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# Glycostem launches pivotal oncology trial with evolved naked natural killer cells

**Glycostem, a clinical-stage company, which in 2017 published a successful phase 1 trial with naked natural killer (NK) cells for acute myeloid leukemia (AML), is about to launch its first pivotal trial using an off-the-shelf NK cell therapy for patients with AML.**

Glycostem's pivotal trial is planned to start in late 2020 and will involve five European countries, eight clinical trial centers and 33 patients with minimal residual disease (MRD) positive status. It aims to achieve MRD negative status for these patients.

A successful trial should result in European product approval in 2023.

"The NK therapy, oNKord, is a continuation of the product we trialed in 2015, with about 80% to 85% commonality," said Troels Jordansen, Glycostem CEO, "However, it is effectively a new product because it is cryopreserved and therefore available off the shelf, whereas the earlier therapy was manufactured patient-specific and required a 42-day delivery timeframe."

NK cells are part of the immune system, and oNKord, Glycostem's technology platform, uses stem cells harvested from umbilical cord blood (UCB). The cells are first expanded, then in a two-step process are differentiated to mature NK cells. UCB, a rich source of stem cells, is not restricted by ethical considerations and is readily available commercially.

Glycostem's earlier phase 1 trial involved dose escalation of naked NK cells, and after 5 years 50% of patients were still alive. The trial cohort was aged over-65, too fragile for further stem cell transplants and had no other treatment options.

oNKord showed no dose limiting toxicity, expanded in vivo, migrated to the bone marrow and killed leukemic blasts. "It was a really positive outcome, and many hematologists are stunned," Jordansen commented.

The new trial, which will test a three-dose course of treatment, has been met with a very positive response from clinical trial centers in Europe. "We thought we would have to speak with up to 20 centers in order to get eight. We only had to contact the eight we are working with—everybody wanted to sign up immediately because there really isn't any other treatment option for these patients," said Jordansen.

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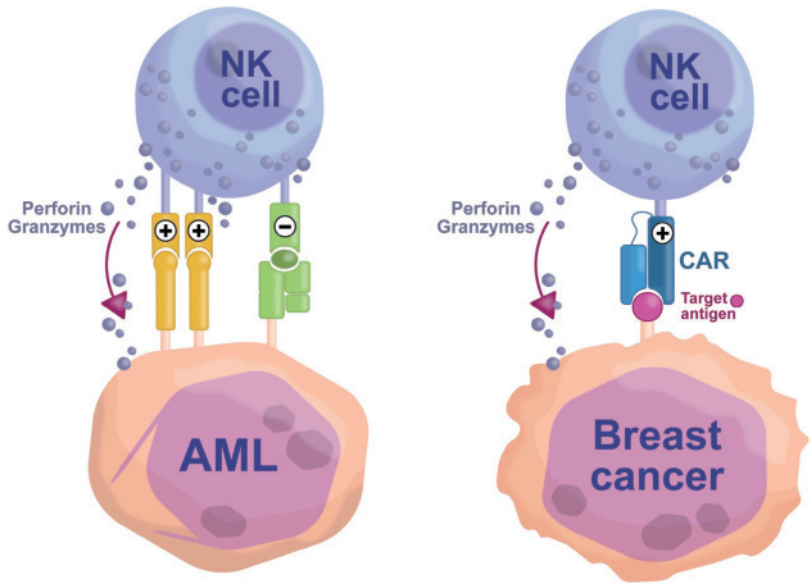



**Fig. 1 | Action of naked NK cells targeting AML compared with CAR-NK cell action targeting breast cancer.** AML, acute myeloid leukemia; CAR, chimeric antigen receptor; NK cell, natural killer cell.

## Naked NK cell therapies before CAR-NK products

Glycostem is amongst the few NK cell producers to develop naked NK cell therapies before CAR (chimeric antigen receptor)-NK products (Fig. 1). "While there is clearly a place for both therapies, it is essential to explore and fully understand naked NK before progressing to CAR-NK cells," Jordansen explained. "This is not well understood, as CAR-NK cell products are seen as sexier, more effective and the holy grail of NK cell therapies. But there are cancers that will not be cured using CAR-T or CAR-NK, and that is where we believe naked NK cells have a significant role to play. Not all cancers have a target, and naked NK therapies kill in a different way compared to CAR-NK and CAR-T therapies. Naked NK cells can kill AML cells—we showed that in our first phase 1 trial. CAR-T cells and CAR-NK cells cannot do that because there is not yet a defined, validated target for AML."

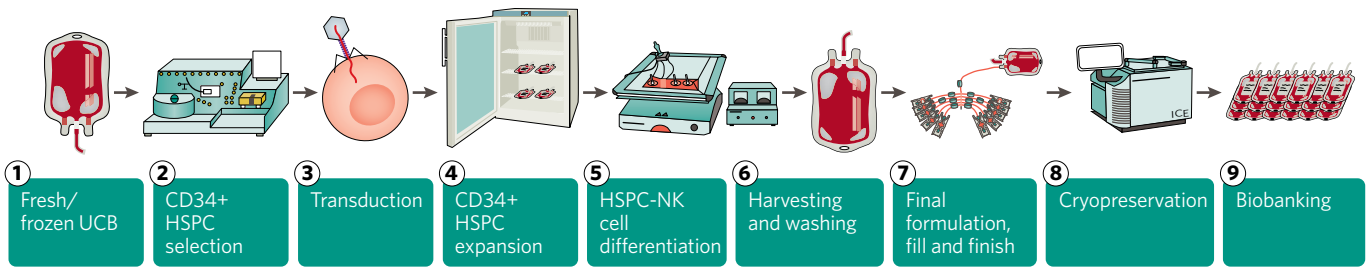
While a solid tumor in breast cancer has a target, so genetically manipulated CAR-NK cells can very specifically target those tumor cells. "Only because we started with naked NK cells do we already now have our own large-scale production system for NK and CAR-NK products (Fig. 2). With minor and simple modifications to the production system we can produce large-scale batches of CAR-NK products in a cost- and time-effective way," continued Jordansen.

## GMP-licensed production system

NK cell production takes place in the Netherlands in Glycostem's fully closed, large-scale production system which has a good manufacturing practice (GMP) licence. This allows Glycostem to produce cellular products for global markets.

Glycostem is one of the very few cellular therapy companies in the world with its own completely closed large-scale system for cancer immunotherapy. Contamination risk is negligible, and the company protects its intellectual property, while having full control over production and timelines.

The process is also extremely efficient and cost effective. Glycostem has a 10,000 $m^2$ site on which it plans to build a new facility capable




UCB cell sources*: Anthony Nolan (UK), NHS cord blood bank (UK), Sanquin (NL) and many others.

**Fig. 2 | Glycostem's proprietary manufacturing platform.** The manufacturing process is already GMP compliant. The GMP license was obtained in June 2019. GBGM, Glycostem basal growth medium; HSPC, hematopoietic stem and progenitor cell; NK cell, natural killer cell. *Umbilical cord blood (UCB) cells are tested for the following before CD34$^+$ selection: HIV-1, HIV-2, hepatitis B and C, syphilis, human T-lymphotropic virus, toxoplasma, parvovirus and cytomegalovirus.

of producing CAR-NK cells for 75,000 patients a year. Jordansen compares this with another company that has recently built a 19,000 m$^2$ facility in Amsterdam for the production of CAR-T cells for 4,000 patients a year.

"We can produce nearly 20 times the volume on a site which is about half the size. This shows our production technology is significantly more developed and efficient," he said. Another major benefit of Glycostem's process is that it does not require feeder cells, a feature that Jordansen believes is unique amongst NK cell companies.

## Risks of cancer feeder cells

Feeder cells can be used in suspension cultures to help cells to expand more quickly, enabling a very high number of NK cells to be obtained quickly. However, intracellular communication means the cancer cells can communicate with the NK cells.

"This could lead to re-differentiation, but more importantly, when you're treating a cancer patient you do not want any risk at all that DNA fragments from cancer cells, or the cancer cells themselves, will be part of the final product," explained Jordansen.

While feeder cells are often used in research, Jordansen believes commercial production should avoid them because they generate too many regulatory hurdles. Glycostem has created a 'cocktail' of cytokines and other substances that it uses for cell expansion. The cell yield is 'explosive', producing an up to 50,000-fold expansion in Glycostem's development model. 'This gives us great hopes for large cell yields in our large scale model as well,' Jordansen explained.

NK cells can be acquired from a number of sources, including bone marrow, peripheral blood and umbilical cord. Glycostem's use of umbilical cord cells is the result of more than ten pre-clinical papers it has published over the past 13 years.

Umbilical cord-derived hematopoietic stem cells differentiated into NK cells have a greater capacity to kill cancer cells than those from peripheral blood because their cytotoxicity is higher.

"Because of the lower cytotoxicity and plasticity of peripheral blood-derived NK cells, 10 to 15 times the number of cells may be needed for treatments compared with the turbocharged UCB-derived NK cells," Jordansen said.

Other technologies are in development around the world, and the relatively new technology of induced pluripotent stem cells (iPSCs) involves the engineering of, for example, skin cells to become stem cells and then NK cells.

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This process utilizes a very rich source of raw material; however, Jordansen refers to research from Japan (a leader in iPSC technology) that raises the possibility of the cells inadvertently transforming into other cell types. iPSCs can be grown in conjunction with cancer feeder cells, and the cells have changed their morphology three times. That creates the risk that the cells will spontaneously differentiate and become cancer cells.

"iPSC is a cell line which takes months to grow. The longer the growth period, the less toxicity the cells have, so a very large number of cells are required for cancer treatment," explained Jordansen.

## Allogeneic NK cells ready at the bedside

Allogeneic NK cells can be quickly produced for more than one patient and held ready in hospitals. CAR-T cell therapies are autologous, and while there have been some very early clinical trials with allogeneic T cells, Jordansen believes it may take about a decade before such trials succeed. "As autologous CAR-T cells take between 2 and 4 weeks to be returned to patients, it is estimated that about 15% of patients die while on the waiting list," Jordansen said. "Because of the side effects of CAR-T cell therapy, particularly cytokine release syndrome, about 80% of patients are transferred to intensive care units."

As it is patient-specific, CAR-T cell therapy is very costly to produce, whereas Glycostem can produce naked NK cells for between five and eight patients receiving oNKord or 25–40 patients receiving CAR-NK from a single umbilical cord.

In 2 years, that patient number should rise to between 15 and 20 patients on oNKord or 75–100 patients on CAR-NK, meaning the cost per patient will drop dramatically. The NK cells are very pure, containing hardly any measurable T or B cells, which frequently play a role in the side effects and mortality associated with allogeneic stem cell therapy.

The phase 1 clinical trial of oNKord also showed that matching on human leukocyte antigen (HLA) and killer cell immunoglobulin-like receptor (KIR) is not necessary with oNKord.

"If you have to match on HLA and KIR, you need a large number of batches in order to match all the HLA variations in any population. Our NK cells have very little expression of KIR on the surface, so KIR matching is not something that needs to be considered," concluded Jordansen.

This means that oNKord cells can be held in Glycostem's biobank and shipped to any patient anywhere in the world, or held in hospitals. Glycostem is open to developing collaborations and has a strategy that enables partnerships to develop combination therapies or second-generation products.

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