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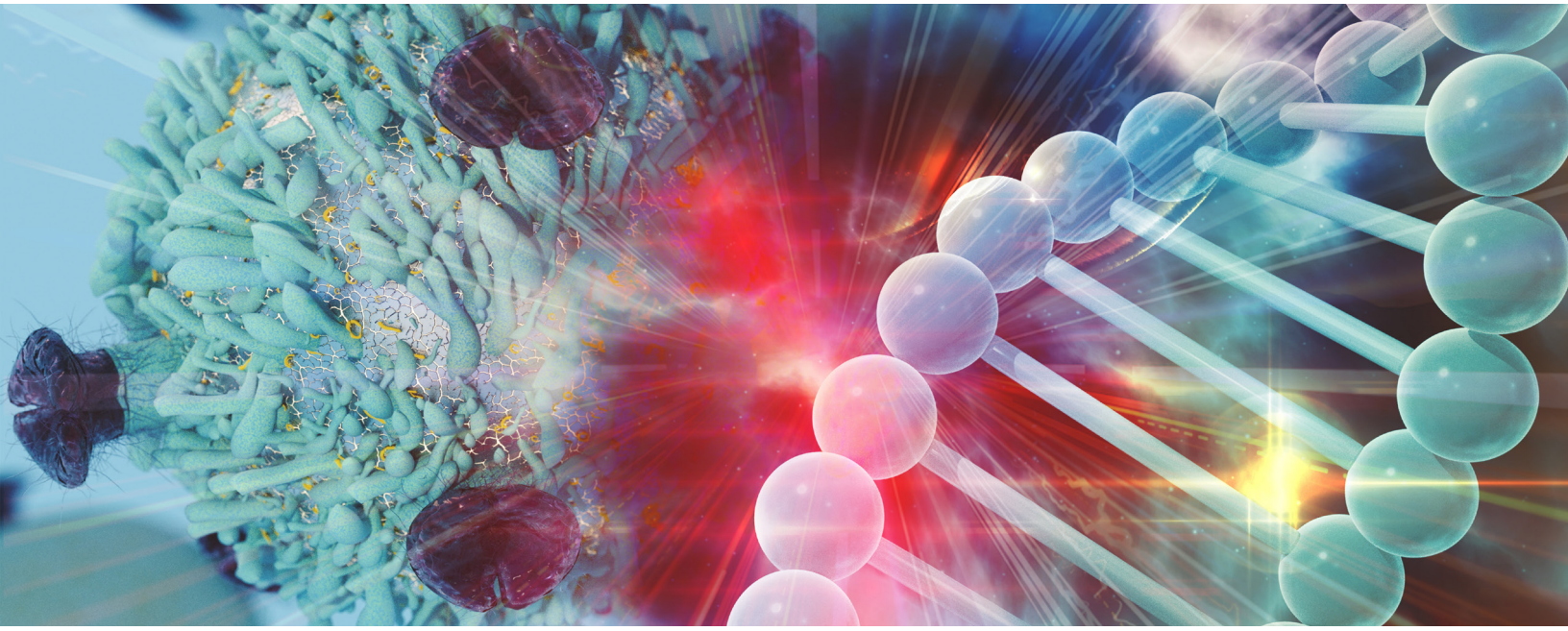
The ABC's of Oncology: Looking Beyond Alpha-Beta Cells for Cell Therapies



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Executive Summary

Cell therapies for cancer, particularly chimeric antigen receptor (CAR)-modified αβ T cells, have rapidly proven their utility. However, as limitations of these therapies have become clearer, interest in alternative approaches has grown. A second generation of companies built on several scientific discoveries is advancing cell therapies of the innate immune system (such as γδ T and NK cells) to address the limitations of CAR T-cell therapies. With established investor interest, the potential of these approaches to impact the standard of care has become clear. The translatability of next-generation cell therapies will rely on developing a strategy to achieve proof-of-concept and optimal clinical positioning, which may lead to improved patient outcomes, broader interest in the biopharmaceutical community, and returns for investors.

Introduction

Over the last decade, scientific advances in understanding the immune system have transformed cancer care. Improved knowledge of the adaptive immune response, driven by T and B cells, has allowed scientists and clinicians to harness the tumor-killing power of the immune system. Cell therapies, or "living drugs," are among the most effective new medicines, in which αβ T cells are removed from the body and modified before being returned to the patient. Currently, the most efficacious oncology cell therapies use T cells modified by a chimeric antigen receptor (CAR), which have demonstrated groundbreaking success in hematologic malignancies. However, CAR T-cell therapies are still constrained by toxicities, manufacturing logistics, and in the case of solid tumors, the ability to both travel to the site of tumor growth and overcome the immunosuppressive effects of the local tumor microenvironment. Although several approaches in early development are aiming to address these limitations by further modifying CAR T-cell therapies, using alternative immune cells may be a more effective strategy.

Cell therapies using the cells of the innate immune system may address crucial gaps in patient care. Natural killer (NK) and gamma-delta (γδ) T cells—both components of the innate, rather than the adaptive, immune system—can utilize a variety of properties for tumor killing and may hold the key to commercial success. This article examines the scientific rationale for NK and γδ T-cell therapies and assesses both the investment landscape in and company development around next-generation cell therapies in oncology.

Evolution of CAR T-cell therapies

T cells are characterized by their distinct T-cell receptor (TCR), which in approximately 95% of all T cells, consists of two glycoproteins: the α (alpha) and β (beta) chains. αβ T cells have a variety of roles in the adaptive immune response that make them attractive, but imperfect, tumor cell killers. As αβ T cells mature, they are selected to recognize small portions of intracellular proteins—nine to ten amino acid sequences—that are presented on the cell surface bound to major histocompatibility complex (MHC) proteins. When a unique αβ T cell receptor recognizes a distinct peptide-MHC protein, the αβ T cell becomes activated, begins proliferating, and differentiates into an αβ T cell subset, which can directly kill the cell. This mechanism has evolved to allow the body to recognize and destroy cells infected with foreign material—viruses, intracellular pathogens, and interestingly, the mutated proteins that arise as a result of tumor growth. However, cancerous cells that successfully proliferate in some cases have evolved mechanisms to "cloak" themselves from a T-cell response. Therefore, researchers have long been interested in harnessing the killing ability of αβ T cells and recently uncovered a groundbreaking way to help them recognize tumors previously seen as healthy tissue: the CAR T cell.

CAR T-cell therapies are the result of αβ T cells that are genetically engineered to express chimeric antigen receptors (or CARs) targeting tumor associated antigens (TAAs), such as CD19. Although αβ T cells have an intrinsic capacity to target TAAs, CAR T-cells cells are armed with an antibody to increase their killing capacity when they recognize a TAA. More specifically, CAR T-cells cells are engineered to express several components, including an antigen-binding domain, a hinge, a transmembrane domain, and an intracellular signaling domain. Ultimately, this enables the CAR T-cells cell to recognize native proteins, removing the restriction of peptide-MHC recognition. When the antigen-binding domain recognizes the TAA, the CAR T-cells cells become constitutively active, secreting cytokines, cloning, and activating killing mechanisms in a reaction that would not occur without the engineered binding domain.

Despite clinical success, this approach has several biological limitations. First, the CAR T-cells cells are extremely persistent, leading to actively armed and proliferating cells that can linger long after a tumor is eradicated, causing severe side effects. Second, antigen escape has been documented, with cancerous cells losing or downregulating the CAR T-cells TAA target. Lastly, CAR T-cellss only recognize TAAs on the cell surface, limiting the available targets to 1% of all cellular proteins. Each biological limitation of CAR T-cellss is linked to a major challenge. Cytokine release syndrome is a side effect of an overactive immune response occurring in more than 75% of patients, antigen escape has been documented in 30% of patients, and limiting targets to the cell surface restricts the patients eligible to receive CAR T-cellss (1, 2). Therefore, differentiated strategies to improve cell therapies are of both scientific and clinical interest.

In contrast to αβ T cells, both NK and γδ T cells play roles in the innate immune system. While the role of NK cells in providing rapid responses to invading pathogens is well documented, γδ T cells are not as well understood, and they account for only ~5% of T cells in the body. There are several biological advantages for using NK and γδ T cells in cell therapies.

- NK and γδ T cells do not require MHC proteins, meaning they do not require prior antigen exposure to begin to act on tumor cells directly. In the case of CAR-NK and CAR-γδ T-cell therapies, this limits TAA escape, as CAR-NK and CAR-γδ T-cell therapies retain an intrinsic capacity to recognize tumor cells through receptors native to NK and γδ T cells. More specifically, NK cells express either activating or inhibitory germline-encoded receptors, which have killing mechanisms complementary to T cells that limit TAA escape.
- This feature means the cells do not recognize the many "marker-of-self" proteins produced by the body, enabling the cells harvested from one patient to be used in other patients without causing graft-versus-host disease and making an "off-the-shelf" approach viable for CAR-NK and CAR-γδ T-cell therapies.
- NK and γδ T cells have limited clonal expansion and persistence capabilities in the body, ultimately restricting the occurrence of side effects.
- Research into NK and γδ T cells has shown both cell types have an abundant cytokine secretion capacity, activating the adaptive immune response. By indirectly activating the adaptive immune response, NK and γδ T cells stimulate the anti-tumor response without over-activating killer cells that can cause toxicities.

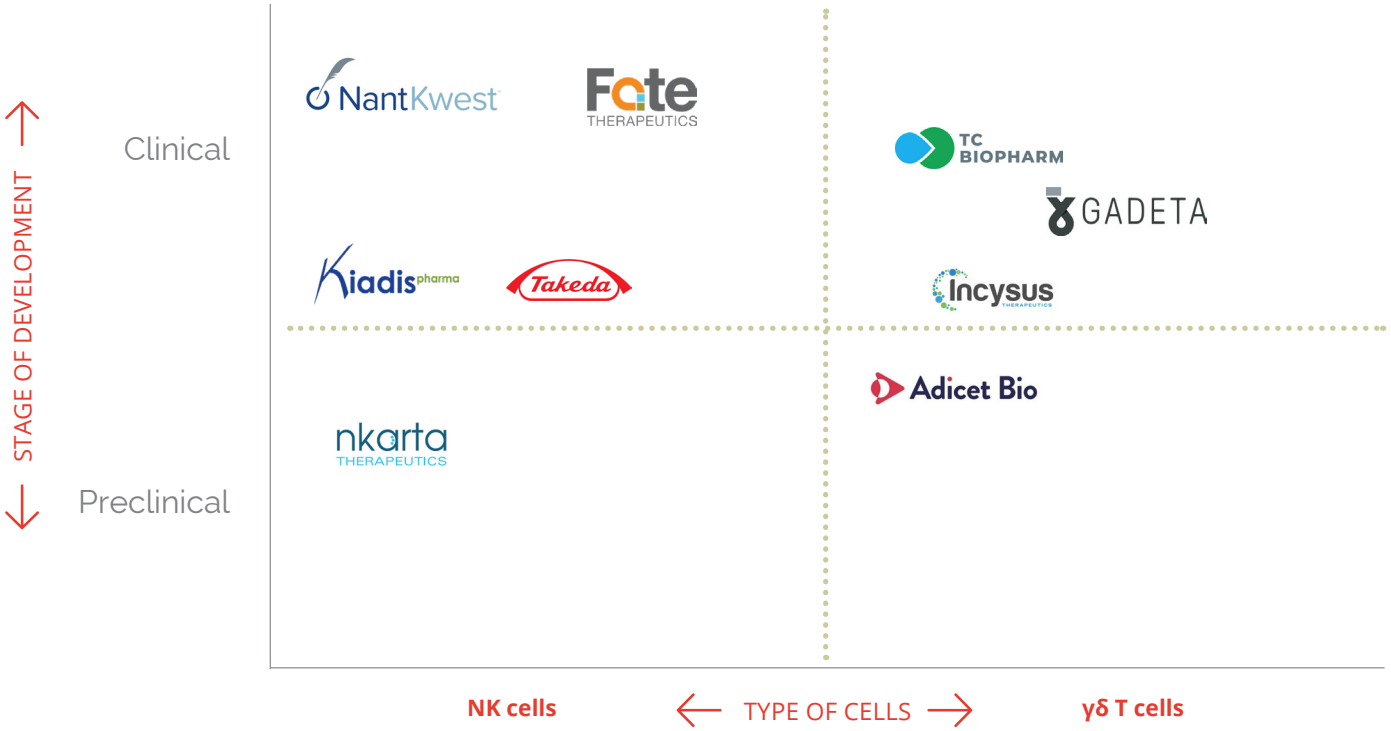
Company Development

Established NK cell therapy companies are nearing pivotal trials, with next generation approaches just beginning to initiate clinical development (Figure 1).

Mature, public NK cell therapy companies **Fate Therapeutics** and **NantKwest** are advancing multiple assets in hematologic malignancies and solid tumors. Fate Therapeutics has built a platform of induced pluripotent stem cell (iPSC) derived NK cells (iNKs). The company has aimed to differentiate itself by advancing cell therapies that can be multi-dosed as either monotherapies or combinations, with a low manufacturing cost of $2,500-$3,000/dose.

NantKwest differentiates itself with its platform of NK cells that bind to antibodies, CAR-NK cells, and a combination of the two (5). NantKwest's lead asset is in a Phase 2 combination study in advanced refractory metastatic Merkel cell carcinoma.

Figure 1:
Current Status of Company Development



Gadeta and **TC Biopharm** are the leaders in γδ T cell therapy development, having both reached the clinical trial phase and completed deals to advance their platforms. TC Biopharm was founded in 2013 in the UK and has brought its lead asset, an unmodified allogeneic γδ T cell product, into initial human studies in AML. Similarly, Gadeta was founded in 2016 and has built a platform of TEGs, αβ T cells engineered with γδ TCRs. Gadeta's first TEG was brought into the clinic in 2017 and is also being studied in AML patients.

Several earlier-stage companies are beginning to initiate clinical trials, having already built proprietary cell processing platforms. **Nkarta Therapeutics'** platform is based on NK cell expansion and cryopreservation technology. Nkarta is expecting to file three INDs in 2020 for its lead CAR-NK therapies: NKX101, an NKG2D activating receptor engineered to target NKG2D ligands in solid and liquid tumors, and NKX019, which targets CD19. In contrast, **Kiadis Pharma** has developed off-the-shelf NK-cell therapies that do not utilize CARs. Kiadis has 3 products in clinical development, with its lead asset K-NK002 having demonstrated proof-of-concept in 24 patients. In addition, both **GammaDelta Therapeutics** and **Adicet Bio** have built platforms of unique methods to isolate, engineer, activate, and expand γδ T cells.

Differentiated early-stage platform approaches are advancing combination strategies and alternative innate immune cell therapies. **Incysus Therapeutics** has developed a platform to deliver γδ T cells in combination with chemotherapeutics. Incysus' lead candidate received IND clearance in April of 2019 in glioblastoma and clinical trials are expected to begin this year.

In contrast, **Carisma Therapeutics** has built a platform of CAR-engineered macrophages, the antigen-presenting cells of the innate immune system, and has announced a lead program targeting HER-2.

Takeda has been the most active consolidator in the area, completing deals for both CAR-NK and γδ T cell therapies. In 2017, Takeda signed an exclusive buy-out agreement and equity investment to support moving **GammaDelta Therapeutics'** platform into the clinic. The following year, GammaDelta Therapeutics acquired Lymphact, a Portuguese company advancing a subset of γδ T cells called Delta One T (DOT) cells. More recently, Takeda agreed to a licensing pact with MD Anderson Cancer Center for 4 CAR-NK cell therapy programs in 2019, for which it aims to initiate pivotal clinical development in 2021 (6). The programs acquired were "off-the-shelf" therapies that have already been tested on humans. Like NantKwest's lead asset, the lead CAR-NK in the partnership is "armored" with IL-15, which enhances the proliferation and survival of CAR-NK cells in the body (7). The Takeda program published clinical data from 11 patients in February, highlighting that there were no adverse events, and eight patients had a response (4).

Evolution of Company Financings and Partnering

Investors have an established interest in CAR-NK cell therapies due to the longstanding scientific rationale for NK cells in oncology. Leading companies Fate Therapeutics and NantKwest completed banner IPOs for the space in 2013 and 2015, respectively. Fate Therapeutics' IPO in October 2013 was priced below expectations, ultimately raising $40M at a valuation of ~$115M. Since then Fate Therapeutics has outperformed, raising its valuation to ~$2B. In contrast, NantKwest raised the largest ever biotechnology IPO at the time in July 2015, reaching a market capitalization of $2.6B. However, the company has underperformed since, losing almost $2B in valuation.

More than $330M has been invested in private innate immune system cell therapy companies since 2016, coinciding with the impressive data generated from first-generation CAR T-cells, their approval, and evidence of limitations in solid tumors (Table 1). Nkarta Therapeutics, the leading private company in next-generation NK cell therapies, was founded based on the interest in NK cells in 2015 during NantKwest's IPO, subsequently raising $125M over two financings since.

Table 1:

Selected Disclosed Financings for Innate Immune System Derived Cell

COMPANY	YEAR	ROUND	TOTAL RAISED ($M)	FOCUS
Adicet Bio	2019	Series B	$80	Moving lead γδ T cell therapy into NHL studies
nkarta THERAPEUTICS	2019	Series B	$114	Two clinical trial programs of NKX101
Incysus THERAPEUTICS	2018	Series A	$10	Launch of two phase 1 programs
carisma THERAPEUTICS	2018	Series A	$53	CAR-macrophage therapies
nkarta THERAPEUTICS	2017	Series A	$11	CAR-NK platform development
TC BIOPHARM	2017	Series A	$7.97	Advancing its lead into pivotal studies
GADETA	2016	Series A	$7.78	Initiation of early-stage clinical studies
Adicet Bio	2016	Series A	$51	Nondisclosed universal cell therapies

Sources: Company websites and press releases

In contrast, γδ T cells were a relatively unknown area for investors until 2015, when a paper demonstrated that γδ T cells are the leukocyte type most correlated with favorable prognostic associations in 25 cancers and 14 solid non-brain tumors (3). This paper sparked a variety of investments in both γδ T-cell targeting antibodies and cell therapies, with γδ T-cell therapy companies having raised more than $152M since 2016. In addition, γδ T-cell companies using an antibody-based approach include Adaptate Biotechnologies, ImCheck Therapeutics, and Lava Therapeutics, which have all completed fundraises since 2017.

Multiple large and mid-cap companies have licensed NK and γδ T-cell therapies, validating earlier-stage VC investments and betting on a variety of approaches. Takeda Pharmaceuticals has completed deals for both CAR-NK and γδ T-cell therapies, with smaller companies such as Regeneron, Celgene (now Bristol-Myers Squibb), Kite Pharma (part of Gilead Sciences), and Bluebird Bio all having completed deals in the space since 2016 (Table 2).

Commercial Implications and the Road Ahead

With an increase in CAR T-cells clinical trials and the growing experience of clinicians using CAR T-cells therapies in a "real world" setting, several potential commercial opportunities have emerged for novel cell-based products:

- Due to the time it takes to generate an autologous CAR T-cells option from a patient's own cells, CAR T-cell therapies are not an option for patients with aggressive/fast-growing cancers. As a result, CAR-NK or γδ T-cell therapeutics may be best used in patients with fast-progressing disease or who have limited immune system function.

- Additionally, CAR-NK and γδ T cell therapeutics will likely be explored as combination approaches with a variety of different agents. Since it is unknown why first-line immunotherapeutic options such as PD-1/L1s lead to durable responses in some patients but not others, boosting response rates by even a small amount may be a meaningful clinical improvement to the standard of care, even though combinations in oncology often present cost challenges. This could be particularly beneficial in patients without primary T cells, which are not always present in heavily pre-treated patients.

- Further, given the safety/toxicity concerns with CAR T-cells therapies such as cytokine release syndrome and neurotoxicity, use is restricted to the inpatient setting, limiting the eligible patients and presenting reimbursement challenges (8). However, CAR-NK and γδ T cell therapies are aiming to be administered in an outpatient setting due to their clean safety profile and may enable the treatment of more patients (7). Although the implications of outpatient administration for price and reimbursement are nuanced, this may be a significant advantage if considered early in development (9).

Table 2:
Select Licensing Agreements

LICENSEE	LICENSOR	YEAR	TOTAL ($M)	UPFRONT ($M)	FOCUS
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center	Takeda	2019	Not disclosed	Not disclosed	4 CAR-NK cell therapies
Dragonfly THERAPEUTICS	Celgene	2019	Not disclosed	$50	Tri-specific, NK cell Engager Therapeutics
GADETA	Kite A GILEAD Company	2018	Not disclosed	Not disclosed	γδ TCR therapies
TC BIOPHARM	bluebirdbio	2018	Not disclosed	$16	CAR-engineered γδ T cells
GAMMADELTA THERAPEUTICS	Takeda	2017	$100	Not disclosed	γδ T cells derived from human tissues
Adicet Bio	REGENERON	2017	Not disclosed	$25	Nondisclosed cell therapies

Sources: Company websites and press releases

Looking Ahead

Beyond the initial clinical positioning of innate immune system cell therapies, there are long-term implications for the promise of safe and "off-the-shelf" therapies. In the future, it is likely that sponsors will take a page from the oncology drug development playbook and begin to explore these products earlier and earlier in the treatment paradigm, assuming cost and reimbursement do not present significant issues. With the growing evidence supporting the biological rationale for NK and γδ T-cell therapies drawing early interest from the VC and biopharma community, clinical evidence of their efficacy or lack thereof will begin to develop. Beyond NK and γδ T cells, there is even interest in developing CAR-based products from cells of other parts of the immune system, such as macrophages.

Despite this, the field is still in early stages, with large pharma partners dipping their toes in the space with licensing agreements rather than outright acquisitions. However, if the key value proposition of these products is validated in early clinical studies, one could envision a "land grab" similar to what was seen at the end of 2017 in the CAR T field, when both Juno Therapeutics and Kite Pharma were acquired by Celgene and Gilead within a five-month period.

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