Mission Therapeutics Ltd.
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Leveraging novel chemistry to inhibit previously undruggable DUB targets

Attracting both investors and big pharma, Mission Therapeutics is targeting a range of unmet medical needs, including Parkinson's disease, with its unique deubiquitylating enzyme (DUB) platform.

Mission Therapeutics combines novel biology, proprietary chemistry, and bespoke screening assays to address a previously undruggable class of enzymes, deubiquitylating enzymes (DUBs). This unique mix of capabilities has positioned Mission to deliver first-in-class programs in multiple areas of high unmet medical need, such as cancer, fibrosis, inflammation and neurodegeneration, including a disease-modifying treatment for Parkinson's disease.

Cambridge, UK–based Mission was founded on the work of Steve Jackson of the University of Cambridge. The work exploited the modification of proteins with the small protein ubiquitin (ubiquitylation), as well as the removal of ubiquitin (deubiquitylation) by DUBs. This process controls the targeting of proteins and organelles for degradation and is linked to many disease pathways. Jackson earlier discovered the first PARP inhibitor, olaparib, which is now marketed by AstraZeneca and Merck.

Since its foundation in 2011, Mission has raised £87 million from the venture capital wings of leading pharma companies and blue-chip institutional investors. The preclinical-stage biotech attracted this money and investors' interest on the strength of its potential to be the first company to drug DUBs and to have an impact on diseases with major unmet medical needs, from cancer to neurodegeneration.

The pharma industry increasingly recognizes and is interested in DUBs as potentially important drug targets. To date, research has connected about 20 DUBs to oncology indications, with a similar number linked to central nervous system (CNS) disorders, inflammation, immunity, and infectious disease[1].

Researchers have spent 15 years trying to trigger protein and organelle degradation processes, but specificity and selectivity issues have rendered DUBs tough to drug. Mission, which is focused solely on DUBs, was founded on the belief that it can succeed where earlier groups have struggled. This belief, which is becoming a reality, is built upon a chemistry platform that generates selective, potent inhibitors of DUBs that selectively bind to the active catalytic site of the DUB of interest.

Targeting USP30 to treat Parkinson's

The importance of this platform to Mission's ability to develop first-in-class medicines for major unmet medical needs is evident in its USP30-inhibitor program. The mitochondrial DUB USP30 emerged as a target of major interest to drug developers in 2014, when researchers at Genentech published a paper on its role in Parkinson's[2].

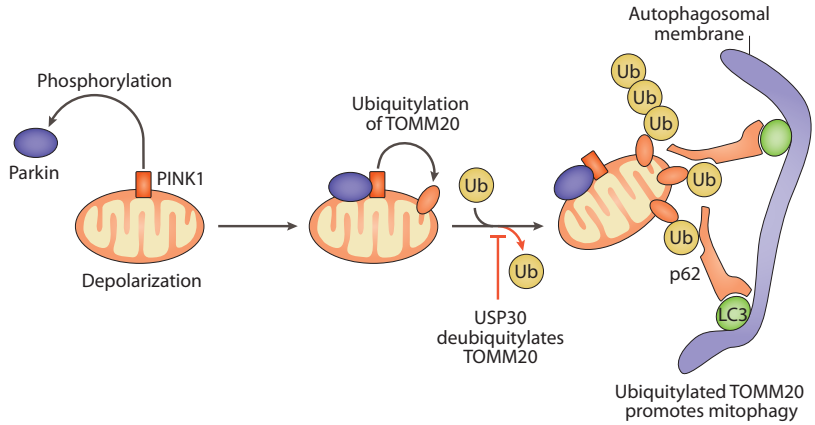

Figure 1: Targeting ubiquitylation: USP30 deubiquitylates TOMM20 promoting mitophagy.

Research has long suggested that mitochondrial dysfunction and the stress it causes play a primary or secondary role in many diseases, including Parkinson's, fibrosis, and mitochondrial disorders.

Typically, dysfunctional mitochondria are degraded through the mitophagy quality control process. If that process fails to degrade the mitochondria, the presence of dysfunctional energy-producing organelles causes oxidative stress in cells, giving rise to conditions including Parkinson's.

What the Genentech paper did is place USP30 at the center of the regulation of this process.

USP30, unlike most DUBs, is localized to the mitochondrial outer membrane. This positions it to interact with parkin and other mitochondrial-resident ubiquitin E3 ligases that regulate mitochondrial quality (**Fig. 1**).

The publication of the Genentech paper started a race to validate and drug USP30. From a standing start, Mission has taken the lead.

Mission's fast response was underpinned by its proprietary chemistry platform, which has provided a rich seam of compounds that are highly potent and selective against DUBs, including USP30. This has enabled Mission to perform compound-related target validation to complement traditional validation approaches such as gene knockdown.

Leveraging the networks of its scientific leaders, Mission has enlisted the help of external experts to add to its in-house capabilities. The biotech is working with Sir Doug Turnbull, a professor of neurology at Newcastle University, on primary mitochondrial disorders. Mission is also working with Richard Wade-Martins, head of the Oxford Parkinson's Disease Centre, who is applying his models of Parkinson's disease to the program with a grant from the Michael J. Fox Foundation.

The support of these external experts has enabled Mission to move toward investigational new drug status (IND)-enabling studies and the clinic. Mission plans to move multiple programs toward the clinic.

This planned multi-pronged move into human testing reflects the breadth of Mission's chemistry and the range of diseases in which USP30 is implicated. Mission has compounds with structures likely to penetrate the CNS that are suitable for use against Parkinson's. Other compounds do not cross the blood–brain barrier; these are ideal as potential treatments for fibrosis. Compounds in a third group fall between these two extremes and are suitable for treating certain mitochondrial disorders.

The INDs for these candidates will mark the first steps in the clinical validation of Mission's science. Given the breadth of Mission's chemistry platform and the diseases in which DUBs are implicated, they could be the first steps on a journey to develop first-in-class programs against multiple diseases with major unmet medical needs.

1. Harrigan, J.A., Jacq, X., Martin, N.M. & Jackson, S.P. *Nat. Rev. Drug Discov.* http://dx.doi.org/10.1038/nrd.2017.152 (2017).
2. Bingol, B. *et al. Nature* **510**, 370–375 (2014).

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