NEWS RELEASE

Prothena Announces Poster Presentation on its TDP-43 CYTOPE® Program at Neuroscience 2025

2025-11-19

- TDP-43 CYTOPE® preclinical data demonstrates the potential of Prothena's CYTOPE technology as a novel modality for delivering large molecules into cells, enabling precise targeting of intracellular disease pathways
- Systemically-administered TDP-43 CYTOPE rapidly and efficiently distributed to the brain and periphery, internalized into the cytosol and significantly reduced intracellular TDP-43 pathology in an ALS mouse model
- TDP-43 CYTOPE meaningfully reduced intracellular TDP-43 pathology and associated RNA dysregulation caused by cryptic exon inclusions - key pathogenic features of TDP-43 proteinopathies - in a human-derived neuronal cell line

DUBLIN, Ireland--(BUSINESS WIRE)-- Prothena Corporation plc (NASDAQ:PRTA), a late-stage clinical biotechnology company with a robust pipeline of investigational therapeutics built on protein dysregulation expertise, announced a scientific presentation at Neuroscience 2025, hosted by the Society for Neuroscience (SfN) in San Diego, CA.

Session Title PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development
Poster Title PSTR440.04: Treatment with a Cell-Internalizing CYTOPE® Targeting pTDP-43 Reduces Intraneuronal Pathology in a Mouse Model of ALS
Date: November 19, 2025
Time: 1pm PT

CYTOPE® is a novel drug delivery modality enabling cytosolic delivery of macromolecules in the brain and periphery through an efficient endosomal escape mechanism that preserves membrane and vesicle integrity following

systemic administration. This technology potentially allows for targeting of previously undruggable intracellular disease targets. To demonstrate this, we developed and investigated our TDP-43 CYTOPE program in multiple preclinical models.

Preclinical data from in vivo transgenic mouse model of ALS expressing human mutant TDP-43:

- Systemically-administered TDP-43 CYTOPE rapidly and efficiently distributed to the brain, internalized into the cytosol and colocalized with intracellular pTDP-43 pathology in rNLS8 mice
- Systemically-administered TDP-43 CYTOPE significantly reduced intracellular pTDP-43 pathology in rNLS8 mouse motor cortex and neuromuscular junction

Preclinical in vitro data from rat and human-derived neuronal cell lines and human iPSC motor neurons:

- TDP-43 CYTOPE rapidly and efficiently internalized into the cytosol and colocalized with pre-formed cytosolic pTDP-43 aggregates
- TDP-43 CYTOPE promoted significant clearance of cytosolic pTDP-43 aggregates and meaningfully reduced RNA dysregulation driven by cryptic exon inclusions, defining pathogenic features of ALS and other TDP-43 proteinopathies

These results demonstrate the potential of our CYTOPE technology as a novel modality for delivering large molecules into cells, enabling precise targeting of intracellular disease pathways.

About Prothena

Prothena Corporation plc is a late-stage clinical biotechnology company with expertise in protein dysregulation and a pipeline of investigational therapeutics with the potential to change the course of devastating neurodegenerative and rare peripheral amyloid diseases. Fueled by its deep scientific expertise built over decades of research, Prothena is advancing a pipeline of therapeutic candidates for a number of indications and novel targets for which its ability to integrate scientific insights around neurological dysfunction and the biology of misfolded proteins can be leveraged. Prothena's pipeline includes both wholly-owned and partnered programs being developed for the potential treatment of diseases including ATTR amyloidosis with cardiomyopathy, Alzheimer's disease, Parkinson's disease and a number of other neurodegenerative diseases. For more information, please visit the Company's website at **www.prothena.com** and follow the Company on X (formerly Twitter) @ProthenaCorp.

Forward-Looking Statements

This press release contains forward-looking statements. These statements relate to, among other things, our CYTOPE® drug delivery modality that potentially enables (i) cytosolic delivery of macromolecules in the brain and

periphery through an efficient endosomal escape mechanism that preserves membrane and vesicle integrity and (ii) the targeting of previously undruggable intracellular disease targets and pathways. These statements are based on estimates, projections and assumptions that may prove not to be accurate, and actual results could differ materially from those anticipated due to known and unknown risks, uncertainties and other factors, including but not limited to uncertainties related to the completion of operational and financial closing procedures, audit adjustments and other developments that may arise that would require adjustments to the preliminary financial results included in this press release, as well as those described in the “Risk Factors” sections of our Quarterly Report on Form 10-Q to be filed with the Securities and Exchange Commission (SEC) on November 6, 2025, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. We undertake no obligation to update publicly any forward-looking statements contained in this press release as a result of new information, future events, or changes in our expectations.

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Source: Prothena Corporation plc