Amyl Therapeutics
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Amyloidosis: untangling the hardest knots to clear organs of toxic plaques

Amyl Therapeutics is developing a novel treatment for clearing misfolded proteins that aggregate into fibrils to form amyloid plaques that bind to organs, causing neurodegenerative diseases and other systemic conditions.

For proteins, function follows form. Misfolded proteins not only lose their normal physiological functions, but can also acquire new properties that drive pathological processes leading to disease. Amyloid plaques comprising tangled fibrils of misfolded proteins are well-known drivers of neurodegenerative diseases including Alzheimer's and Parkinson's disease, but they are also present in a number of systemic amyloidosis conditions including light chain amyloidosis and transthyretin amyloidosis.

Amyl Therapeutics, headquartered in Liège, Belgium, is developing a novel anti-amyloid protein therapeutic that binds to a common structural feature of amyloids, the cross-β amyloid fold, disrupting the interactions between peptides essential for the formation of fibrils (Fig. 1). Not only does Amyl's candidate prevent the formation of new fibrils and plaques, it also binds to established fibrils deposited on organs, where it attracts immune cells such as macrophages that destroy the fibril complexes and clear the organs. In addition, unlike other attempted treatments for amyloid designed to inhibit the production of fibrils by specific proteins in a given disease, Amyl's candidate has a mechanism of action that works against a broad variety of amyloid-forming proteins.

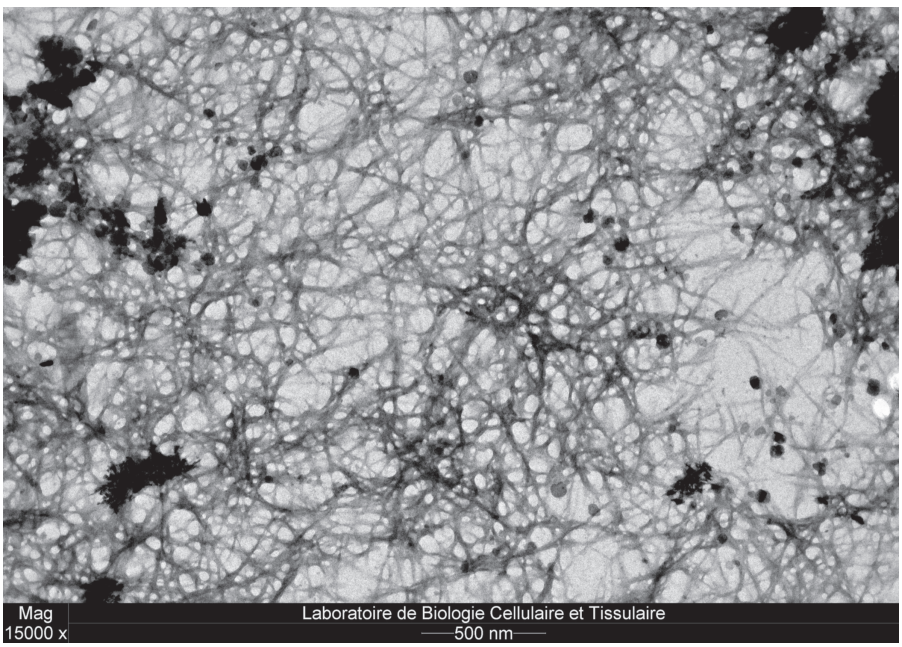

Fig. 1 | Untangling amyloidosis. Amyloid aggregates form through a series of steps when protein monomers clump together into oligomers that go on to form proto-fibrils, mature fibrils and, finally, amyloid plaques that cause cellular and organ damage. Amyl's therapeutic candidate is designed to prevent the formation of new fibrils and plaques, and clears existing plaques to rescue organ function.

Targeting amyloid

Amyloid diseases result from normal proteins that, for reasons that remain unclear, begin to aggregate into amyloid plaques, which in turn serve as the seed for the formation of new plaques and the spread of disease within organs or throughout the body. Amyloid plaques, which can form outside as well as within cells, cause cellular cytotoxicity through a number of mechanisms, including sequestering of carbohydrates, lipids, nucleic acids, proteins, metal irons and protein-degrading proteasomes. Within the cell, small fibrils disrupt the endoplasmic reticulum, block transport of proteins and RNA across the nucleocytoplasmic membrane, while oligomers of amyloidogenic proteins generate reactive oxygen species. Together, these effects can lead to life-threatening organ failure.

Amyloid aggregation proceeds through a number of steps, each of which presents an opportunity for therapeutic intervention. To date, only one drug, the small-molecule tafamidis, has been developed to interfere with this cascade, but tafamidis is limited to treating amyloidosis specifically driven by aggregation of the transthyretin (TTR) protein. Although some amyloidosis diseases, for example TTR amyloidosis, are caused by the aggregation of a single type of protein, other amyloid diseases are typically characterised by the build-up of multiple different types of protein aggregate, and so therapies targeting specific amyloidogenic proteins are unlikely to have broad enough effects to effectively prevent the formation of new plaques. And tafamidis, along with many other therapies in development, are unable to clear established plaques and rescue organ function.

Clinical candidate

Amyl's candidate is a polypeptide fusion molecule that comprises the Fc portion of an antibody and a binding site that attaches to the cross-β amyloid fold found in all amyloid aggregates. Many different proteins with varying amino acid sequences can form the cross-β amyloid fold, but by recognising the common shape of the amyloid fold rather than specific amino acids, Amyl's candidate has the potential to interrupt the formation of amyloid aggregates and disrupt existing plaques that are causing tissue and organ damage.

These anti-amyloidosis effects of Amyl's lead candidate have been demonstrated in in vitro models of amyloid plaque formation, and the company is currently extending this research into human tissues ex vivo and in vivo animal models, such as mice carrying human amyloid plaques. Because the blood–brain barrier may pose a particular challenge for the delivery of large, protein-based therapies, Amyl's focus is currently on systemic amyloidosis diseases.

Amyl Therapeutics is committed to addressing the unmet medical need posed by amyloid diseases, and welcomes discussions with investors and strategic partners to bring Amyl's promising candidate therapeutic to patients suffering from these conditions.

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