Next-generation cytokines for cancer

Cytokines are **small proteins** produced by numerous cell types. They are **major regulators** of the innate and adaptive immune systems, enabling the immune cells to communicate over short distances. Cytokines also stimulate the survival, proliferation and function of natural killer (NK) and T cells, which **mediate the immune response to cancer**. Researchers have explored the use of cytokines in cancer therapy, leveraging the immune system's ability to identify and destroy cancer cells.

Classification and functions

There are seven main cytokine families.

Cytokines	Examples	Functions
Interleukins	IL-2, 12, 15, 21...	Regulation of cell proliferation and differentiation, immune regulation, and inflammation
Interferons	IFN-α, β, γ...	Antiviral, antitumor and immunomodulation
Chemokines	C, CC, CXC, CX3C...	Regulation of cell migration, promotion of angiogenesis and inflammation
Tumor necrosis factors	TNF-α, β...	Proinflammation, apoptosis and immunomodulation
Colony stimulating factors	HM-CSF, G-CSF, M-CSF, IL-3...	Proliferation and differentiation of hematopoietic progenitor cells
Transforming growth factors	TGF-β, BMP...	Immunomodulation, development and morphogenesis
Growth factors	EGF, FGF, VEGF...	Regulation of cell growth and differentiation

Cytokines as immunotherapies

The US FDA has approved IL-2 and IFN-α for cancer immunotherapy so far. Other cytokines, such as IL-12 and IL-15 have also shown efficacy in clinical models.

IL-2 (FDA approved)

Promotes the expansion of natural killer (NK) cells and T lymphocytes.

Approved for metastatic renal cell carcinoma and metastatic melanoma.

IFN-α (FDA approved)

Has pro-apoptotic, antiproliferative and anti-angiogenic activities.

Approved for hairy cell leukemia, various other hematological malignancies and melanoma.

IL-12

Activates innate and adaptive cytotoxic immunity responses and inhibits angiogenesis.

Evaluated in clinical trials in many malignancies such as advanced solid tumors and metastatic cancers.

IL-15

Promotes the formation and proliferation of immune cells, induces cytotoxic effects, and enhances immune responses.

Tested in clinical trials, including metastatic kidney cancer and breast tumors.

Challenges

However, certain characteristics of cytokines hamper their widespread clinical use.

Lack of tumor targeting — Short circulating half-life — Severe toxicity

Next-generation cytokine therapies

Overcoming these challenges is a major goal in developing next-generation cytokine therapies. Engineered cytokines with lower toxicity and longer half-life are promising approaches to improve therapeutic efficacy.

Immunocytokines

Immunocytokines are antibody–cytokine fusion molecules consisting of a targeting-antibody moiety, an amino acid linker and a cytokine load, providing the molecule with the ability to target tumor-associated antigens.

Representative immunocytokine formats

Immunocytokines based on **full-scale antibodies**

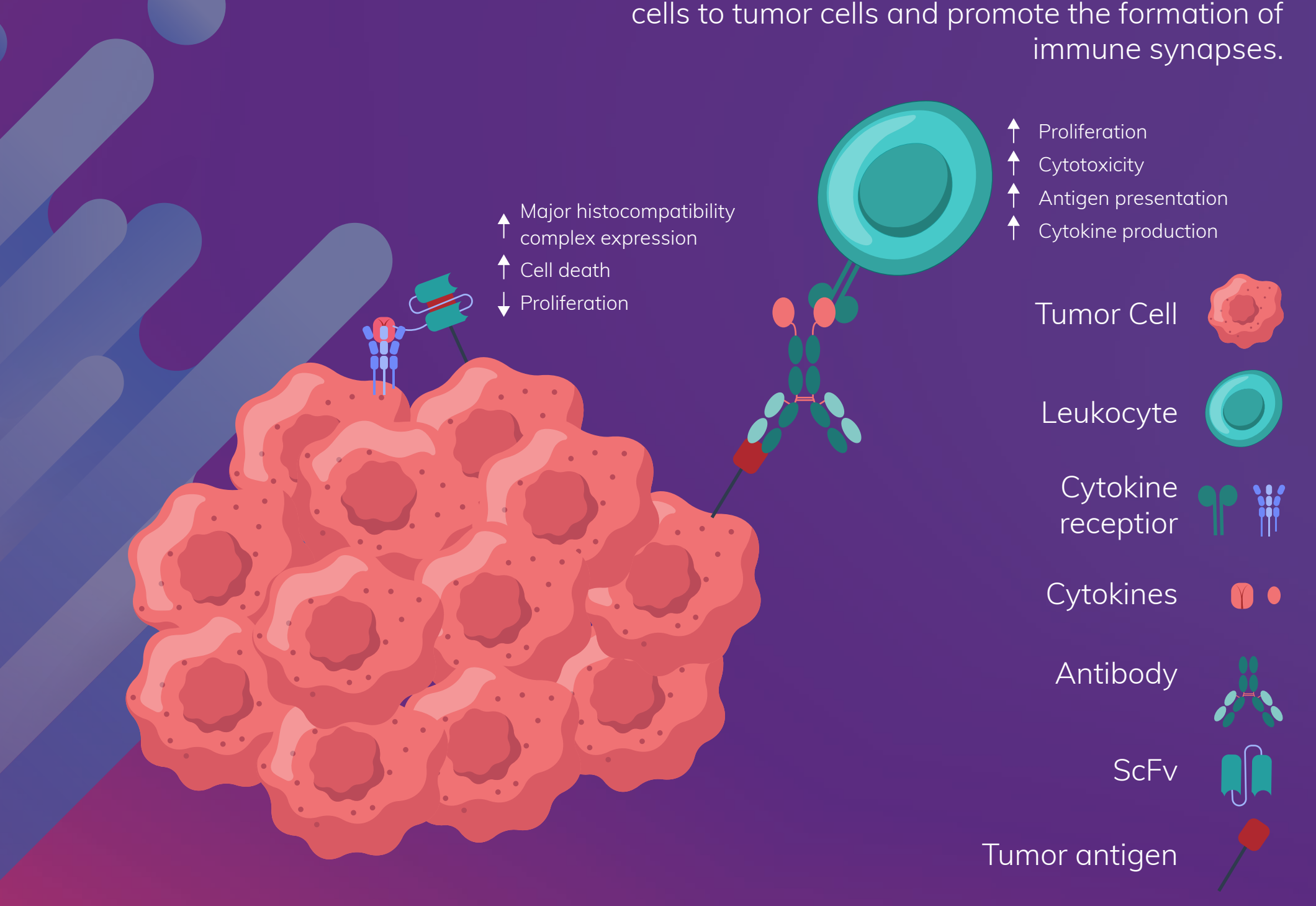
Facilitate a long circulating half-life in the bloodstream

Small-size immunocytokines based on antibody fragments

Blood concentration can be kept as low as possible to prevent side effects

Mechanisms of action

Immunocytokines activate and redirect immune cells to tumor cells and promote the formation of immune synapses.

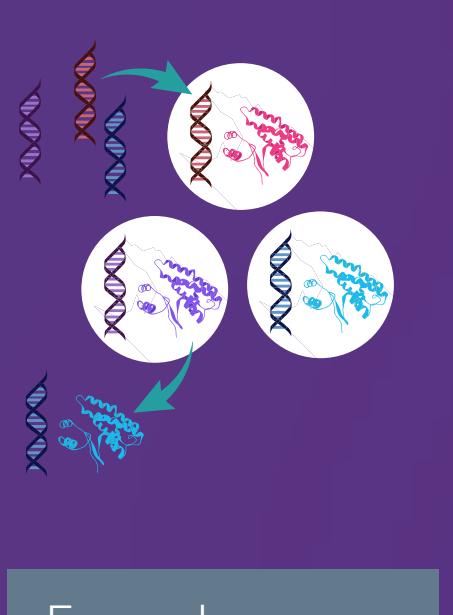


Re-engineered cytokines

Protein engineering techniques can be utilized to re-engineer cytokines to improve their function and pharmacokinetic properties.

Directed evolution

Directed evolution is based on the functional selection of mutants, introducing mutations into the gene of interest and obtaining a protein with the desired function.

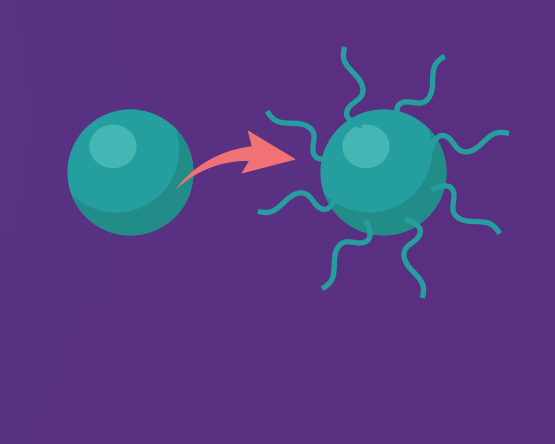


Example:
MDNA11

MDNA11 is an IL-2 mutant protein with a 200-fold higher affinity for the IL-2Rβγ complex [1]. It's currently undergoing a clinical trial (NCT05086692) in patients with advanced solid tumors.

PEGylation

PEGylation is a process through which polyethylene glycol (PEG) chains are conjugated to proteins, increasing their hydrodynamic radius and extending the half-life of cytokines. PEGylation also reduces immunogenicity and nonspecific binding, and increases the stability of therapeutic cytokines.

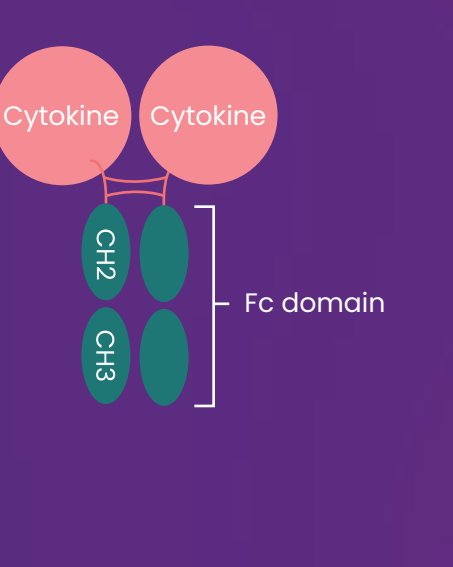


Example:
THOR-707

THOR-707 is a PEG-IL-2 variant that enhances effector T- and NK-cell expansion and activation and improves safety and pharmacokinetic profiles [2]. Clinical trials are investigating it as a therapy for advanced or metastatic solid tumors.

Fc fusion

Fc fusion proteins modify the pharmacokinetics of active molecules and improve cytokine targeting. The Fc domain increases the plasma half-life of the fusion protein, improving its therapeutic efficacy and slowing down renal macromolecular excretion.



Example:
N-803

N-803 is an IL-15 superagonist that promotes the proliferation and activation of immune cells, providing sustained anti-tumor activity. N-803 has received FDA approval for the treatment of non-muscle invasive bladder cancer [3].

What solutions are available?

Solutions are available to help with the research and development of cytokine immunotherapies. Sino Biological, named 'Growth Supplier to Watch in 2024' by CiteAb, offers a comprehensive range of high-quality GMP- and RUO-grade cytokines and growth factors.

Vast selection

250+ molecules, 800+ cytokines (20+GMP-grade)
Covering growth factors, ILs, TNFs, CSFs, IFNs and more

High quality

High purity, validated activity and established stability

Quality control

ISO 9001/ISO 13485/GMP quality systems

Click here to find out more.

1. Merchant R, Galligan C, Ankathatti M *et al.* Fine-tuned long-acting interleukin-2 superkine potentiates durable immune responses in mice and non-human primate. *J. Immunother. Cancer* 10(1), e003155 (2022).
2. Milla ME, Ptacin JL, Ma L et al. THOR-707, a novel not-alpha IL-2, promotes all key immune system anti-tumoral actions of IL-2 without eliciting vascular leak syndrome (VLS). Ann. Oncol. 30(5), V501 (2019).
3. Nature Reviews drug discovery. First-in-class IL-15 receptor agonist nabs FDA approval for bladder cancer [Accessed 10 June 2024].