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Manufacturing the next generation of cancer immunotherapeutics

Lokon Pharma's immunostimulatory gene therapy, delivered in oncolytic adenoviruses, are poised to enter pivotal trials for cancer. Biovian Oy is manufacturing Lokon's immunotherapeutics for these trials and beyond.

A little more than 20 years ago, PhD student Angelica Loskog was poring over data on the effects of immunostimulatory viruses, which, in mouse models, have the ability to activate antitumor immunity and lyse and kill cancer cells. To Loskog's amazement, she found that all of the mice treated with a particular adenovirus were tumor-free. Since then, Loskog, as CEO of Swedish biotech Lokon Pharma, has been building on these early studies to create next-generation immunotherapeutics for cancer using proprietary oncolytic adenoviruses armed with transgenes encoding immunostimulatory proteins, a platform dubbed LOAd.

Today, after two decades of intensive R&D, Lokon has a highly promising clinical candidate in the LOAd703 program, including phase 2 trials for pancreatic ductal adenocarcinoma (PDAC). "One of our trial participants, telling his story on the Swedish TV show *Malou*, told how, a year after the study, he was stable, asymptomatic and feeling healthy despite having no other treatments," said Loskog. "We want this outcome for as many cancer patients as possible".

LOAd703, an engineered version of adenovirus serotype 5/35, is double-armed with two transgenes—TMZ-CD40L and 4-1BBL—that potently induce local and systemic anti-tumor immunity. Locally, TMZ-CD40L and 4-1BBL activate antigen-presenting cells and stimulate macrophages, cytotoxic lymphocytes (CTLs) and natural killer cells to attack cancers cells. Systemically, they lead to migration of dendritic cells to lymph nodes where they activate naive CTLs and also enhance immune surveillance by CTLs and natural killer cells (Fig. 1).

In addition to PDAC, LOAd703 is also being developed for a range of other cancers, including ovarian, biliary and colorectal cancer, as well as malignant melanoma. For clinical development, however, the current focus is on PDAC, a particularly aggressive malignancy with a 5-year overall survival of less than 8%, and the fourth most common cause of cancer-related deaths worldwide—with an incidence that is rising.

Promising trial results

At the American Society of Clinical Oncology Gastrointestinal Cancers symposium in 2020, Lokon reported early results from a phase 1/2 trial of LOAd703 administered in conjunction with a chemotherapy regimen of nab-paclitaxel/gemcitabine, one of the current standards of care for pancreatic cancer. Data from the first 13 patients treated revealed that 6 showed a partial response, and data from the remaining patients in the first arm of the trial will be published soon. In the second arm, LOAd703 is being evaluated in combination with Roche's checkpoint inhibitor Tecentriq (atezolizumab) for PDAC. Enrollment for the trial is ongoing.

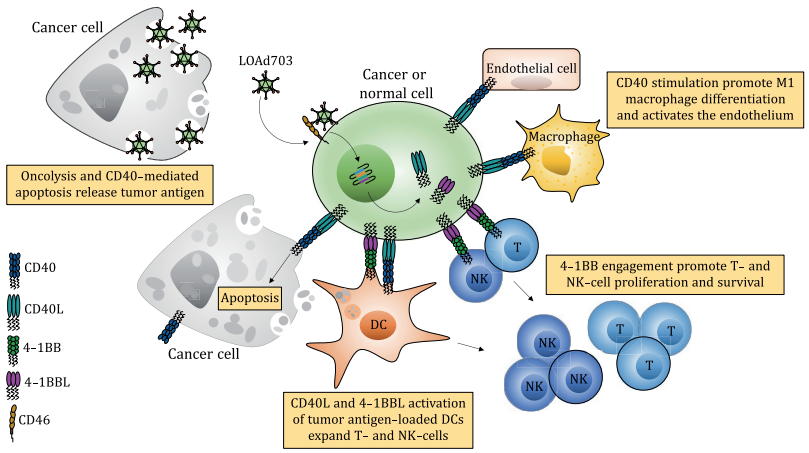

Fig. 1 | Immune cell activation. DC, dendritic cell; NK, natural killer.

Based on the phase 1/2 results, Lokon is now planning phase 3 trials of LOAd703, which will require the robust, large-scale manufacture of high-quality, potent, safe and stable batches of LOAd703 at an acceptable cost. For Lokon, like many small-to-medium-sized enterprises that drive so much innovation in today's global economy, this means outsourcing production of trial materials to a reputable contract development and manufacturing organization (CDMO).

The complexity of LOAd703 means that Lokon had to find a CDMO with the technical expertise to not only handle the different aspects of manufacturing LOAd703, but also the capacity to perform all the necessary steps in house and, looking beyond clinical trials, to manufacture LOAd703 as a commercial product.

Partner of choice

In searching for a CDMO that could deliver on these goals, Lokon found a perfect partner in Finnish CDMO Biovian. Established in 2003, Biovian offers a truly 'one stop shop' service that covers both the supply chain, from cell banking to aseptic fill and finish, and the value chain, from preclinical to clinical and commercial production, all carried out in fully inspected and certified facilities in accordance with good manufacturing practice (GMP).

Biovian has long experience with manufacturing viral products, and, owing to the happy working culture Biovian nurtures, most of the highly qualified staff (50% with an MSc or PhD) have stayed at the company for years (retention rate >96%), creating an invaluable pool of in-house knowledge and expertise that helps guide clients through the trials and tribulations of drug development. Biovian matches this expert understanding with the capability to deliver on client needs: the company recently doubled its viral vector manufacturing capacity and aseptic filling.

Biovian prides itself on embodying Nordic values such as integrity, which is attractive to small and medium-sized enterprises like Lokon, who saw in Biovian a partner able to tackle manufacturing problems. "We selected Biovian because the company embodied the Nordic values of honesty, friendliness and integrity," said Sara Häggblad, Lokon's head of Chemistry, Manufacturing and Control. "Biovian had the necessary viral vector experience, capacity and they listened to our needs. We needed a partner that would help us overcome problems that might occur in manufacturing our complex product and would collaborate to solve any unanticipated issues and ensure all deliverables are met. In short, it was a pleasure discussing our project with them."

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