There is little if any debate among the scientific community about the importance of immune cells in fighting cancer and keeping it at bay. The billion-plus dollar question instead revolves around how best to unleash or augment its capacity to do so. Perhaps more so than any other modality to date, cancer cell therapies have captured the imaginations and wherewithal of industry, investor, and oncologist communities alike for their perceived ability to drive a robust and tailored antitumor immune response across varied oncology settings.

A fundamental but often vaguely understood component of cell therapy platforms is the cell itself. The endogenous immune system is in fact a patchwork of different cell types, each with different aims, means, and lifecycles. Two of the more prominent cells within the burgeoning cell therapy landscape, T- and NK cells, comprise important but by no means sole components of the adaptive and innate immune cell compartment, respectively. In addition, macrophages, dendritic cells, and rarer subtypes such as NKT cells and γδ T-cells all play equally important, complementary, and often nuanced roles in the body. Adding still more complexity, each of these sub-populations develop as plastic progenitor cells in complex, interwoven growth cycles that shape unique phenotypes and population structures in response to myriad exogenous threats.

With dramatic improvements in our understanding of immunology, disease pathology, and gene editing technology, immune cells are readily being modified and manufactured as clinical-grade therapeutic candidates. But why should we care about the cells themselves?
More to the point, why are investors and companies deploying hard-earned resources to develop platforms comprised of novel cell types when first-mover T-cells have already demonstrated clinical and regulatory success? After all, Novartis and Gilead have both commercialized autologous (patient-derived) CAR-T cell products with eye-popping response rates in end-stage patient populations.

"Competition in this arena will continue to be prohibitive for all but a few until the utility of cell therapies finally begins to encompass at least some if not significant potential across solid tumors"

For those who follow the field closely, the answers to such questions have everything to do with both the excitement for and shortcomings of these first-mover brands: drug resistance, treatment-related or even host-mediated adverse events, manufacturing complexity, protracted vein-to-vein times, unsustainable costs and profit margins, and lack of replicability across tumor types and settings. While many different gene-modifying tactics are being positioned to further unlock value of established cell types (e.g. CRISPR-mediated knock-out of PD1 in autologous CAR-T candidates), an increasing number of companies believe that engineering alone will be an insufficient substitute for biological properties honed over millions of years within different cell types. And given the amount of crowding around a limited number of hem-onc targets (CD19, BCMA), competition in this arena will continue to be prohibitive for all but a few until the utility of cell therapies finally begins to encompass at least some if not significant potential across solid tumors.

What follows are brief snapshots of different cell types, their potential promise as therapeutic platforms, and the companies developing them. The objective is to help elucidate the complex biology and positioning strategy being brought to bear in the capital-intensive but opportunity-laden endeavor of advancing novel cancer therapies to market. Each of these profiles are supported by discussions our group has been having with executive management at these companies, along with our own knowledgebase and in-house cell therapy databases that we curate for clients at Cello Health BioConsulting. Given the long and diverse list of companies in this arena, this is just the first in a series of posts to profile relevant therapeutic platforms and companies. So, if you enjoy this, rest assured there is yet more to come!
What are NK cells?  Natural killer (NK) cells are CD56+CD3− innate immune lymphocytes serving as an integral part of the first line of defense against cancer and virally-infected host cells.  NKs are potently cytotoxic without need for prior stimulation.  They are also capable of killing in a serial manner before ultimately becoming exhausted.  As with other effector cells, cytotoxicity is achieved via release of small granules from the cytoplasm containing special proteins such as perforin and granzymes.

So what?  NK cells can be derived from replenishable allogeneic sources such as peripheral blood mononuclear cells (PBMCs), umbilical cord blood (UCB) or induced pluripotent stems cells (iPSCs), making them a compelling alternative to autologous (i.e. patient-derived) T-cells.  NKs also lack T-cell receptors (TCRs) and MHC-restrictions which, in the case of T-cells, can result in undesirable effects such as graft versus host disease (GvHD).  While they lack long-term in vivo persistence relative to T-cells, longer term benefits of treatment with some NK cell therapies suggest that they may activate a more protracted innate immune response within the host.  Furthermore, novel engineering approaches such as introduction of a cytokine payload are being validated as means to enhance persistence.

How is Kiadis positioning its NK cell platform?  Kiadis’s therapeutic candidates (known as K-NKs) are sourced from a rare subset of “universal” healthy donors known to produce NKs with an optimal combination of molecules (e.g. Killer cell immunoglobulin-like receptors [KIRs]) for donor/patient matching purposes.  Furthermore, K-NKs are expanded in the presence of cell membrane fractions (PM21 particles) which reduce CMC costs and simplify QC-based release criteria.  Finally, Kiadis has
learned to harness the plastic nature of progenitor NK cells in their manufacturing process. According to Marcel Zwaal, Kiadis’s SVP of Corporate Development, K-NKs are not genetically manipulated but instead exposed to different stimuli during expansion (known as imprinting) to induce epigenetic modifications and desired phenotypic profiles, such as desensitization against the effects of TGFβ, an immunosuppressive checkpoint molecule in the tumor microenvironment (TME).

**What is Kiadis’s go-to-market strategy?** To date, Kiadis has reported encouraging topline data for two of its clinical stage programs: K-NK002 (adjunct to SoC haplo HSCT with post-transplant cyclophosphamide), and K-NK003 (AML R/R 2nd line salvage after chemo). The company is also developing a number of preclinical and discovery-stage programs directed at solid tumors. According to Zwaal, Kiadis is interested in the opportunity to go-it alone with monotherapy applications but could potentially partner programs where a polypharmacy approach is needed (e.g. K-NK + mAb). As with other cell therapy platforms, Kiadis believes its K-NKs could also be readily positioned to address nonmalignant conditions such as infectious disease.

*Kiadis is unique in its ability to reproducibly generate desirable NK phenotypes without need for engineering*

**Competitive outlook** NKs will no doubt play a role in the future treatment landscape, likely in combination with other modalities due to their complementary role in the immune response and clean safety profile. Early-mover advantage, informed positioning strategies, and well-executed partnerships are likely keys to success. According to our in-house analysis, there are number of companies pursuing NK-based approaches, including those developing engineered CAR-NKs (e.g. Takeda, Nkarta, Artiva, Fate), NK-redirecting biologics (e.g. Affimed, Dragonfly, Kleo), and NK functional modulators (e.g. Innate, oNKo). Kiadis is unique in its ability to reproducibly generate desirable NK phenotypes without the need for engineering, which could be a major differentiating factor in helping drive and support the endogenous host antitumor immune response without concerns of host-mediated rejection. This competency around imprinting, along with the use of NK cells derived from universal donors and expressed with PM21 particles, are what set Kiadis apart from the competition. The onus is now on Kiadis, a company that has pivoted multiple times since its inception in the late 1990s, to execute on its positioning strategy and rapidly bring products through the clinic.
**Incysus Therapeutics** ([https://www.incysus.com](https://www.incysus.com))

**Cell type:** gamma-delta (γδ) T cells  
**Cell source:** patient- or donor-derived  
**Additional platform details:** overexpression of DNA damage-repair enzyme for chemoresistance  
**Clinical status:** Phase 1 trials initiated in patients with newly-diagnosed GBM (patient-derived DRI cells + standard chemotherapy therapy) and post-transplant leukemias (donor-derived cells)  
**Headquarters:** New York, NY; Birmingham, AL  
**Financial information:** private, venture-backed ($10M Series A round closed in January 2019)

**What are γδ T-cells?** γδ T-cells are a rare population of cells which comprise 1–5% of circulating lymphocytes and are so-named based on their expression of a γδ TCR that is distinct from the more common version found in alpha-beta (αβ) T-cells. Like other 'unconventional' T-cell subsets bearing invariant TCRs (e.g. NKT cells profiled below), γδ T-cells exhibit several characteristics that place them at the border between the more evolutionarily primitive innate immune system, which permits a rapid beneficial response to a variety of foreign agents, and the adaptive immune system, where so-called B- and T-cells coordinate a slower but highly antigen-specific immune response leading to long-lasting memory against subsequent challenges by the same antigen.

**So what?** γδ T-cells are activated independent of MHC-mediated antigen presentation, a property which, along with their high levels of cytokine secretion and natural affinity for different tumor-associated antigens, has long suggested that they would be an effective, well-tolerated, and potentially durable off-the-shelf cellular therapy modality. And as noted by Incysus CSO and co-founder Lawrence Lamb PhD, γδ T-cells are also notable for their enrichment in the tumor microenvironment of cancer patients that achieve positive outcomes. While correlation never implies causation, this last observation is turning heads at Pharma and elsewhere as rationale for an investment in this rare subpopulation of cells.

**How is Incysus positioning its γδ T-cell platform?** Incysus was launched to advance its γδ T-cell therapies to address novel niches across the competitive landscape. Its lead product (known as DRI, or Drug Resistant Immunotherapy) consists of patient-derived γδ T-cells engineered to overexpress a DNA damage-repair enzyme (known as MGMT) for
co-administration with chemotherapy. It is being positioned in combination with the standard frontline alkylating agent Temodar in glioblastoma multiforme (GBM). Beyond such clinical considerations, Incysus CEO William Ho pointed out that alkylating agents like Temodar trigger a DNA damage response and corresponding upregulation of innate immune ligands on the tumor that can be detected by γδ T-cells. Given the challenges in overcoming antigen heterogeneity and adaptive resistance to CAR-T therapy in GBM, Incysus’s approach could leave tumor cells with fewer escape routes needed for the disease progression that is so commonly (and tragically) observed following frontline therapy.

**What is Incysus’s go-to-market strategy?** While Incysus has noted that GBM is a proof-of-concept opportunity to validate its technology, unmet need is sufficient to justify pursuit of commercialization for any therapies that can move the needle in such a deadly tumor type. Beyond GBM, Incysus is advancing a preclinical pipeline that will explore additional applications and settings where alkylating agents are used. The company has also initiated testing of unengineered allogeneic γδ T-cells taken from transplant donors in leukemia patients recovering from stem cell transplant.

"Where Incysus stands out is not so much in its choice of cell type but the application it has chosen to pursue"

**Competitive outlook** A host of companies in addition to Incysus are developing engineered γδ CAR-Ts (Adicet, GammaDelta Therapeutics) or TCR-Ts (Immatics), along with alternative approaches such as γδ TCR-modified conventional T-cells (Gadeta) or therapeutic antibodies to modulate γδ T-cell activity (Adaptate, a spin-out of GammaDelta). Where Incysus stands out, perhaps, is not so much in its choice of cell type but the application it has chosen to pursue with such an otherwise already compelling cell type. It is not, for example, taking advantage of the ability to administer γδ T-cells as an allogeneic (donor-derived) therapy, at least with its lead engineered (DRI) program. Instead, Incysus is exploiting the observation that DNA damage triggered by alkylating agents may induce sensitivity to chemo-resistant γδ T-cells. The approach is elegant for its simplicity and potentially replicable across other tumor types where alkylating agents remain an entrenched component of the standard of care. In this respect, Incysus is not competing with other γδ T-cell companies so much as any modalities positioned to supplant chemotherapy in high unmet need tumor types, an arguably higher bar but one that could be breached by any number of different modalities.
Kuur Therapeutics (https://kuurtx.com; formerly Cell Medica)

**Cell type:** Natural Killer/T-cells (NKTs)

**Cell source:** patient- or donor-derived

**Additional platform details:** express IL-15 to improve persistence and efficacy

**Clinical status:** KUR-501 (autologous, anti-GD2 CAR-NKT) and KUR-502 (allogeneic, anti CD19 CAR-NKT) in clinic trials; KUR-503 (allogeneic, anti-GPC3 CAR-NKT) in preclinical development

**Headquarters:** Houston, TX

**Financial information:** private, venture-backed (re-launched in March 2020)

What are NKT cells? Natural killer T cells (NKTs, also known as invariant or type 1 NKTs) are a rare subset (<1% of T-cells) of innate-like adaptive lymphocytes. As with γδ T-cells, NKTs straddle the innate-adaptive boundary: like NK cells, they respond quickly upon stimulation (within hours), but as with other T-cells, they mature in the thymus and express a TCR that undergoes somatic rearrangement. What is unique about NKTs, however, is the ability of their TCRs to recognize glycolipids presented by CD1d, a non-polymorphic MHC-I-like molecule, arming them with the ability to quickly respond to lipid antigenic stimulation within minutes by secreting a wide variety of cytokines needed to recruit other immune cells. NKTs are also capable of effecting cytolytic activity that is on par with that of conventional T cells. This broad functional scope has placed iNKT cells at the frontlines of many kinds of immune responses.

So what? Kuur’s CMO Kurt Gunter MD believes that the value proposition of this cell type is in its ability to serve as an off-the-shelf option for solid tumors with minimal risk of GvHD, for which Kuur has developed a well-honed expansion protocol yielding hundreds of doses from each healthy donor. While he also notes that the cell has its own endogenous TCR which recognizes CD1d, an antigen present not only on certain myeloid and lymphoid cancers but also tumorigenic macrophages known as TAMs, he believes the primary anti-tumor activity will be derived from the CAR transgene. Any CD1d-mediated ablation would provide an ancillary benefit in the clinic rather than serving as a dominant mechanism of action for these therapies. In addition, NKT cells are known to home to tissue from blood and may therefore be better adapted for treatment of solid tumors.
How is Kuur positioning its NKT cell platform? Kuur Therapeutics, which was formerly known as Cell Medica, shifted away from autologous EBV-specific T cells that the company was previously developing to focus instead on its CAR-modified NKT (CAR-NKT) technology licensed from Baylor University in 2016 (Kuur is now headquartered in Houston in part for proximity to its academic collaborators at Baylor). According to Dr. Gunter, the company has broad IP and know-how specifically around manufacturing and engineering of NKT cells, which are selectively isolated from patient- or donor-derived sources, expanded, and transduced with a CAR transgene. Cells are further modified to include both an IL15 payload for in vivo persistence and, in the case of donor-derived products, shRNA-mediated knock down of HLA class 1 and 2 molecules to diminish allogeneic (non-self) reactivity.

What is Kuur's go-to-market strategy? Kuur is presently adhering to the often-advisable strategy of de-risking a novel platform with validated or at least de-risked therapeutic targets. The company currently has two candidates in the clinic (KUR-501, an autologous anti-GD2 CAR-NKT for neuroblastoma and KUR-502, a donor-derived anti CD19 CAR-NKT for CD19 positive malignancies), along with a third program in preclinical development (KUR-503, a donor-derived anti-GPC3 CAR-NKT for hepatocellular carcinoma). The platform also includes a fully-human scFv for future portfolio programs, though no targets have been disclosed.

Kuur is adhering to the often-advisable strategy of de-risking a novel platform with validated or at least de-risked therapeutic targets.

Competitive outlook Kuur and its collaborators at Baylor believe NKTs offer a truly unique route to next-generation off-the-shelf CAR therapies for a broad range of hematological and solid tumor indications. According to our in-house cell therapy database built and maintained by CHBC, Kuur appears to be the only CAR-NKT company in the US if not worldwide. While there is little question that the underlying biology of NKT cells is distinct, however, the platform must achieve clinical differentiation, either in the ability to improve upon existing approaches in validated applications (e.g. anti-CD19 CARs in lymphoma) or penetrate novel applications that have not yet been addressed by existing cell therapies (e.g. anti-GPC3 CARs in liver cancer), both of which are being pursued by Kuur. Time will tell whether either or both are viable opportunities to be pursued with CAR-NKTs, and the extent to which Kuur is able to achieve clinically-meaningful differentiation among the crowded competitive set.
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As a Principal and practice lead at Cello Health BioConsulting, Joel provides insight to various oncology and CNS therapeutics-focused clientele (biotechnology/pharmaceutical) on fundamental issues in drug development and partnering based on a comprehensive analysis of the key scientific, clinical, regulatory, and commercial questions relevant to the client’s particular situation.

In previous industry roles, Joel was instrumental in the scouting and evaluation of licensing and partnering opportunities for various oncology assets. Prior to his BD&L activities, Joel spent ten years focused on the discovery and characterization of bioactive compounds for cancer and infectious disease research at several leading academic institutions. His work has resulted in numerous grants, fellowships, patent filings, and peer-reviewed publications.

He received his BA with honors from Cornell University, a PhD in Organic Chemistry from UCSD/Scripps, and was a NIH Postdoctoral Fellow at The Rockefeller University.

He is a member of numerous professional societies, including the American Academy of Neurology (AAN), American Neurological Association (ANA), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the American Association for Cancer Research (AACR).