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# Finding needles in haystacks: Omass unveils pipeline aimed at tough-to-drug targets

*By Nuala Moran*

LONDON – There's not yet proof of the pudding, but Omass Therapeutics Ltd.'s new structure-based technology has passed a key test, in enabling the discovery of orally available small molecules aimed at intractable and poorly drugged membrane and complex-bound protein targets.

The targets, including G protein-coupled receptors (GPCRs), intracellular protein complexes and solute carriers, are relevant to immunology indications and rare diseases with high unmet need.

Rosamond Deegan, CEO, Omass

Over the past three years, Omass has taken the underlying gas phase mass spectrometry technology, with which it is possible to study the binding of small molecules to protein assemblies, through to the unveiling of its pipeline earlier this month.

The mass spec technology was developed by Carol Robinson, professor of chemistry at Oxford University, who pioneered its use as a tool for studying intact membrane proteins and intracellular protein complexes, and in understanding how they interact with their immediate environment.

It is possible to observe targets at high resolution in their native form, and with interactions preserved, showing how they are influenced by regulatory proteins, pH, ions and lipids.

Oxford, U.K.-based Omass has industrialized the platform and demonstrated how it can be used to interrogate validated but elusive targets, to show exactly how they interact with their immediate environment.

Amongst the targets Omass believes it has got a handle on is gasdermin D, which earlier this year sank Quench Bio, a Cambridge, Mass., company that was set up with the sole objective of drugging the pore-forming protein.

Gasdermin D sits at the heart of multiple inflammatory cell death pathways. When activated, it forms lytic pores in the cell membrane, leading to the release of inflammatory cytokines.

It is relevant to a slew of inflammatory diseases, but gasdermin D "has a bit of a reputation," with attempts to find a binding site and drug it, "like looking for a needle in a haystack," said Rosamond Deegan, CEO of Omass. "The point about our technology is it can pick out a needle in a haystack," she told *BioWorld*.

Quench certainly found gasdermin D a difficult customer. The company launched in January 2020 with $50 million in series A funding from leading biotech investors, including Atlas Venture, Arix Bioscience, RA Capital and Abbvie Ventures, but in March this year said it was handing back the remaining cash after failing to come up with any good hits.

Deegan said the ability of its technology to look at gasdermin D in the context of its ecosystem meant it was possible to examine all of its physical interactions without having to accommodate the confounding complexity of the cell, but at the same time gaining richer insights than in stripped down structure-based design using crystal structures or cryo-electron microscopy.

"You want enough of the ecosystem in play so it is relevant. But you don't want to be measuring things that are not relevant to the target," Deegan said. "We are trying to sit somewhere in between and retain fidelity to the living system."

Providing cytokines a passage through the cell membrane makes gasdermin D inhibition relevant to a range of inflammatory diseases. "Interleukin-1 beta can only get out of cells through pores; the clinical data is very broad," said Deegan. That includes inhibition of the cytokine with monoclonal antibody drugs in rheumatoid arthritis and lupus and, evidence of its involvement in Alzheimer's disease.

"There is even potential in cancer, though the story is not as clear there," Deegan said. As the first and so far only gasdermin D inhibitor, the Omass molecule encompasses a pipeline in a single program, she said.

It is now planned to test this potential in familial Mediterranean fever, an inherited autoinflammatory disease that causes recurrent episodes of fever and pain in the stomach, joints and muscles.

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"There is very strong data in [a] mouse [model]; it is a rare disease, but quite prevalent, [in which] we will exemplify and get clinical proof of concept," said Deegan.

**A rich pipeline**

Omass raised $18 million in a series A round in November 2018, as it switched from providing the mass spec technology as a service, to applying it to in-house discovery. In February 2020, the company closed a £27.5 million extension of the round, bringing the total to $54.9 million.

Deegan said the company is now two to three years from starting clinical trials. "The programs are quite close to each other – it is a rich pipeline and because the mission is to drug things that are undruggable, the value comes early," she said.

The ambition is to take products all the way to market. However, Deegan also expects to carry out work on targets for partners. "We are a platform company, so we will do deals," she said. The earlier history as a service company shows there is interest from others in getting access to the technology.

The other programs that will be progressed in-house include a melanocortin-2 antagonist (MC2) for treating rare endocrine disorders. MC2 is a GPCR that binds to the adrenocorticotropic hormone. "This is the only one in the portfolio where we are going for best in class rather than first in class. It is inadequately drugged," Deegan said. "We have found a great small-molecule binding site."

Another GPCR target, GPCR65, the dominant proton sensing receptor on immune cells, lacks classic binding sites. That has made it difficult to understand the biology. However, Deegan said, strong links to inflammatory bowel disease in genome-wide association studies encouraged Omass to pursue the target and carry out supporting biology research. In vivo testing of the agonist it has discovered has now begun.

A fourth target, the potassium chloride transporter family member 12 (KCC2), is broadly implicated in multiple indications related to seizures. It belongs to the second largest family of membrane proteins, of which there are more than 400. Of those, half are linked to disease, but there is chemistry against only 20 or so.

Omass intends to take the program forward in Rett's disease, a rare genetic disorder that causes frequent seizures and affects brain development. Deegan said KCC2 has been shown to have reduced expression in Rett's, and also is known to drive seizures. "We think it is the best-in-class target for Rett's," she said.

Finally, solute carrier family 15 member 4 (SLC15A4) is highly validated in immunological disorders. Omass intends to develop its molecule in lupus, where there is a strong genetic link to the chronic autoimmune disease. Researchers at Genentech Inc. reported earlier this year that SLC15A4 knockout mice are protected from lupus-like disease.