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Crescendo CEO says Takeda's decision to exercise licence option is validation of its immunotherapy platform

Takeda's decision to exercise a licence option much earlier than planned as part of a $790 million collaboration with Crescendo Biologics is a validation of its novel approach to immunotherapies, the chief executive of the UK-based biotech has said.

Takeda and Crescendo partnered in October 2016 to allow the Japanese pharma access to Crescendo's 'Humabody' platform, which is used to develop molecules that work in a similar way to antibodies but are smaller, allowing them to penetrate and accumulate in tissue and tumours while clearing quickly from circulation to minimise systemic toxicity.

The deal included $36 million as an upfront payment and up to $754 million in milestones.

Crescendo on Monday said Takeda has now taken an exclusive licence to Humabodies directed to one of its oncology targets, adding that this "comes substantially earlier than planned".

The deal is a major boost for Crescendo and its technology, the company's CEO Peter Pack told APM at the end of last week, ahead of the public announcement.

"It's going so well that they have decided to take the licence much earlier than planned, which for us is important because it validates our platform, it validates the way we are doing things."

Transgenic mouse platform

Crescendo's Humabody platform is based on a genetically modified mouse that has the full range of the human gene repertoire. From this transgenic mouse, Crescendo's scientists can create a human variable domain (VH) of a heavy-chain antibody that still has the binding functions of the full antibody. These can be used as building blovks that can be combined to engage therapeutic targets.

"So what we have is much smaller than an antibody – it's basically a tenth of an antibody but it does the same job in terms of affinity and specificity", said Pack in an interview at Crescendo's headquarter in Cambridge, UK.

Smaller than antibodies

This has a lot of advantages, said Pack, who was initially an investor in Crescendo before joining as CEO in 2015.

For instance, it is easier to create bispecific or even trispecific molecules that can be directed against multiple targets in the body. And even when multiple VHs are combined in such a way, they are still smaller than an antibody.

"Because it's much smaller, it has a superior biodistribution – it can go through tissues into tumours much faster. It's not just five or tenfold – it is even higher."

He added: "The important thing in the end if to have more potent biologics. And if something goes much deeper and faster into tumours, delivers something into tumours or binds something or activates the immune system in tumours, it is a more potent approach than to work with a much bigger, slower, conventional antibody."

Lead programmes

Outside the Takeda deal, Crescendo has several main oncology programmes based on this platform, the most advanced of which is CB307, a bispecific T-cell engager that is designed to bind to CD137, a molecule expressed by a tumour, in order to encourage T-cells to attack the cancerous cell.

Several monospecific monoclonal antibodies that can agonise CD137 are already in development and are known to be potent T-cell activators. However, these molecules can also lead to damaging side effects as they can also impact non-cancer cells, said Pack.

CB307 is designed to retain the ability to activate T-cells but to reduce potential toxicity, as it is deliberately monovalent for CD137 and as such is unable to cause CD137 clustering in normal tissue. Instead, the bispecific Humabody is also designed to bind to PSMA, which are highly expressed on tumour cells in prostate cancer, and only then does it cause clustering of CD137, activating T-cells to target only the cancer cell.

The molecule is now on course for Phase I studies in prostate cancer and is currently in the chemistry, manufacturing, and controls stage of development, said Pack.

This development has been supported by $70 million in series B financing Crescendo received back in April

Partnering

Other key programmes for Crescendo include CB201, a PD-1 antagonist, and CB213, a bispecific molecule that is an antagonist of both PD-1 and LAG-3 that is being developed as a treatment for patients non-responsive to PD-1 blockade alone.

These latter two programmes are potential partnering opportunities for Crescendo, according to the company's website.

The company will be selective in its collaborations, however, said Pack. "We are not a service company, so our goal is not to make as many partnerships as possible."

Looking ahead, Pack said he expects the company to have several programmes in clinical development five years down the line.

The platform also has the potential to more easily develop drugs for other indications, using the VH as a building block.

For instance, CB307 is designed to treat prostate cancer by targeting PSMA, but Crescendo can just take the initial VH that binds to CD137 and combine it with another that is directed against a target that is highly expressed on the tumour cells of another type of cancer.

"So at some stage you will have a lot of building blocks already in the fridge," he said.

"It's not starting from scratch. It's basically combining something which you already have, and it's an even more rapid approach to come up with novel bispecific and trispecific approaches. The more building blocks we have, the easer it is for us."