Wren Therapeutics Announces Publication in Nature Research Journal

Paper demonstrates predictive capability of chemical kinetics in assessing clinical-stage molecules for Alzheimer's disease ("AD")

- Significant paper published in Nature Structural and Molecular Biology
- Co-authored by Wren's scientific founders and senior Biogen scientists
- Aducanumab compared, in a blinded study, to three clinical-stage antibodies using chemical kinetics
- Only aducanumab dramatically reduces the flux of amyloid-β oligomers, a key neurotoxic species associated with AD
- Wren advancing its own lead small molecule programs against amyloid-β and α-synuclein using the same kinetics approach
- Wren to nominate clinical candidate for AD in the first quarter of 2021
- Other targets including TDP-43, tau and IAPP in earlier stage discovery

CAMBRIDGE, United Kingdom, September 28, 2020 – Wren Therapeutics, ("Wren", the "Company"), a biopharmaceutical company pioneering a unique approach to drug discovery, today announces that a research paper entitled "Kinetic fingerprints differentiate the mechanisms of anti-Aβ antibodies" has been published in Nature Structural & Molecular Biology, a prestigious scientific journal. The paper was co-authored by Wren's scientific founders together with senior scientists at Biogen.

The publication describes the use of chemical kinetic analysis to assess the mechanisms of action of four clinical stage anti-Aβ antibodies: aducanumab (Biogen), gantenerumab (Roche), bapineuzumab (Elan) and solanezumab (Eli Lilly). The results provide unique insights into potential correlations between suppression of specific molecular steps in the aggregation process and clinical outcomes.

Wren founding scientist and lead author, Professor Sara Linse commented:

The relative characteristics and mechanisms of action of different anti-Aβ therapeutic agents have proved highly challenging to assess. Our analysis reveals the strikingly different effects that four antibodies targeting the same peptide have on the individual molecular steps in the aggregation process. This translates to the antibodies having different capacities to reduce the level of oligomers. The chemical kinetics approach is unique in its ability to deliver these important insights.

Looking forward, the paper highlights that stronger inhibition of the relevant molecular steps could enable even more effective future therapies for Alzheimer's disease, and it's exciting to be working with the Wren team using the same

kinetics approach to develop our own small molecule therapeutics with the most effective mechanism of action against Aβ oligomers.

All four of the antibodies studied bind to Aβ. However, the chemical kinetic analyses show that each has different and distinctive effects on the individual microscopic processes that contribute to the overall aggregation pathway. Importantly, even though several of these antibodies preferentially bind to the same aggregated forms of Aβ, they have substantially different effects on the kinetics.

The results demonstrate that, singularly among these four antibodies, aducanumab selectively inhibits the catalytic cycle that generates new Aβ oligomers, a key neurotoxic species associated with AD. The study emphasises the critical importance of quantifying the effects of potential therapeutic agents on the underlying microscopic steps in the misfolding and aggregation pathway. The publication can be found here.

Dr. Andrew von Eschenbach, former FDA Commissioner and member of the Wren Therapeutics board of directors commented:

By shedding light on their biophysical mechanisms of action, this paper greatly augments the observed clinical results of antibody therapies and can foster a new era for the treatment of Alzheimer's disease.

Wren's chemical kinetics technology can and should play a central role in therapeutic advancement of antibodies and small molecules that can benefit patients suffering from a wide range of protein misfolding diseases.

Wren's proprietary platform is based on chemical kinetics, a pioneering approach to address protein misfolding diseases. The company was established in 2016, after two decades of prior academic research in the area, and is a spin-out from the University of Cambridge and Lund University. The company's scientific founders and co-authors of today's publication, Professors Sir Chris Dobson, Sara Linse, Michele Vendruscolo and Tuomas Knowles, are credited with multiple important breakthroughs contributing to the understanding of the molecular basis of protein misfolding and its connection to more than 50 diseases. Their work has been published in over 1,000 peer-reviewed papers.

Dr. Samuel Cohen, Chief Executive Officer and co-author commented:

The complexity of protein aggregation has made it resistant to analysis using conventional drug discovery approaches; but now, by tackling directly the dynamic molecular-level steps that drive aberrant biology in Alzheimer's disease, the Wren platform offers a route to drug them effectively. This paper provides a further demonstration as to how our proprietary kinetics platform delivers predictive, actionable and highly valuable information to enable the discovery and development of molecules for protein misfolding diseases.

At Wren, we have spent the past four years industrialising the kinetics platform for drug discovery, and using it to develop our own small molecule therapeutics against multiple misfolding protein targets. We expect, in the first quarter of 2021, to nominate a clinical candidate for the treatment of Alzheimer's disease.

About Wren

Wren (www.wrentherapeutics.com) is a spin-off company from the University of Cambridge (UK) and Lund University (Sweden), focused on drug discovery and development for protein misfolding diseases. Wren is advancing an entirely novel approach to address this class of diseases, based on more than a decade of research from its scientific founders focused on the chemical kinetics of the protein misfolding process. Wren's predictive, quantitative platform is built on concepts from the physical sciences and is a fundamental shift from the descriptive, qualitative methods of traditional biology, which have failed to successfully address these complex systems. Wren is using its unique approach to develop a broad pipeline of therapeutics for protein misfolding diseases.

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