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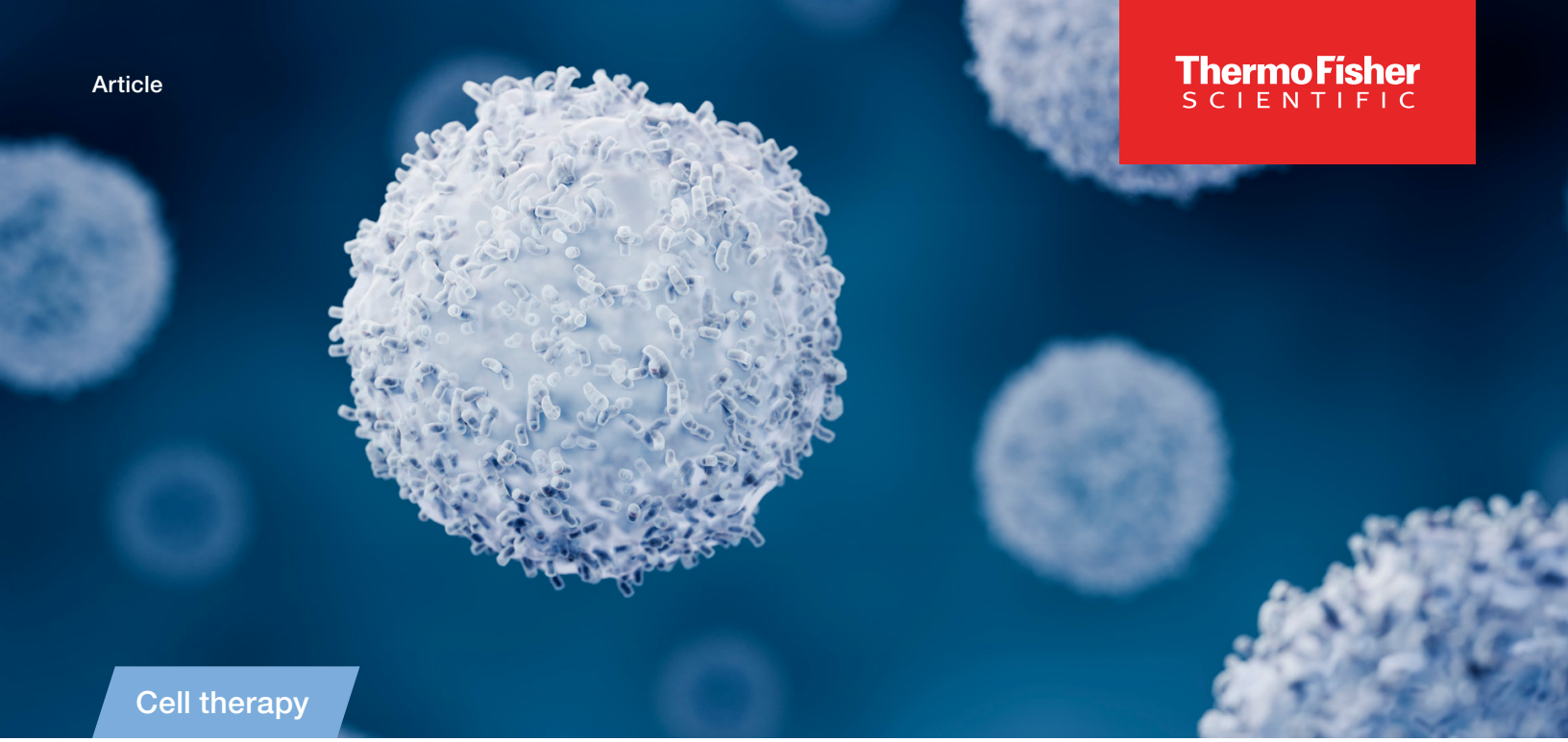

Cell therapy

Q&A: Exploring NK cells and TILs

Emerging strategies in immunotherapy

Cell-based immunotherapies are reshaping the landscape of cancer treatment. Over the past decade, CAR T cell therapies have demonstrated the power of engineering the immune system to precisely target disease—but they have also revealed critical limitations in scalability, safety, and durability. These challenges have sparked an urgent search for next-generation therapies that can overcome today's bottlenecks and expand access to patients worldwide.

Among the most promising approaches are natural killer (NK) cells and tumor infiltrating lymphocytes (TILs). Both represent distinct ways of harnessing the immune system—offering the potential for broader tumor reactivity and reduced toxicity. They also raise pivotal questions about manufacturing and scalability that biopharma leaders must address if these therapies are to reach their full potential.

To explore where the field is heading, we spoke with Dennis Clement and Daniel Palacios, Research Scientists at Thermo Fisher Scientific. In this Q&A, they share their perspectives on the scientific foundations, emerging technologies, and future directions of NK and TIL therapies—and what these developments could mean for the future of immuno-oncology.

Q. Can you provide a brief overview of cell-based immunotherapies and their role in cancer treatment?

Dennis Clement (DC): Traditionally, cancer treatment has involved surgery, radiotherapy, and chemotherapy. Surgery and radiotherapy are effective at quickly removing tumor mass, but they are limited in highly metastatic cancers or tumors in critical tissues. Chemotherapy has been used in these cases because of its systemic effect, but there is a high risk of treatment resistance and side effects.

Increasingly, attention has turned to therapies that harness the immune system, such as monoclonal antibodies (mAbs) and small-molecule inhibitors. After all, the immune system is designed to eliminate foreign cells, including cancerous ones. However, even with these newer modalities, responses remain inconsistent, and relapse rates are high. As a result, this has led to the emergence of cell-based immunotherapies that offer the potential for more durable and effective responses.

Q. What has been the leading approach so far in cell-based immunotherapy?

Daniel Palacios (DP): The first FDA-approved cell-based immunotherapy was CAR T cell therapy, in 2017. CAR T cell therapy has become the most prominent approach because it has been found to be very effective, particularly for certain hematological cancers. However, its success has also highlighted some important issues.

Q. What are the main challenges associated with CAR T cell therapy?

DC: Firstly, patients can relapse following treatment with CAR T therapy. This is because CAR T therapy only targets one antigen, and tumor cells without the target antigen escape treatment. There is ongoing research into dual targeting, but it is unlikely that every tumor cell will bear the antigens of interest.

Toxicity is another problem. T cells proliferate extensively once they are activated *in vivo* which can lead to cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome.

DP: Furthermore, while CAR T therapies are usually autologous—where the patient's own cells are used for treatment—donor T cells can be used. Unmodified, these can trigger severe side effects, most notably graft-versus-host disease (GVHD). Adapting these cells to prevent GVHD adds cost and complexity, so is not appropriate for patients with rapidly progressing disease.

CAR T therapy has also shown limited efficacy against solid tumors. As such, several other approaches are being developed, such as natural killer (NK) cell and tumor infiltrating lymphocyte (TIL) therapies.

Q. Could you tell us more about these emerging therapies, starting with NK cell therapies?

DP: NK cells are a part of our innate immune system—our body's first response. One of the most interesting things about them, particularly when it comes to their potential as a cell therapy, is that they are not restricted by antigen recognition and so have broad tumor reactivity. Instead, NK cell activity is governed by a balance of inhibitory and activating receptors that respond to cells undergoing stress, with thresholds to prevent autoreactivity.

Because of their mechanism of action, NK cells can be used in an allogeneic setting, meaning they can be donated and injected into another person. Their safety profile and reduced risk of off-target reactivity makes them highly attractive for off-the-shelf use.

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Q. What strategies are developers using to harness NK cells and turn them into effective therapies?

DC: One way is to use primary NK cells sourced from a healthy donor. These are typically expanded using feeder cells, which are irradiated cancer cells that can be genetically engineered to express activating ligands and cytokines needed for NK cell proliferation.

Other sources of NK cells include umbilical cord blood and induced pluripotent stem cells (iPSCs) derived and differentiated from fibroblasts, offering the advantage of scalability. Immortalized cell lines, such as NK-92 cells, have also shown success in clinical trials.

Q. Are there any limitations to NK cell therapies?

DP: One of the biggest hurdles is persistence. Whereas T cells have a natural ability to replicate and undergo clonal expansion when they encounter an antigen, NK cells do not replicate to the same extent.

Another challenge is that NK cells from certain sources, such as umbilical cord blood or iPSCs, exhibit lower cytotoxicity. This cytotoxicity can be enhanced by engineering the cells with CARs or T cell receptors (TCRs), or combining them with therapeutic antibodies, but this adds an extra layer of complexity.

Also, like CAR T cell therapy, NK cells have mostly been used in hematological malignancies. Both therapies have shown limited success against solid tumors because of the hostile tumor microenvironment.

Q. Which cell-based immunotherapies show greater promise for treating solid tumors?

DP: TILs are isolated directly from the tumor tissue, meaning they have already managed to penetrate the tumor mass and persist. This intrinsic ability to survive and function within the tumor makes TILs a particularly exciting avenue for treating solid malignancies.

Q. Could you tell us more about TILs as an emerging cancer treatment?

DP: TILs are a mixture of immune cells. This heterogeneous population will be different from patient to patient, tumor to tumor, and even from different metastatic sites. The most potent and cytotoxic component of TILs are CD8 T cells. Other less abundant TIL components include CD4 helper T cells, Gamma Delta T cells, and regulatory T cells—the latter of which play an immunosuppressive role which can help tumors evade immune control. TILs can also include memory T cells which have the capacity to persist in the patient, continually recognizing and killing tumor cells, providing ongoing protection against relapse. T cells found in TILs will have a TCR specific for that tumor and that can be exploited in treatment. However, the number of TILs present is typically very low, necessitating ex vivo expansion for therapeutic infusion.

Q. How are TILs currently being developed into therapies?

DC: One approach is to extract immune cells from a tumor and expand them. However, it is unclear which cells are being expanded or driving patient response.

A more tailored approach involves targeting neoantigens. These are cancer-specific proteins generated by tumor mutations and absent in normal tissues, making them highly attractive targets for T cells. Some neoantigens are unique to individual patients. Others, however, are recurrent across patients because they stem from common cancer-driving mutations, raising the possibility of designing successful therapies. In such cases, donor-derived T cells could be engineered with validated, shared neoantigen-specific TCRs—although this requires extensive safety testing and depends on patients having homogeneous expression of the targeted neoantigen across their tumor cells.

Once a TCR has been found to respond to a specific neoantigen, it can be sequenced and introduced into other cells. For example, you can introduce a neoantigen-specific TCR into a NK cell, combining broad innate reactivity with antigen specificity. Since each patient's cancer is genetically unique, therapies can be tailored to the specific neoantigens present in that individual's tumor.

Q. What are some of the challenges when developing next-generation cell-based immunotherapies?

DC: Manufacturability is one of the biggest bottlenecks when developing cell-based immunotherapies. Cost per dose remains high, production is labor intensive, and manufacturing must be done under CGMP conditions. Scalability is a challenge because it is limited by the amount of starting material and lengthy expansion times. Autologous therapies also face a unique 'scale-out' challenge, where every patient dose represents its own batch, each with stringent requirements for release testing and quality control. One way to improve manufacturability and scalability is by integrating automation to reduce hands-on work, enhance cost-effectiveness, and provide flexibility.

Access is another major hurdle, particularly for autologous therapies. These therapies require specialized centers capable of collecting patient blood, isolating viable cells, and preparing them for expansion. The availability of treatment is therefore not only limited by technical challenges but also by logistics, socioeconomic factors, and the structure of healthcare plans. Unfortunately, these complexities and associated costs have not gone unnoticed by investors and, as a result, many have pulled back from the immunotherapy space.

DP: It is also important to understand the safety and quality hurdles associated with developing cell-based immunotherapies. For example, feeder cells are relied upon heavily for NK cell expansion and ideally more CGMP friendly alternatives are needed for feeder-free expansion of human NK cells.

Recently it has become clear that many companies are failing during clinical trials not because of efficacy, but due to a lack of scalable, phase-appropriate infrastructure. Early collaboration with suppliers and CDMOs that have expertise and capabilities for large-scale immune cell manufacturing can support scalable and cost-effective production for these developers, helping improve access to next-generation therapies.

Q. Beyond what we have already discussed, are there any emerging developments or trends in immunotherapy that you find particularly exciting or impactful?

DP: There are so many exciting developments in immunotherapy. One area generating a lot of buzz is the use of NK cell engagers—small molecules that link NK cells with cancer cells while also supporting NK cell expansion. This concept builds on the success of FDA-approved T cell engagers.

DC: Another advancement is stealth technology for off-the-shelf products. Each therapeutic dose can trigger an immune response. Stealth strategies remove surface molecules to help cells evade detection and persist longer. Spatial immunoprofiling is also emerging to help map immune cells across tumors. This reveals how therapies interact with the tumor microenvironment and helps identify biomarkers.

Q. Looking ahead, how do you see the future of immunotherapy evolving?

DC: The immunotherapy field is expanding rapidly. It is likely that one day there will be the possibility to combine immunotherapies. For example, CAR T cell therapy could be used to kill off large tumor burden and NK cells would follow to control residual disease.

DP: While NK cell therapies are still under clinical development, 2024 saw the first FDA approved TIL therapy, Lifileucel, marking a major milestone. It seems cancer treatment is reaching a stage of personalization that's really exciting and it feels like we're just at the beginning of something extraordinary.

Scaling cell therapy: From discovery to global impact

The future of immunotherapy depends not just on scientific innovations, but on the ability to manufacture therapies reliably, affordably, and at scale. Emerging approaches such as NK and TIL therapies require:

- Automated and closed systems—such as the Gibco™ CTS™ DynaCellect™ Magnetic Separation System—to reduce risk and increase consistency
- Cell-specific media and reagents to optimize performance at every stage, such as the Gibco™ CTS™ OpTmizer™ T Cell Expansion Medium and the Gibco™ CTS™ NK-Xpander™ Medium
- Global CGMP standards that enable therapies to reach patients everywhere

By rethinking workflows today, the industry can overcome bottlenecks and bring next-generation cell therapies to more patients, faster.

Explore how Thermo Fisher is enabling scalable solutions: thermofisher.com/celltherapysystems

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