Asgard Therapeutics AB
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# Reprogramming anti-cancer immunity

**Asgard Therapeutics is moving cancer immunotherapy forward with an off-the-shelf direct cell reprogramming platform that turns cancer cells into immunogenic dendritic cells that induce potent anticancer immunity.**

Cancer immunotherapy has proven efficacy in some cancer subtypes but it often fails to deliver clinically meaningful benefits to patients because their tumors are poorly immunogenic. A major goal of many immunotherapy approaches is to turn such 'cold tumors' into 'hot tumors' that elicit a strong and sustained immune response to eliminate malignant cells. Asgard Therapeutics, headquartered in Lund, Sweden, is developing a new way of heating up the tumor microenvironment (TME) by reprogramming tumor cells so they become professional antigen-presenting dendritic cells (DCs) that activate cytotoxic T cells against themselves.

Asgard's platform technology, which grew out of research done at Lund University, uses a viral vector to deliver three genes encoding transcription factors that rewire transcriptional and epigenetic signatures within transduced cells[1,2]. This rewiring turns the cells into DCs—specifically, conventional type 1 DCs (cDC1s)—that can effectively present tumor antigens and induce antitumor immune responses. The platform is off-the-shelf and, at the same time, induces a personalized immune response based on the specific antigenic profile of each patient's cancer (Fig. 1).

When delivered into the tumor, the transcription factors encoded in Asgard's gene-delivery vehicle, are able to reprogram tumor cells, turning them into functional cDC1s, which are more effective than other DC subtypes at cross-presenting antigens and inducing antigen-specific T cell responses. The cDC1s also recruit cytotoxic T cells to tumors, and secrete cytokines and chemokines to create a pro-inflammatory TME that switches tumors from cold to hot.

The presence of cDC1s in tumors is important for a good cancer prognosis, as well as a response to immune checkpoint inhibitors (ICIs). However, cDC1s are quite rare, and there is currently no way to generate a pure population of cDC1s for therapy. Fortunately, the high functional specialization of cDC1s means that few of these cells are required to be present in tumors—approximately 0.1%—to achieve effective anticancer immunity.

## Engineering tumors

Direct cell reprogramming induces functional cDC1-like features in transduced cells within 3 days after expression of the transcription factors, and the process is complete after 9 days, without any transition through stem or progenitor intermediates. Although cDC1s are naturally short-lived, they increase the infiltration of $CD8^+$ T cells into the TME and create long-lasting immune responses at a systemic level.

In vivo direct cell reprogramming offers several advantages over other immunotherapeutic approaches. It is cheaper, more scalable and poses fewer logistical challenges than autologous and allogeneic cell therapies, which require expensive and time-consuming ex vivo cell modification. In addition, cell therapy and gene-replacement strategies need to establish long-term expression and engraftment of the delivered treatment. By contrast, the long-term effects of in vivo direct reprogramming to induce professional antigen presentation rely on immunological memory, which sidesteps the problems of sustaining expression or engraftment.

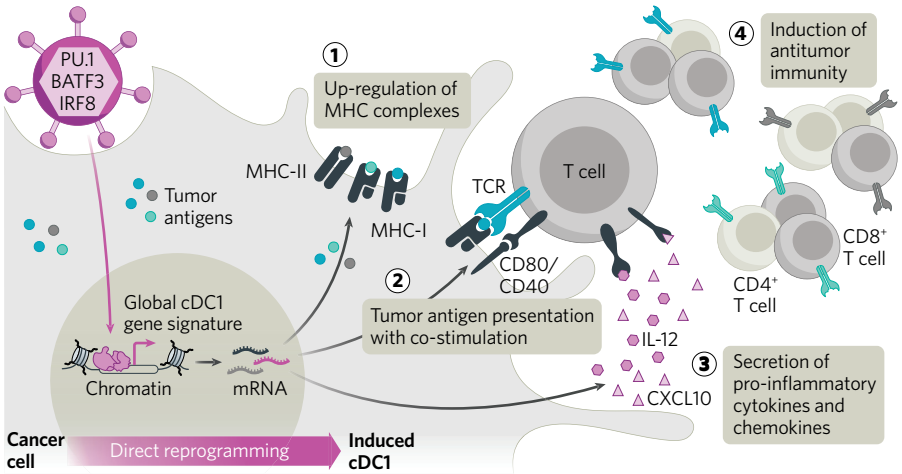


**Fig. 1 | Asgard's direct cell reprogramming approach.** A vector overexpresses transcription factors that reprogram cancer cells to conventional type 1 dendritic cells (cDC1). Induced cDC1s present MHC-loaded tumor (neo)antigens (**1**) with co-stimulatory signals (**2**), and secrete cytokines and chemokines (**3**), inducing polyclonal T cell responses and antitumor immunity (**4**). MHC, major histocompatibility complex.

Asgard has confirmed that cells directly reprogrammed with the selected suite of transcription factors recapitulate the key features of naturally occurring cDC1s, and this has been demonstrated in more than 80 cell types, including human cancer cells taken from biopsies. When reprogrammed, cancer cells lose their tumorigenic potential, and acquire a cDC1-specific phenotype and transcriptional profile independent of the human cancer type of origin. Importantly, the induced cDC1s show strong upregulation of antigen presentation (MHC class I and II) and co-stimulatory molecules, as well as secretion of pro-inflammatory cytokines—the three signals required for efficient T cell activation. Moreover, induced cDC1s are able to load and present their own endogenous tumor antigens on the MHC, capturing the heterogenous nature of the tumor and activating both naive and memory polyclonal T cell responses.

In syngeneic mouse models, reprogrammed cDC1s are able to induce local antitumor effects, resulting in an increase in antigen-specific cytotoxic T cells in tumors, as well as systemically in blood and lymph nodes, leading to dramatically slower tumor growth and prolonged survival.

## Building for the future

Asgard is currently optimizing the in vivo delivery of its direct cell-reprogramming therapy, and is conducting studies to demonstrate abscopal effect and systemic immunity. The company is also evaluating the effects of cell reprogramming in combination with ICIs. These studies will open the door for the next stage of refining its processes for chemistry, manufacturing and controls (CMC) and good manufacturing practice (GMP) while doing final dose-ranging, safety pharmacology and good laboratory practice (GLP) toxicity studies in preparation for an investigational new drug (IND) application.

The company plans to begin first-in-human trials in 2025, with melanoma and head-and-neck cancer as prioritized indications, given their accessibility to intratumoral administration, high tumor mutation burden, incomplete response to ICIs, high reprogramming efficiency, and high market potential.

Asgard welcomes potential new partners, including investors and pharmaceutical companies that would like to join the next leap forward in cancer immunotherapy.

1. Rosa, F. F. et al. *Sci. Immunol.* **3**, eaau4292 (2018).
2. Rosa, F. F. et al. *Sci. Immunol.* **7**, eabg5539 (2022).

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