of amyloid-beta 1-42 peptide in human plasma with utility for studies of Alzheimer's disease therapeutics. *Alzheimers Res Ther* **8**, 58 (2016).

22. White, V. & Ramesh, N. Re-circulating Phagocytes Loaded with CNS Debris: A Potential Marker of Neurodegeneration in Parkinson's Disease? *AIMS Medical Science* **2**, 26-34 (2015).
23. Feigin, V.L. *et al.* Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study. *JAMA Neurol* (2020).
24. Abbott. Abbott Receives FDA 510(k) Clearance for the First Rapid Handheld Blood Test for Concussions. (https://abbott.mediaroom.com/2021-01-11-Abbott-Receives-FDA-510-k-Clearance-for-the-First-Rapid-Handheld-Blood-Test-for-Concussions, 2021).
25. MarketsandMarkets. Biomarkers Market by Product (Consumables, Service), Type (Safety, Efficacy, Validation), Disease Indication (Cancer, Cardiovascular Disorders), Application (Diagnostics Development, Drug Discovery and Development, Disease-Risk) - Global Forecast to 2021 (2017).
26. Grandviewresearch. Neurological Biomarkers Market Size, Share & Trends Analysis Report By Application (Alzheimer's, Parkinson's, Multiple Sclerosis, Autism Spectrum Disorder), By Type, By End-use, By Region, And Segment Forecasts, 2019 - 2026. (2019).