CHAPTER 3

Therapeutic Potential of Cells of the Immune System

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INTRODUCTION

When challenged to write a chapter for a compilation of second generation cell therapies, we could not help but reflect on the early discoveries of tumour antigens and adoptive immunity. Those first steps led to a growing interest in cancer immunology and to the development of early strategies to leverage tumour immunity into strategies for immunotherapy today (Dougan and Dranoff, 2009a,b; Disis et al., 2009). As various lymphocyte subsets were identified, more specific approaches for immunotherapy began to develop, most of which have focused on natural killer (NK) cells or cytotoxic T lymphocytes (CTL) as the primary mediators of antitumour immunity (Yannelli et al., 1996; Bloom et al., 1997; Colella et al., 2000; Dudley et al., 1999; Fleischhauer et al., 1997; Kawakami et al., 1998; Kim et al., 1998; Mateo et al., 1999). In addition, these cell types can easily be isolated, expanded and activated ex vivo leading to manufacturing strategies that have shown promise in effecting durable remissions for a growing number of cancers. With the advent of chimeric antigen receptor T cell (CAR-T) technology, initially referred to as T-bodies (Eshhar, 2008), it is possible to target specific tumour-associated antigens (TAA) and initiate a powerful, antigen specific immune response that is precisely activated at the time the CAR-T makes contact with the designated ligand (Maude et al., 2014). Indeed, CAR-T therapy has produced dramatic and lasting remissions for patients with haematopoietic malignancies that would otherwise have been fatal.

Early on, 100-day outcomes of patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) strongly suggested that the same alloreactive T cells responsible for graft-versus-host disease (GvHD) could also be beneficial in both facilitating engraftment and eliminating residual leukaemia through an adoptive immune response that came to be known as the graft-versus-tumour effect (Horowitz et al., 1990). However, initial trials of unmanipulated allogeneic T cell therapy were met with uneven success, and the predictability of developing GvHD was difficult to assess. As the race to develop more specific T cell therapies for haematopoietic cancers progressed, others

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targeted immune subsets that could demonstrate additional unique anticancer properties. While αβ T cells are plentiful and relatively easy to expand, therapies based on allogeneic recognition have similar limitations as unmanipulated T cells, specifically downregulation of tumour-associated major histocompatibility complex (MHC) and GvHD (Bubenik, 2003). While not a significant challenge with the early autologous CD19 CAR-Ts, evolution of allogeneic therapies must occur to generate a more scalable and commercially viable product with the ultimate goal of an 'off-the-shelf' cell therapy.

While arguably the most significant therapeutic advance in cancer therapy in recent memory, the long-term economic risk to CAR-T therapy is that unless tumour response rates are sufficiently high, effective and easier to deliver, cheaper and off-the-shelf therapies could gain advantage unless the present day commercial challenges are solved. In an outcome frighteningly analogous to Dendreon's Provenge (sipuleucel-T) in prostate cancer, on the entrance of Cougar's (Los Angeles, CA, USA) abiraterone (Zytiga) and Medivation's enzalutamide (Xtandi). While Provenge was the first FDA approved immunotherapy, in April 2010, Dendreon was never able to generate profitability despite generating as much as $325 million in revenues in the year ended 2012. That year, the cost of Dendreon's product revenue remained 70% of sales! Unfortunately, Dendreon eventually filed for Chapter 11 bankruptcy protection in December 2014 and was sold to Canada-based Valeant Pharmaceuticals International, Inc. Astellas acquired Universal Cells, Inc. in February 2018, obtaining technology to adapt recombinant adeno-associated virus technology editing of pluripotent stem cells to provide the potential to lower immunological rejection in numerous therapeutic areas including CAR-T immunotherapy although this technology remains in the very early preclinical stage.

With properties almost opposing that of αβ T cells, NK cells have also been an area of interest for cellular therapies. Unlike the αβ T cells, NK cells naturally increase cytotoxicity as MHC is downregulated and their killing is not MHC-restricted, allowing for allogeneic cell delivery without the risk of potentially fatal GvHD. Furthermore, while αβ T cells generate target-specific killing through antigens presented through MHC and their αβ TCRs, NK cells respond rapidly to increased cellular stress through their NKG2D ligands without priming (Bauer et al., 1999).

Among the earliest innate and NK cell companies were Innate Pharma of Marseille France and ZelleRx Corporation in Chicago, IL. Innate Pharma was founded in 1999 by four European scientists in the field of innate immunity and two members from the biopharmaceutical industry. With the expertise of scientists including Marc Bonneville and Jean-Jacques Fournié, early on, Innate Pharma targeted the in vivo expansion and activation of γδ T cells using Bromohydrin Pyrophosphate (BrHPP) (Constant et al., 1994) Known as IPH1101 or Innacell γδ, BrHPP mimics the biological properties of natural phosphoantigens in combination with low-dose IL-2 to drive in vivo expansion of Vγ9Vδ2 lymphocytes. Over a period of 10 years, Innate Pharma conducted six

clinical trials with IPH1101 across 200 patients and demonstrated safety and signs of clinical activity (Pharma, 2010). Best-observed responses included complete responses, and remarkably these superior responses were especially attained when the cell-based therapy was combined with antibodies such as rituximab to generate antibody-dependent cell-mediated cytotoxicity (ADCC) due to the active FcγRIIIα receptor (CD16) found in γδ T cells (Gertner-Dardenne et al., 2009). Interestingly, responses with IPH1101 were likely limited due to the concurrent administration of IL-2 leading to the upregulation of T_{regs} during in vivo expansion as was observed in an in vivo expanded γδ T cell immunotherapy trial for refractory neuroblastoma as published in 2016 by Lamb et al. (Pressey et al., 2016).

On March 2, 2011 Innate Pharma announced the termination of IPH1101 and its cell therapy programmes to focus efforts on its internal antibody programmes. In a press release, CEO Hervé Brailly noted, '2010 has been a year of major progress and renewed interest for cancer immunotherapy, notably with the emergence of a new class of antibodies modulating immune regulatory mechanisms, which could transform the treatment of cancer and inflammatory disorders in the next decade. Our anti-KIR antibody is one of the most advanced candidate [sic] of this class and as such, is attracting a lot of attention from the medical community and from the industry'. It was at the American Society of Clinical Oncology (ASCO) meeting in June 2010 when positive Phase 3 data from Bristol-Myers Squibb's ipilimumab in metastatic melanoma was announced. Unfortunately, the new interest in immunotherapeutic antibodies was 18 months ahead of the Novartis' alliance with the University of Pennsylvania to develop CTL019, a personalised T cell therapy for treating cancer. That deal would lead to the explosion of the CAR-T industry, which would be named Advance of the Year in the Annual ASCO Report in 2018.

Founded in late 2002 by Hans Klingemann, MD, PhD, ZelleRx Corporation (Chicago, IL, USA) was one of the early players targeting NK cells with its NK-92 cell line. NK-92 is an immortalised NK cell line derived from a non-Hodgkin's lymphoma patient that does not express CD16 or the inhibitory killer cell immunoglobulin-like receptor (KIR) (Klingemann et al., 2016). By late 2014, ZelleRx would be known as Conkwest, had 10 employees, treated 40 patients and advanced into phase 2 clinical trials and had raised $12 million in total equity financing.

In December 2014, Conkwest entered into a joint development and licence agreement with Sorrento Therapeutics, Inc. to develop Conkwest's NK-92 cells exclusively with Sorrento's antibody library to form CAR-TNKs ('Car-Tank'). Subsequent to this collaboration, an investment from Nantworks Inc. and billionaire biotech entrepreneur Dr. Patrick Soon-Shiong resulted in the formation of NantKwest, which raised $207 million in a record-setting IPO valued $2.6 billion only 7 months later. Unfortunately, the NantKwest IPO marked a top to the biotech market as tweets, pricing concerns and scandals dropped biotech industry share prices precipitously in the fall of 2015 and early 2016.

Interestingly, another billionaire biotech entrepreneur had also found early interest in cell stress signalling and the properties of innate lymphocytes such as NK cells. As disclosed in NantKwest's S-1 filing with the Securities and Exchange Commission (SEC), Randal J. (RJ) Kirk's Intrexon Corporation had entered into a worldwide 17-year licence with NantKwest's predecessor company in February 2010 for exclusive rights in certain indications to develop and commercialise modified NK-92 cells that express Intrexon's proprietary gene sequences for use as therapeutic agents.

γδ T CELLS AND THE RECOGNITION OF MALIGNANT DISEASE – MULTIPLE WEAPONS, MULTIPLE TARGETS

γδ T cells are thought to be multispecific, and antigen recognition demonstrates remarkable diversity (Vantourout and Hayday, 2013). These T cells can recognise malignant cells through less-specific mechanisms that do not require prior antigen exposure or priming, a function that is shared by other innate immune cells such as macrophages and NK cells. Unfortunately, the tumour responses of adoptive cellular therapies against haematopoietic cancers has not, with rare exceptions, been replicated in solid tumours. The immunogenic heterogeneity of solid tumours even within a single tumour has frustrated attempts to target specific TAA (Brown et al., 2016; Reuben et al., 2017; Jimenez-Sanchez et al., 2017) and has called for strategies that can more broadly distinguish and target malignant cells while still limiting the potential for damage to the host. More recently, Michael Barish from the City of Hope National Medical Center (Duarte, CA, USA) demonstrated in a poster at the AACR CNS immunotherapy conference 2018 that tumour antigen heterogeneity creates a significant challenge to tumour eradication (Barish, 2018). Their cohort of 44 high-grade brain tumour samples demonstrated four major histological regions of interest and significant antigen diversity within each individual region. Moreover, a CAR-T targeting three individual antigens, IL13Rα2, EGFR and HER2 was still predicted to leave at least 7% of the tumour remaining (Barish et al., 2018). Consequently, the potential antineoplastic effect of γδ T cells, a minor T cell subset with distinct innate recognition properties, has recently become an area of intense investigation.

Most mature T cells express the αβ T cell receptor (TCR), reside in the secondary lymphoid organs and function primarily in adaptive immune responses. CD3+γδ+ T cells are a relatively rare immune effector population in peripheral blood (4%–10% of T cells) but are substantially enriched in epithelial tissues (Haas et al., 1993), where they function as primary responders by recognising intact structures such as stress-associated proteins, heat shock proteins and lipids (Haas et al., 1993; Hayday, 2000) in a classical MHC-unrestricted manner (Haas et al., 1993; Allison and Havran, 1991). Here, they also manifest lytic activity and proinflammatory cytokine secretion. These cells provide a link between the innate and the adaptive immune responses. It is now known that γδ T cells

play a critical role in tumour immunosurveillance (Zocchi and Poggi, 2004; Kabelitz et al., 2007; Girardi et al., 2001; Liu et al., 2008) and in the immune response to cancer (Ferrarini et al., 1994; Choudhary et al., 1995; Zhao et al., 1995; Xu et al., 2007; Corvaisier et al., 2005; Zocchi et al., 1990). In many instances, γδ T cells that are cytotoxic to a specific tumour type will cross-react with other tumours but not with the tumour's nontransformed counterpart (Xu et al., 2007; Corvaisier et al., 2005; Bryant et al., 2009a). Furthermore, certain γδ T cell subsets can respond early to infection or transformation and recruit adaptive responses from CD4+ and CD8+ T cells by internalising antigens, processing them and displaying the antigens complexed with MHCs on their cell surface (Anderson et al., 2012). As professional antigen-presenting cells (pAPCs), γδ T cell lymphocytes express equivalent levels of costimulatory molecules and CCR7, home to lymph nodes and are equally potent at promoting proliferative responses in αβ T cells when compared to dendritic cells (DC) (Vantourout and Hayday, 2013). Activating ligands for γδ T cells as well as the process by which they recognise stressed or malignant cells are complex and incompletely understood, but are fundamentally different from both αβ T cells and NK cells (Hayday, 2000; Boismenu and Havran, 1997; Chien and Konigshofer, 2007; O'Brien et al., 2007). Vδ receptor subsets share some activation pathways while also possessing unique activating properties as detailed below.

Vδ2+ T Cells

The most prevalent circulating population of γδ T cells expresses an invariant Vγ9Vδ2 TCR (Parker et al., 1990). The Vδ2+ chain usually pairs with a Vγ9 chain to form the Vγ9/Vδ2 heterodimer. Vγ9/Vδ2+ T cells are thought to be activated via the TCR principally by three groups of nonpeptide antigens: alkylphosphates such as isopentenyl pyrophosphate (IPP) generated by eukaryotic isoprenoid biosynthesis using the mevalonate pathway (Morita et al., 1995), alkylamines (Bukowski et al., 1999) and synthetic aminobisphosphonates (N-BP) (Kunzmann et al., 2000; Miyagawa et al., 2001). The first two compounds are naturally occurring in bacteria, plants and some eukaryotes.

Nonpeptide alkylphosphates such as IPP, a product of the mevalonate pathway of isoprenoid biosynthesis, is upregulated in virally infected and transformed cells (Morita et al., 1995). This process is dysregulated in tumour cells and upregulated in individuals exposed to bone-strengthening N-BP compounds such as Zoledronate and Pamidronate. Some haematologic malignancies and solid tumour cancers also produce IPP at concentrations that render them vulnerable to recognition and lysis by Vγ9Vδ2+ T cells, likely through overexpression of nonpeptidic phosphorylated mevalonate metabolites (Hayday, 2000; Bonneville and Scotet, 2006; Gober et al., 2003). In addition, N-BP compounds bind to and inhibit IPP-consuming enzymes such as farnesyl pyrophosphate synthase and geranylgeranyl pyrophosphate synthase (Guo et al., 2007), leading to the accumulation of IPP within the tumour cell, a process that was recently shown to activate Vγ9Vδ2+ T cells (Li et al., 2009). These findings suggest that N-BP compounds have a

dual role in the initiation of innate antitumour immune response both by activating and expanding Vγ9Vδ2+ T cells and by rendering selected tumours more vulnerable to Vγ9Vδ2+ T cell–mediated lysis.

Both Vδ1+ and Vδ2+ T cells express NKG2D, a C-type, lectin-like homodimeric-activating receptor also expressed by NK cells and some αβCD8+ T cells. NKG2D is a ligand for MHC class I–like proteins such as MHC class I–related chain A/B (MICA/B), the UL-16 binding proteins (ULBP1-6) and MutS homologue 2 (MSH2). These NKG2D ligands provide a powerful danger signal to the immune system and are upregulated in response to cell stress including infection and malignant transformation (Gleimer and Parham, 2003; Raulet, 2003). NKG2D ligation has been thought to play a costimulatory role in the activation of γδ T cells (Bauer et al., 1999; Das et al., 2001); however, recent findings indicate that NKG2D ligation may be sufficient to independently activate certain γδ T cell subsets (Whang et al., 2009; Rincon-Orozco et al., 2005).

NKG2D activation is an important factor in tumour recognition and lysis by Vγ9Vδ2+ T cells, potentially playing a costimulatory role in cooperation with TCR-dependent activation (Das et al., 2001; Wrobel et al., 2007), although direct ligation of the Vγ9Vδ2+ receptor by the NKG2D ligand ULBP-4 has been recently reported (Kong et al., 2009). In some situations, NKG2D activation may be the primary stimulus, whereas TCR stimulation has a secondary role or is not required (Rincon-Orozco et al., 2005; Nitahara et al., 2006).

Vγ9Vδ2+ T cells recognise and kill haematologic malignancies such as Daudi Burkitt's lymphoma (Wright et al., 1989; Freedman et al., 1997) and other non-Hodgkin's lymphomas (Wilhelm et al., 2003) and multiple myeloma (Kunzmann et al., 2000). Vγ9Vδ2 γδ T cells also recognise and lyse cell lines from glioblastoma (Suzuki et al., 1999), lung cancer (Ferrarini et al., 2002), breast cancer (Gober et al., 2003), bladder cancer (Kato et al., 2001) and melanoma and pancreatic cancer (Kabelitz et al., 2004). Vδ2+ T cells with antitumour effector function can be manufactured in large numbers and have been employed in early phase autologous cell therapy trials against solid tumours with mixed results (Bennouna et al., 2008; Kobayashi et al., 2007). Wider implementation of Vδ2+ T cell therapy protocols has been hampered by uneven responses to ex vivo stimulation, the propensity to upregulate regulatory T cells (T_{regs}) with in vivo expansion, and their strong tendency to undergo activation-induced cell death (AICD), limiting persistence of effector functions (Pressey et al., 2016; Bryant et al., 2009a; Argentati et al., 2003; Kabelitz et al., 1991).

Vδ1+ T Cells

The second most prevalent subset of γδ T cells in the heterodimer bears a common Vδ1 receptor. Vδ1+ T cells are a minor circulating subset (5%–15% of circulating γδ T cells) that principally resides in epithelial tissues. In contrast to Vδ2+ T cells, the Vδ1+ T cell population is not as susceptible to AICD and once activated can persist in the circulation for many years (Lamb et al., 1996; Godder et al., 2007). Additionally, they do not

preferentially pair with a specific Vγ chain and are not activated by IPP or N-BP (Tanaka et al., 1994, 1995; Bukowski et al., 1995). This subset has distinct innate recognition properties and possess powerful tumoricidal activity. Vδ1+ T cells can be activated by a host of ligands including stress-induced self-antigens, glycolipids presented by CD1c and others as discussed in detail below (Spada et al., 2000; Leslie et al., 2002; Ismaili et al., 2002).

Vδ1+ T cells are predominant in the intestines and skin (Groh et al., 1998; Ebert et al., 2006). As discussed above, Vδ1+ T cells are activated by stress-induced self-antigens such as MICA/B and ULBP1-6, many of which are constitutively expressed by solid tumours as well as some leukaemia's and lymphomas (Poggi et al., 2004a,b; Wu et al., 2002; Groh et al., 1999). Although there is some controversy regarding the use of NKG2D by γδ T cells, several lines of evidence suggest that the Vδ1 TCR is required for γδ T cells to engage cells that express MICA/B. MICA tetramers have been shown to bind an NKG2D-cell line transfected with various Vδ1+ TCRs that had previously been shown to react against MICA-expressing targets (Wu et al., 2002). Furthermore, Zhao (Zhao et al., 2006) found that coupled V domains from the MICA-induced T cells expressed as a single polypeptide chain soluble TCR that can specifically bind to MICA expressed by HeLa cells and to immobilised MICA molecules. Vδ1+ cells also recognise glycolipids presented by CD1c on the surface of immature DC and can induce DC to mature and produce IL-12 (Spada et al., 2000; Leslie et al., 2002; Ismaili et al., 2002). Specific populations of Vδ1+ T cells can also exhibit immunosuppressive and regulatory properties, a function which is discussed at greater length below.

Vδ1+ T cells infiltrate and kill a wide variety of lymphoid and myeloid malignancies (Poggi et al., 2004b; Groh et al., 1999; Dolstra et al., 2001; Duval et al., 1995; Lamb et al., 2001; Catellani et al., 2007), neuroblastoma (Schilbach et al., 2008) and cancers of the lung, colon and pancreas (Maeurer et al., 1995; Ferrarini et al., 1996; Maeurer et al., 1996). Primary myeloid and lymphoid leukaemias activate Vδ1+ T cells (Dolstra et al., 2001; Duval et al., 1995; Lamb et al., 2001), which are cytotoxic both to primary leukaemia and leukaemia cell lines. Vδ1+ T cells show a restricted CDR3 repertoire in patients with leukaemia (Meeh et al., 2006). In addition, supranormal recovery of leukaemia-reactive Vδ1+ T cells is associated with long-term leukaemia-free survival after allogeneic bone marrow transplantation (Lamb et al., 1996; Godder et al., 2007).

Virus-infected cells are also vulnerable to recognition and lysis by γδ T cells, particularly the Vδ1+ and Vδ3+ subtypes. It has recently been shown that γδ T cells that are reactive against EBV and CMV are cross-reactive to various tumours. Vδ1+ γδ T cells recognise EBV-transformed B cells (Hacker et al., 1992) and expand in vitro and in vivo using clonally restricted δ1 CDR3 repertoire that persists for several years (Fujishima et al., 2007). Vδ1+ γδ T cells are also highly active against CMV-infected cells, and these CMV-reactive cells are cross-reactive against the colon cancer line HT29 (Halary et al., 2005; Dechanet et al., 1999; Pitard et al., 2008). The mechanism of cross-reactivity has not been fully described as yet but may have therapeutic implications for other

malignancies with an EBV or CMV component such as glioblastoma, which has been shown to be vulnerable to γδ T cell responses (Bryant et al., 2009a; Fujimiya et al., 1997; Scheurer et al., 2008; Lau et al., 2005; Cobbs et al., 2007; Mitchell et al., 2008).

Regulatory γδ T Cells

Certain subsets or γδ T cells with regulatory/suppressor functions have also been identified (Hayday and Tigelaar, 2003; Pennington et al., 2005) and described in recent reviews by Fleming (Fleming et al., 2017) and Kabelitz (Fleming et al., 2017; Chitadze et al., 2017). Initially, a suppressive γδ T cell population of γδ+ TIL characterised in breast cancer specimens (Peng et al., 2007) as Vδ1+ T cells that expressed IL-17 and GM-CSF when stimulated by autologous tumour or anti-CD3. Other cytokines typically expressed by effector γδ T cells such as TGF-β were not expressed by this population. Additionally, suppressor γδ T cells did not express FoxP3. Suppressive activity could be reversed by TLR-8 ligands, suggesting a potential immunotherapeutic strategy in breast tumours with a high percentage of suppressive γδ T cells. Coffelt et al. (2015) later showed that breast cancer metastases can also be potentiated by interaction between suppressor Vδ1+ T cells and neutrophils via an IL-1β and IL-17 interaction that occurs in the tumour microenvironment. It has also been shown that FoxP3-expressing γδ T cells can be generated from mouse splenocytes following stimulation with anti-TCR-γδ and TGF-β (Kang et al., 2009). These γδ T cells also expressed CD25, TGF-β and GITR and showed a potent immunosuppressive effect on anti-CD3 stimulated T cell activation and proliferation. A small population of FoxP3+ expressing γδ T cells were also identified in human peripheral blood although they could not be expanded with anti-TCR-γδ and TGF-β as in the mouse model. Hua et al. (2013) showed that a classical regulatory phenotype could be induced in blood-derived Vδ1+ T cells by stimulation via plate-bound anti-Vδ1 antibody, promoting expression of regulatory markers FoxP3, CD25 and CTLA-4 and corresponding suppression of CD4+ T cell proliferation. Moreover, TGFβ1 production by Vδ1+ T cells fed into a positive feedback loop, sustaining FoxP3 expression; these cells also produced the antiinflammatory cytokine IL-10 (Hua et al., 2013).

Potential for γδ T Cells as Primary Effectors in Immunotherapy of Cancer

A number of in vitro and in vivo studies suggest that γδ T cells might be ideally suited for immunotherapy via in vivo activation or adoptive cellular therapy within the context of HSCT and/or as a donor innate lymphocyte infusion (DILI). The potential advantages and disadvantage of autologous versus allogeneic donors is also a subject of much investigation. Issues with the various strategies are discussed as follows:

In vivo Activation and Expansion of γδ T Cells

The most attractive and logistically simple approach would be in vivo expansion and activation of γδ T cells in the cancer patient using pharmacologic agents that are

currently available for clinical use. One early trial compared the bisphosphonates Pamidronate, Zoledronate and Ibandronate with respect to their ability to induce proliferation of γδ T cells in patients with multiple myeloma (Kunzmann et al., 2000). Only the N-BP Pamidronate induced γδ T cell expansion. In addition, viable bone marrow plasma cells were significantly reduced following administration of Pamidronate at 24 h prior to marrow sampling when compared to controls. Wilhelm treated a series of patients with low-grade non-Hodgkin's lymphoma using intravenous Pamidronate after determining that their γδ T cells would respond to Pamidronate + IL-2 in vitro. Significant in vivo activation/proliferation of γδ T cells was observed in 5/9 patients, and objective responses were achieved in 3/9 as determined by CT scanning and biopsy (Wilhelm et al., 2003). Dieli compared Zoledronate alone and in combination with IL-2 (ZOL/IL2) in patients with hormone-refractory prostate cancer. In patients who received the ZOL/IL2 regimen, the numbers of effector-memory γδ T cells showed a statistically significant correlation with declining prostate-specific antigen levels and objective clinical outcomes that consisted of three instances of partial remission and five of stable disease. By contrast, most patients treated with ZOL alone failed to sustain γδ T cell numbers and did not show a clinical response (Dieli et al., 2007). Bennouna conducted two Phase I clinical trials combining intravenous IL-2 and bromohydrin pyrophosphate (BrHPP, IPH1101), a synthetic phosphoantigen that directly activates of Vγ9Vδ2 γδ T cells, against solid tumours. Both trials showed acceptable safety data with IL-2 toxicity as the principal concern; however, results were mixed and inconclusive (Bennouna et al., 2008, 2010), possibly due to concurrent expansion of T_{regs} as elucidated by Lamb in a later study of Zoledronate/IL-2 in vivo expansion in Stage IV neuroblastoma patients (Pressey et al., 2016).

Autologous γδ T cell Therapy

Although autologous cellular therapy carries with it the advantages of limiting the potential for GvHD and immunologic rejection of the infused therapeutic cell product, there is evidence that γδ T cells from cancer patients are reduced in number and impaired in their potential for activation and expansion as described in recent findings from patients with melanoma (Argentati et al., 2003), leukaemia (Meeh et al., 2006), breast cancer (Gaafar et al., 2009) and glioblastoma (Bryant et al., 2009b). Indeed, it has been known as early as 1991 that TCR/CD3 signalling can induce apoptosis (Janssen et al., 1991) in mature γδ T cells. Daudi lymphoma cells, which are killed by Vγ9Vδ2+ γδ T cells, also induce apoptotic death in the γδ T cell effectors on TCR triggering (Ferrarini et al., 1995), possibly a result of a negative feedback mechanism which may limit the time span of γδ T cell expansion during infectious diseases, even when pathogens are not eliminated and persist in the host.

These findings do not rule out the potential for autologous γδ T cell therapies, but importantly they may limit their application to patients with sufficient γδ T cell function to

warrant the undertaking of a complex cell manufacturing procedure. Indeed, large numbers of cytotoxic γδ T cell effectors can be obtained from selected cancer patients using either N-BP or phosphoantigen stimulation (Kondo et al., 2008). Two small trials of autologous γδ T cell therapy have been conducted in patients with metastatic renal cell carcinoma, a tumour with documented sensitivity to host immune function. In the first trial (Kobayashi et al., 2007), γδ T cells were expanded and activated using a synthetic phosphoantigen 2-m ethyl-3-butenyl-1-pyrophosphate (2M3B1-PP). No severe adverse events were seen in this trial, and three of five patients showed slower tumour progression. Patients in whom a response was documented also showed an increase in the absolute peripheral γδ T cell count and a strong in vitro response to phosphoantigen stimulation. In the second trial, 10 patients were treated with BrHPP-expanded γδ T cells in a dose-escalation Phase I trial to determine the safety of this therapy and the maximum tolerated cell dose (Bennouna et al., 2008). Although there was no measurable effect on disease progression in this study, the data indicate that repeated infusions BrHPP-expanded γδ T cells up to a dose of 8×10^9 total cells, either alone or in combination with IL-2, are well tolerated. These early trials show promise for the development of autologous γδ T cell therapies in eligible patients.

Allogeneic γδ T cell Therapy in the Setting of Haematopoietic Stem Cell Transplantation

To date, there have been no studies performed in which expanded and activated γδ T cells have been specifically introduced in HSCT. Wilhelm (Wilhelm et al., 2014), however, studied a series of patients with advanced haematologic malignancies who are not eligible for allogeneic transplantation for whom he combined adoptive transfer and in vivo expansion of haploidentical γδ T lymphocytes. This group was able to achieve a marked in vivo expansion of donor γδ T cells. Three out of four patients achieved a complete remission and the longest lasted for 8 months in a patient with plasma cell leukaemia. For the potential in combination with HSCT, some information can be gained from studies in which αβ T cells were specifically depleted from allogeneic grafts, thereby enriching the cell product for γδ T cells and NK cells. One single-centre study compared outcomes of patients who received an αβ T cell depleted (αβTCD) grafts with patients who received pan T cell depleted grafts (Lamb et al., 1996, 1999). In this study, a significant number of patients who received αβTCD cells subsequently developed spontaneous increases in the absolute count of circulating γδ T cells during the first year following HSCT. These cells were predominately Vδ1+ and were cytotoxic to primary leukaemias and leukaemia cell lines in vitro. The patients experienced a significant long-lasting improvement in disease-free survival when compared with similar risk patients (Godder et al., 2007). Conversely, another single-centre study of 535 patients who received αβTCD grafts versus pan-CD3 TCD (Keever-Taylor et al., 2001) showed no difference in disease-free survival for either TCD method, although patients with increased γδ T cell counts, if present, were not analysed separately.

Increased interest in αβ T cell depletion (TCD) parallelled the introduction of CliniMACS technology (Miltenyi Biotec, Bergisch Gladbach, Germany) that employs antibody-coated ferromagnetic microspheres for TCD (using the IgG clone BMA-031) resulting in a 3–4 log reduction of the αβ T cells (Schumm et al., 1999). The efficacy of this depletion strategy was tested in 200 procedures performed over 3 years in one published study (Li Pira et al., 2016). The resurgence of interest in αβTCD enabled Airoldi to confirm the homeostatic reconstitution of γδ T cells following αβ T cell/CD19 + B cell depletion in children receiving haplo HSCT that was reported by Lamb over 20 years earlier (Airoldi et al., 2015).

Indeed, both animal and human studies suggest that allogeneic γδ T cells can be safely infused within the setting of HSCT. Although γδ T cells can be activated in the setting of GvHD, evidence has not been found to suggest that donor-derived γδ T cells are primary initiators of GvHD (Ellison et al., 1995; Drobyski et al., 2000). Remarkably, it was observed that arge doses of IL-2 expanded γδ T cells can be infused into lethally irradiated MHC-disparate mice (C57BL/6 [H-2^b] > B10.BR [H-2^k] and C57BL/6 [H-2^b] > B6D2F1 [H-$2^{b/d}$]) without causing GvHD (Drobyski et al., 1999). In vitro studies provide evidence that γδ T cells are not substantially activated in the allogeneic mixed lymphocyte culture (Lamb et al., 2001; Schilbach et al., 2000). In addition, animal studies and indirect evidence from human allogeneic transplant studies suggest that γδ T cells can also facilitate alloengraftment (Blazar et al., 1996; Drobyski and Majewski, 1997; Kawanishi et al., 1997; Henslee et al., 1987).

Donor Innate Lymphocyte Infusion Therapy

Although several examples of the successful application of donor lymphocyte infusions (DLI) for relapsed leukaemia have been published (Kolb and Holler, 1997; Guglielmi et al., 2002), acute and chronic GvHD remain as major direct complications from DLI (Montero et al., 2006) even with modifications such as T cell–depleted DLI or graded incremental DLI doses (Dazzi et al., 2000). Innate recognition of tumour-associated stress antigens by lymphocytes such as γδ T cells may provide an ideal source of allogeneic cellular immunotherapy as they respond to malignancy without recognition of allospecific antigens. Given the potentially lower risk for initiation of GvHD by γδ T cells, it may be possible to deliver donor-derived γδ T cells as DLI early after allogeneic HSC transplantation with minimal risk of GvHD. In addition to post-HSCT DLI, the possibility exists for unrelated universal allogeneic expanded/activated γδ T cells to be employed directly in combination with lymphodepleting cytoreductive therapy for the treatment of a variety of malignancies in a nontransplant setting as has been recently described for NK cells (Miller et al., 2005). As of this writing, a γδ T cell–based DILI in a Phase I clinical trial of ex vivo expanded/activated γδ T cells following haploidentical HSCT and post-HSCT cyclophosphamide GvHD prophylaxis is being conducted in a collaboration between the University of Alabama at Birmingham (UAB) and Incysus (New York, NY, USA).

Cell Manufacturing Strategies

As discussed above, several investigators have developed procedures for the expansion and activation of γδ T cells for infusion based on their responsiveness to phosphoantigens and N-BPs. As N-BPs are approved in the United States and Europe as bone-strengthening drugs, strategies that employ cGMP-approvable culture methods for γδ T cells with IL-2 and commercially available bisphosphonates such as Zoledronate or Pamidronate have been previously translated for use in autologous therapies and one allogeneic application discussed above. The synthetic phosphoantigen BrHPP (Phosphostim; Innate Pharma; Marseille, FR), which was developed specifically for innate immune therapy was withdrawn from the market as part of Innate Pharma's decision to exit the adoptive cell therapy market even though early trials showed measurable efficacy in expansion of γδ T cells with no significant toxicity as discussed previously (Bennouna et al., 2008; Salot et al., 2007). Lamb et al. (2018) have recently translated Zoledronate/IL-2 initial manufacturing protocols into an automated, commercial bioreactor system (Prodigy, Miltenyi Biotec; Bergisch Gladbach, GERMANY) for use in an allogeneic transplant setting.

At issue, however, is the finding that both N-BP and phosphoantigen mediated γδ T cell stimulation expand only the Vγ9Vδ2 γδ T cell subset and does not deliver the additional potential therapeutic benefit of an expanded Vδ1+ population (Kabelitz et al., 2007; Schilbach et al., 2008). Indeed, manufacturing of expanded Vδ1+ T cells has presented a formidable challenge for investigators searching for a protocol that could receive clinical approval. The earliest protocol with clinical potential actually expanded both Vδ1+ and Vδ2+ γδ T cell populations in proportion resulting in the potential for a substantially higher expanded Vδ1+ dosing potential than Zoledronate/IL-2 expansion. Lopez and colleagues developed this procedure based on a CD2-initiated signalling pathway that induces a coordinated downregulation of the IL-2Rα chain and a corresponding upregulation of the IL-15Rα chain on γδ T cells. The γδ T cells stimulated in this manner express 10-fold higher levels of message for *bcl*-2 resulting in an inhibition of apoptosis in mitogen-stimulated human γδ T cells and potentially overcoming some of the problems with AICD discussed previously. In addition, this procedure activates and expands all δ-chain phenotypes (Lopez et al., 2000; Guo et al., 2002). As with N-BP, γδ T cells that are expanded and activated using this method retain potent innate antitumour activity against a wide variety of human haematopoietic and solid primary tumours and cell lines (Lopez et al., 2000; Guo et al., 2001). Because substantially higher numbers of αβ T cells are also expanded in this culture protocol than in the bisphosphonate expansion methods, it is also necessary to deplete large numbers of αβ T cells, potentially increasing the cost and complexity of the procedure.

Vδ1+ T cells proliferate in response to plant mitogens and thereby generate a predominant Vδ1+ T cell population in an αβTCD culture as the Vδ2+ cells fall victim to AICD. Schilbach and colleagues purified blood-derived γδ T cells by immunomagnetic selection followed by stimulation of purified cells with PHA and IL-2 in culture. The addition of

Pamidronate stimulated the Vδ2 population, which was subsequently lost from culture and resulted in outgrowth of Vδ1+ T cells with significant activity against neuroblastoma (Schilbach et al., 2008). Knight et al. (2012) generated Vδ1+ T cells with antimyeloma activity from peripheral blood mononuclear cells (PBMNC) using a combination of PHA, IL-2 and allogeneic irradiated feeder cells. Siegers showed similar results using prolonged exposure of positively selected Concanavalin-A stimulated γδ T cells to IL-2 and IL-4 without the use of feeder cells (Siegers et al., 2011a). γδ T cells expanded using this protocol were still viable in a xenograft leukaemia model 5 weeks post infusion after having been injected on day 16–21 of in vitro culture (Siegers et al., 2011b). In subsequent studies, enhanced Vδ1+ T cell expansion (up to 24,000-fold) was seen in PBMNC cultures initially stimulated with Concanavalin-A and then depleted of αβ T cells after 6–8 days (Siegers et al., 2012). Average culture duration was approximately 21 days and did not require feeders (Siegers et al., 2012). Finally, Lamb et al. (2001) was able to generate up to 1200-fold expansion of Vδ1+ T cells from PBMNC after depletion of αβ T cells and culture with irradiated leukaemia feeder cells and low-level IL-2 (Lamb et al., 2001).

At present, however, none of these protocols have direct clinical adaptability, and future methods derived thereof will require substantial modification to move forward into human trials. Such modifications should include steps to facilitate ease of handling, preferably by eliminating feeders and reducing the number of required reagents because these must be of pharmaceutical grade and the protocol performed under GMP to obtain clinical approval for therapeutic cell manufacturing. Most importantly, protocols that seek to manufacture Vδ1+ T cells will likely be required to show that the suppressive phenotype discussed above is not included in the graft. This will be no small feat, as a distinguishing surface marker has not yet been characterised between either the effector or regulatory phenotype. Notably, however, two emerging biotechnology companies discussed below, GammaDelta Therapeutics and Lymphact have developed proprietary technology for Vδ1+ T cell manufacturing, although neither has published extensive phenotyping or functional data nor have initiated a clinical trial as of this writing.

OBSTACLES TO THE DEVELOPMENT AND IMPLEMENTATION OF γδ T CELL THERAPIES

The potential and actual problems that must be considered when developing γδ T cell–based cellular therapies have recently been reviewed in detail (Martinet et al., 2009b). Two issues that deserve mention have been previously explored in this chapter. The first one is the observation that circulating γδ T cells from cancer patients are reduced in number and show impairment of proliferative function, especially following standard-of-care chemo- and radiotherapy, thus limiting the applicability of autologous infusion therapies or strategies that rely on in vivo stimulation of γδ T cells. A separate though related problem is the sensitivity of normal γδ T cells to AICD, which could impact the longevity of ex vivo expanded allogeneic cells once infused (Siegers and Lamb, 2014).

Other obstacles are those common to most T cell–based therapies. To eradicate solid tumours, γδ T cells must be able to traverse the tumour vasculature, migrate in high numbers into the surrounding parenchyma, bypass immunosuppression from regulatory cells such as T_{regs} and target tumour antigens that are clonal. To date, clinical trials using ex vivo expanded γδ T cells have not addressed this issue, although γδs T cells express CXCR3 and CCR5 receptors for cytokines such as CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (ITAC) and CCL5 (RANTES), which are generally produced in the tumour inflammatory microenvironment (Poggi et al., 2004a; Dieli et al., 2003; Glatzel et al., 2002; Poggi et al., 2007). The tumour vasculature can impair T cell migration via endothelin-B mediated inhibition of ICAM-1 and abnormal differentiation and morphology of tumour vasculature. Recent studies also suggest that antiangiogenic agents currently used in cancer therapy can restore normal vascular morphology and thus permit improved T cell migration into the tumour (Martinet et al., 2009b).

A host of tumour-derived inhibitory factors such as TGF-β can effectively paralyse the immune response to tumour via multiple mechanisms such as inhibition of DC maturation, inhibition of antigen presentation, inhibition of T cell activation and expansion of CD3+CD4+FoxP3+ regulatory T cells (Smyth et al., 1991; Inge et al., 1992; Jachimczak et al., 1993), which have recently been implicated in the direct suppression of γδ T cell function (Kunzmann et al., 2009). Of particular concern to innate immune responses is the proteolytic shedding of soluble NKG2D ligands from tumours due to matrix metalloprotease activity, which in turn bind NKG2D (and possibly the γδ TCR) resulting in receptor endocytosis and inhibition of both γδ T cell and NK cell function (Groh et al., 2002). Tumour-derived proinflammatory factors also recruit suppressive cells such as monocyte-derived suppressor cells (MDSC) and mesenchymal stromal cells (MSC) into the tumour microenvironment (Umansky et al., 2016). Although the impact of MDSC on γδ T cell function remains unclear, it is known that MSC actively suppress Vγ9Vδ2+ responses to phosphoantigen via COX-2 mediated production of PGE-2, which in turn suppresses proliferation, TNF-α and IFN-γ production and tumour cytolysis (Martinet et al., 2009a).

INDUSTRY

The first company to focus on the development of γδ T cell–based immunotherapies was Innate Pharma, which undertook numerous trials through the 2000's with its IPH1101 or Innacell γδ in cancer patients (Bennouna et al., 2010). As noted previously, as data were presented and the excitement from checkpoint inhibitor antibodies took off in 2010 and 2011, the management team of Innate Pharma chose to deprioritise its cell therapy efforts and focus its financial resources on the development of its internal checkpoint antibodies.

More recently, positive early CAR-T results drove newfound interest in adoptive cellular therapies, and by 2014, 34 clinical protocols targeting CD19 had already been registered with the National Institutes of Health's (NIH) Office of Biotechnology

Activities. Those seeking to develop next-generation cellular therapies were already thinking about how to effectively target solid tumour cancers and how one may potentially deliver an allogeneic, 'off-the-shelf' therapy. For some, the unique properties of the γδ T cell would become an area of focus. In particular, the γδ T cell's ability to distinguish healthy from tumour tissue may help overcome the targeting challenges that resulted in patient deaths in the early CAR-T and TCR trials targeting HER2 or MAGE-A3. The non-MHC–restricted killing of γδ T cells may also allow the allogeneic delivery of cells without the risk of GvHD as seen with NK cell therapies. Of course, longer term, a lack of GvHD will still need to be balanced with the countering host-vs-graft that can effectively eliminate any donor cells.

There is growing interest in the potential of γδ T cells as a backbone of an adoptive cellular therapy, with several companies having been formed in recent years. In addition to our own γδ T cell company, Incysus, other companies quietly working in the γδ T cell space include OrbiMed's Adicet Bio, Inc., Medicxi's Gadeta B.V., Abingworth's GammaDelta Therapeutics, Ltd., Immatics US, Inc., a subsidiary of Immatics Biotechnologies GmbH of Tuebingen, Germany, Lava Therapeutics BV, Leucid Bio, Ltd., Lymphocyte Activation Technologies SA (Lymphact), Nybo Therapeutics, Inc., a subsidiary of PureTech Health plc, Realist Pharma Inc. and TC Biopharm Ltd.

The first of these γδ T cell companies to form was likely TC Biopharm Ltd in Glasgow Scotland. Founded by Dr. Michael Leek and Angela Scott in early 2013, the company is developing ImmuniCell a genetically unmodified, autologous γδ T cell therapy currently in a Phase II study for patients with melanoma, renal cell kidney cancer and nonsmall cell lung cancers (NSCLC). TC Biopharm licenced its technology from MEDINET Co. Ltd of Japan. MEDINET has a relationship with The Seta Clinic Group in Japan and the groups coauthored a publication of the Phase I data of ImmuniCell in NSCLC in 2009. Ten patients received up to 1×10^9 γδ T cells delivered intravenously, biweekly for six doses. Of the treated patients, the best observed response was stable disease in three patients with no complete or partial responses. Our own preclinical data in orthotopic PDX models suggests that naked γδ T cells in solid tumour cancers are unlikely to provide a significant benefit. In December 2017, TC Biopharm and bluebird bio announced a strategic collaboration to develop γδ T cell–based CAR-T products for cancer immunotherapy.

In 2013, Bruno Silva-Santos, PhD and Diogo R. Anjos formed Lymphact–Lymphocyte Activation Technologies SA, to commercialise and develop the DOT-One, Vδ1+ cells that the Silva-Santos team developed at the Instituto de Medicina Molecular, Universidade de Lisboa in Portugal. Most recently, we understand that Lymphact was considering a potential merger with another player in the space.

Adicet Bio, Inc. was founded in late 2014 by Aya Jakobovits, PhD, previously, the founding President and CEO of Kite Pharma and OrbiMed Advisors, LLC. OrbiMed, the largest healthcare focused investment fund with approximately $13 billion in assets

under management as of this writing, helped launch Adicet with a $51 million Series A financing that closed in January 2016 in conjunction with the acquisition of Applied Immune Technologies Ltd. of Israel. Adicet is focused on developing γδ T cells, particularly the Vδ1+ subset as an allogeneic cellular therapy for treating cancer. With a collaboration with Regeneron signed in August 2016, Adicet is seeking to turn targets from Regeneron's antibody library into CAR-Ts and TCRs to direct γδ T cell killing. On March 7, 2018, Adicet announced that Aya Jakobovits retired from her position as President and Chief Executive Officer of the Company.

Immatics US, Inc. was formed by Immatics Biotechnologies GmbH of Tuebingen, Germany in a collaboration with MD Anderson Cancer Center to develop adoptive cellular therapies for cancer in 2015. The parent company has raised more than $230 million in venture capital funding and committed $40 million into the Immatics US., Inc. joint venture. Immatics was founded by CEO Harpreet Singh, PhD who also serves as Managing Director and Chief Scientific Officer of the parent company. Immatics was a spin-out of Hans-Georg Rammensee's laboratory at the University of Tübingen, Germany and Immatics US, Inc. is based on the work of Patrick Hwu, MD and Cassian Yee, MD at MD Anderson. The University of Tübingen is one major centre for γδ T cell research and clinical trials due to the αβTCD work of Rupert Handgretinger and Karin Schilbach. Immatics US, Inc. is focused on developing allogeneic Vγ9Vδ2+ γδ T cells genetically engineered with CAR-T or TCRs. The parent company with its XPRESIDENT platform has expertise in identifying peptide targets that can be used to develop CAR-T and TCR therapies for cancer.

GammaDelta Therapeutics, Ltd. was founded and seeded by the London-based investment group Abingworth in September 2016. The company is advancing research targeting tissue resident γδ T cells (Vδ1+) by Professor Adrian Hayday and Dr. Oliver Nussbaumer at King's College London and the Francis Crick Institute respectively. The company announced a strategic collaboration with Takeda Pharmaceutical Company Limited in May 2017. The deal drove new investor interest in the field of γδ T cells as it included a $100 million funding commitment from Takeda and Abingworth to accelerate GammaDelta's R&D efforts including Takeda's exclusive right to purchase the company. In May 2017 GammaDelta also announced the recruitment of Paolo Paoletti, MD, as Chief Executive Officer. Dr. Paoletti, was most recently the CEO of Kesios Therapeutics, Ltd. and was formerly the President of GSK Oncology.

In January 2015, Lawrence Lamb, PhD from the University of Alabama at Birmingham (UAB) was stranded in New York City during a blizzard ironically named Juno. With the city deserted and the subway system shut down for the first time in its 110-year history, Dr. Lamb and William Ho were introduced by a transplant colleague from UAB. Over an extended lunch, the pair discussed Dr. Lamb's work, the immunotherapy landscape and the properties of γδ T cells. By late 2015, Incysus, Inc. was founded to advance a γδ T cell programme into the clinic and to develop the innovative drug resistant

immunotherapy (DRI) approach developed at UAB, Emory University and Children's Healthcare of Atlanta. As discussed above, solid tumour cancers utilise multiple mechanisms of immune suppression and evasion. By combining high-dose chemotherapy simultaneously with γδ T cells gene-engineered to resist the killing effect of chemotherapy, DRI has the ability to mitigate the immune-suppressive effects of the tumour microenvironment while upregulating γδ T cell–activating signal through the DNA damage response. Our preclinical data demonstrate the ability to upregulate NKG2D-ligand expression on the tumour by as much as 600% against a chemo-resistant tumour. In October 2017, Incysus and UAB received FDA approval to initiate a clinical trial to test expanded and activated donor γδ T cell infusion in a haploidentical transplant setting. The team filed a second IND to test the DRI technology in newly diagnosed glioblastoma patients in early 2018.

2017 was a breakthrough year for cellular therapies with the FDA's marketing approval of Novartis' Kymriah (tisagenlecleucel) and Kite Pharma's Yescarta (axicabtagene ciloleucel). With the acquisition of Kite for $11.9 billion by the biotechnology company Gilead and of Juno Therapeutics for about $9 billion by Celgene, the race is on to discover and develop the next generation of adoptive cellular therapies for oncology indications. While many challenges lay ahead, the market for solid tumour cancers is roughly 9× bigger than that of the haematologic malignancies with over 1.5 million newly diagnosed patients in the United States annually (Cancer Facts and Figures https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html). Solid tumour cancers present an increased level of difficulty due to cell trafficking, the tumour microenvironment and the close association of tumours with the surrounding healthy tissue. To this date, only a handful of companies and groups have recognised the unique features of γδ T cells and their intrinsic ability to distinguish healthy from dangerous tissue. It is an exciting time with increasingly greater knowledge in a rapidly advancing landscape and inevitably the interest in these cells will continue to grow. We look forward to learning more clinically from researchers and clinicians who work on developing γδ T cell–based therapies as the next few years will witness the initiation of allogeneic approaches and new, next-generation, genetically modified γδ T cell trials.

PERSPECTIVES

The development of strategies to exploit the innate antitumour properties of human γδ T cells – particularly as an adjuvant to more traditional cancer therapies – may allow the treatment of a variety of malignant diseases that are now only partially responsive to HSCT or other cell-based immunotherapies. The increasing knowledge of tumour-derived immunosuppression and immune escape will ultimately lead to strategies that will remove some of the barriers to effectiveness of these therapies. Finally, the recent clinical and translational studies highlighted in this chapter illustrate that the therapeutic numbers of γδ T

cells with significant antitumour activity can be expanded with methods that are easily translated to comply with current GMP cell manufacturing regulatory requirements.

For the above reasons, we envision that it will eventually become possible to specifically transfer tumour-reactive donor-derived γδ T cells as part of both allogeneic and autologous transplant strategies for the treatment of a variety of malignancies. Particularly in the setting of lymphodepleting nonmyeloablative chemotherapy or radiotherapy, evidence strongly suggests that γδ T cell–based innate lymphocyte infusion therapy or strategies to augment γδ T cell activation and expansion in vivo can become important tools in the treatment of selected cancers.

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