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Human Cell-Based Artificial Antigen Presenting Cells for Use in Natural Killer Cell Adoptive Therapy

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Keywords: Artificial antigen presenting cell; Adoptive therapy; Cytokine; K562; Natural killer cells

Abstract

Natural Killer (NK) cells are critical components of the immune system responsible for tumour recognition and eradication. Recent studies of haematopoietic cell transplantation highlighted the utility of NK cell adoptive therapy used to enhance the graft-versus-leukaemia effect without worsening graft-versus-host disease. However, NK cell adoptive therapy is limited by the fact that it is difficult to prepare clinically adequate numbers of NK cells. Artificial antigen presenting cells have been designed and developed as an off-the-shelf strategy to prime NK cell production *in vitro*; facilitating the production of adequate cell numbers capable of efficiently engrafting, persisting, and responding to tumours *in vivo*.

Abbreviations

NK: Natural Killer; HCT: Haematopoietic Cell Transplantation; GVHD: Graft-Versus-Host Disease; GVL: Graft-Versus-Leukaemia; PBMCs: Peripheral Blood Mononuclear Cells; EBV-LCL: Epstein-Barr Lymphoblastoid Cell Line; GMP: Good Manufacturing Practice; aAPCs: Artificial Antigen Presenting Cells; CLP: Common Lymphoid Progenitor; NKP: Pre-Nk Cell Precursor; NCR: Natural Cytotoxicity Receptor; ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity; MCMV: Mouse Cytomegalovirus; CMV: Cytomegalovirus; rh-IL-2: Recombinant Human Il-2; ICAM-1: Intercellular Adhesion Molecule-1; LFA-3: Lymphocyte Function-Associated-Antigen-3; AML: Acute Myeloid Leukaemia; EWS: Ewing Sarcoma; KIRs: Immunoglobulin-Like Receptors; NCRs: Normal Cytotoxicity Receptors

Introduction

More than a century ago, the immune system was recognised to be vital in terms of controlling tumour growth [1]. Cancer immunotherapy exploits the intrinsic power of the immune system to fight disease [2]. The goal of cancer immunotherapy is to build persistent and specific immunological "memory" to prevent cancer recurrence [3]. Adoptive cell therapy is a promising means to this end; anti-tumour immune cells can be manipulated *in vitro* to prepare optimal cell subsets facilitating sustained responses that augment clinical outcomes. Haematopoietic Cell Transplantation (HCT) was the first immune system-based cellular therapy to be developed, and has allowed patients with haematological cancers to enjoy long-term disease-free survival [4]. However, acute Graft-Versus-Host Disease (GVHD) remains a common, unpredictable, and severe inflammatory complication in patients undergoing HCT. Over the past decade, clinical and translational researchers have sought to use NK cells to enhance the Graft-Versus-Leukaemia (GVL) effect without worsening GVHD [5,6]. Clinical trials of the efficacy and safety of NK cell adoptive therapy in patients undergoing HCT are currently underway [7]. When preparing NK cells for use in adoptive therapy, large numbers of such cells must be endowed with the capacities to efficiently engraft, persist, and respond to the tumour *in vivo*.

Originally, feeder cell lines including Peripheral Blood Mononuclear Cells (PBMCs), RPMI8866 cells, an Epstein-Barr Lymphoblastoid Cell Line (EBV-LCL), and K562 cells were used to propagate NK cells *in vitro* [8]. However, the numbers of homogeneous NK cells thus created were inadequate to meet the needs of clinical trials. For example, B lymphoblastoid cells were used as feeders stimulating human PBMCs, but the NK cell numbers rose only 25-fold and the T cell numbers about 3-fold. Thus, the elimination of CD3+/CD5+ T cells to obtain purer preparations of NK cells was required to reduce the risk of GVHD induced by T cell contamination [9]. In compliance with established Good Manufacturing Practice (GMP), Artificial Antigen Presenting Cells (aAPCs) have been designed and developed as a highly efficient off-the-shelf strategy to generate NK cells *in vitro*. In this review, we focus on recent advances in the use of K562-based aAPCs to stimulate NK cell propagation; this may yield effective adoptive cell therapies for cancer.

Our study is a review article, which is not involved the ethical approval of ethics committee and informed consent of patients.

Phenotypic and functional properties of NK cells

NK cells are large granular lymphocytes that are classified as innate immune cells [10]. Unlike T and B cells, NK cells can lyse certain malignant cells and pathogens in an antigen-independent manner [11]. Continual research into the development and function of NK cells has revealed that these cells straddle the line between innate and adaptive immunity and play important roles in controlling infection, autoimmunity, and tumour immune surveillance [11-13].

NK cells are thought to be derived from, and to develop primarily in, bone marrow [10,14]. The cells are not static during development and maturation; the expression of a variety of cell surface molecules is stimulated or inhibited in a particular order during different

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developmental stages. Relevant stages include Common Lymphoid Progenitor (CLP), Pre-Nk Cell Precursor (NKP), NKP, immature NK, and mature NK cells (Figure 1) [10]. Mature human NK cells do not express CD3, but they do express CD56 and they can be subdivided into $CD56^{bright}$ and $CD56^{dim}$ subsets with different functional properties [13,15]. In contrast, murine NK cells do not express CD56, and it has thus been suggested that NKp46, a highly conserved member of the Natural Cytotoxicity Receptor (NCR) family of NK-activating receptors [16], might be a useful cross-species biomarker of NK cells [12,17]. $CD3\text{-}CD56^{bright}$ $NKp46^{bright}$ NK cells produce large amounts of cytokines and chemokines when activated, but this NK cell subset exerts minimal cytolytic functions [18]. The $CD3\text{-}CD56^{dim}NKp46^{dim}$ population is terminally differentiated from the younger $CD56^{bright}$ population, and effectively lyses tumour cell targets [13,19]. Also, the former cells express high levels of the low-affinity Fc receptor for IgG (CD16), which mediates Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) [20].

Recently, it was shown that, like T and B cells, NK cells exhibit several features of adaptive immunity when exposed to pro-inflammatory cytokines or viral infections [10,19,21]. Romee R et al. showed that brief pre-activation with combinations of cytokines, including IL-12, IL-15, and IL-18, followed by a 7- to 21-day rest, induced extensive proliferation of memory-like NK cells exhibiting enhanced IFN-γ production after re-stimulation; this capacity was maintained even after several rounds of cell division [22]. Low concentrations of IL-2, synthesized either by autologous T cells or exogenously administered, were essential to promote NK cell function and proliferation *in vivo* [23].

Work with a Mouse Cytomegalovirus (MCMV)-infected model, in which Ly49H+ NK cells were adoptively transferred into mice lacking the Ly49H receptor, revealed that MCMV infection selectively drove the expansion of a long-lived pool of "memory" Ly49H+ cells [24]. Signaling by IL-12 and STAT4, but (surprisingly) not IFN-γ, was essential for the development of NK cell "memory" [25]. NKG2C forms a heterodimer with CD94 on the NK cell surface [26]. Human CD56dimCD57+NKG2C+ NK cells thus resemble Ly49H+ memory-like NK cells in many respects [27], and it is accepted that such cells are adaptive NK cells induced by Cytomegalovirus (CMV) infection in humans [28]. Lönnqvist B et al. were the first to report that early CMV reactivation protected against the relapse of haematologic cancer in patients undergoing HCT [29]. Follow-up data on the associations between the levels of CMV-induced adaptive NK cells and the extent of relapse have varied by both patient cohort and transplant centre; further work is required [30].

Moreover, previous studies have investigated the antineoplastic effect of allogeneic NK cells in solid tumors. However, immunoglobulin-like receptors (KIRs) mismatched allogeneic NK cells might lead to immune-mediated rejection due to MHC mismatch. The study of Schaffer M et al. reported that donor-derived, alloreactive NK cells may interfere with immunity to infection in the early posttransplantation period [31]. A review article found no advantage of KIR ligand incompatibility on outcomes of unrelated donor bone marrow transplantations [32]. In the study of Igarashi T et al. they showed that KIR-incompatible allogeneic NK cells were more cytotoxic to tumor targets than their KIR ligand-matched counterparts [33].

In general, a developmental continuum is evident as CLP cells mature into NK cells, and when activated effectors become long-lived memory NK cells. Selective propagation of appropriate subpopulations of NK cells exhibiting desired functions may greatly improve the efficacy of adoptive therapy. It is essential to understand phenotypic and functional changes associated with the development of NK cells if it is desired to use such cells for immunotherapeutic purposes.

Cytokines used to expand NK cell populations

Cytokines aid in NK cell expansion prior to the application of adoptive immunotherapy; these materials enhance NK cell anti-tumour activity. The cytokines IL-2, IL-12, IL-15, IL-18, and IL-21 regulate human NK cell development, activation, survival, and function (Table 1) [34-39].

Below, we briefly review the basic biology of IL-2 and IL-15 in the context of NK cell adoptive therapy. IL-2 and IL-15 have been intensively studied, and exert similar biological activities [40]. IL-2 is produced by activated T cells [41], and IL-15 is generated by various APCs [42]. Both cytokines use IL-2/15Rβ and γc receptor components when transmitting intracellular signals activating the downstream Jak1/3, STAT3/5, PI3K, and MAPK pathways, and, ultimately NF-κB

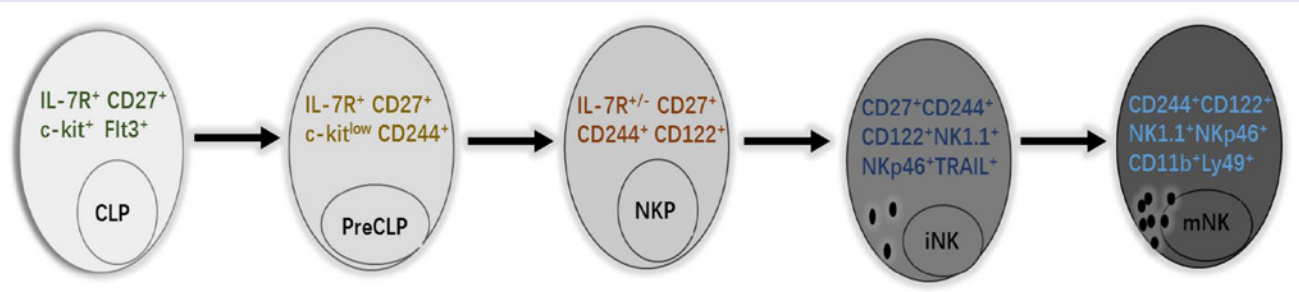

Figure 1: Stages of NK cell development. NK cells are derived from the CLP which is characterized by its expression of IL-7R, c-kit and Flt3. They further develop into preNKP distinguished from the NKP by its expression of IL-7R and losing expression of CD122. Immature NK cells begin to express specific NK cell markers NK1.1 and NKp46, and as they further mature. They express CD11b and Ly49 while lack of CD27 expression, acquire cytotoxic capacities and secrete cytokines such as IFN-γ.

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Table 1: Key cytokines regulating human NK cells.

Cytokine	Source	Receptor and components thereof	Functions
IL-2R	T cells	IL-2Rα IL-2/15Rβ γc	Induces *in*/*ex vivo* activation, maintains *in vitro* survival [33,34], enhances cytotoxic function, and upregulates IL-12 production [35]
IL-12R	DC Mφ	IL-12Rb1 IL-12Rb2	Induces cell activation, promotes cell proliferation and differentiation, and enhances cellular cytotoxic activity and IFN-γ production [34,36]
IL-15R	DC Mφ BM stroma	IL-15Rα IL-2/15Rβ γc	Promotes *in vitro* cell proliferation, survival, maturation, and activation [35,37]
IL-18R	DC Mφ	IL-18Rα/R1 IL-18Rβ/RAP	Augments cell maturation and promotes IFN-γ synthesis [37]
IL-21R	T cell	IL-21R γc	Enhances cellular proliferative and cytotoxic activities; increases expression of IFN-γ, perforin, and granzyme B [33]

† BM: bone marrow
‡ DC: dendritic cell
§ Mφ: macrophagocyte

[35]. Thus, when the two pathways triggered by IL-2 and IL-15 are activated in NK cells, the functional effects are similar [43]. When the cytokines bind to receptors on NK cells, both transduce positive signals important in terms of NK cell development, proliferation, homeostasis, cytokine production, and cytotoxicity [44].

Based on a profound understanding of the fundamental biology of IL-2, Koehl U et al. developed a GMP-compliant NK cell isolation and expansion protocol for the clinical preparation of highly enriched IL-2-stimulated NK cells, and infused these into three paediatric leukaemia patients undergoing haploidentical stem cell transplantation [45]. During recombinant human IL-2 (rh-IL-2) stimulation *in vitro*, NK cell numbers fell over the first 5 days but then recovered to attain 98% viability. By day 14, the median expansion was only 5-fold. However, subsequent studies on the role played by IL-2 in regulatory T cell function showed that IL-2 also activated CD4+CD25+Foxp3+ regulatory T cells, which are known to negatively regulate NK and effector T cells [46]. Moreover, the effects of different doses of IL-2 given to patients after an infusion of NK cells have been investigated in several clinical studie [47,48]. Treatment with a low dose of IL-2 *in vivo* had no obvious effect, whereas a high dose caused severe systemic toxicity [47,49]. Hence, clinical interest in cytokines other than IL-2 resurged when several studies yielded further insight into the various ways in which IL-15 acted on NK cells [50]. Berger C et al. showed in nonhuman primates that IL-15 expanded NK cell numbers and those of memory CD8+ and CD4+ T cells in peripheral blood, with minimal increases in regulatory T cells [51]. Also, IL-15 clearance between doses was achieved by intermittent administration of the cytokine. It was suggested that such a regimen should be clinically considered to mitigate possible toxicity caused by IL-15.

Non-aAPC approaches toward NK cell expansion

To date, the main source of NK cells for adoptive therapy is peripheral blood [52]. Umbilical cord blood, bone marrow, human embryonic stem cells, and induced pluripotent stem cells also generate NK cells at different yields [53-55]. Efficient infusion requires a large number of NK cells, typically 5×10^6 to 5×10^7/kg body weight [49], but NK cells constitute only about 10% of peripheral blood lymphocytes 18. Moreover, as NK cells normally do not exhibit persistent proliferation when responding to tumours after *in vivo* infusion [56], many researchers have sought to generate high numbers of functional NK cells *in vitro*.

In line with GMP, NK cells are obtained by leukapheresis of peripheral blood followed by the depletion of CD3+ T cells, with or without subsequent enrichment of CD56+ cells to obtain pure NK cell products [57]. After one or two rounds of selection, the cells are conventionally incubated with IL-2 overnight and infused the following day [57]. By this means, NK cells are expanded only 5-fold in number after 2 weeks of stimulation but exhibit potent lytic activity [58]. Activated autologous T cells may facilitate NK cell expansion, probably by releasing stimulatory cytokines such as IL-2 [59]. However, the acquisition of autologous T cells is laborious, slow, and expensive, rendering it impractical to expand NK cells using autologous T cells. Beads coated with NKp46 and CD2 are commercially available, rendering it possible to expand NK cell populations 100-fold in 21 days [60]. However, it is important to ensure that the beads are detached from the expanded NK cells before infusion to prevent micro-embolic complications and the development of immune responses to the linked monoclonal antibodies [61].

K562 cells as a platform for human cell-based aAPCs

K562 is a human erythroleukaemic cell line isolated from a patient with chronic myelogenous leukaemia who was in blastic crisis [3,62]. These cells were initially selected as a platform for T cells expansion because the cells presented antigens to, and expanded, T cells *in vitro*, and were safe in humans. Also, the cells do not express endogenous HLA molecules, which can induce allospecific T cells. Finally, the cells constitutively express co-stimulatory molecules, including intercellular adhesion molecule-1 (ICAM-1, CD54) and lymphocyte function-associated-antigen-3 (LFA-3, CD58); these molecules facilitate T cell activation [63,64]. K562 cells are known targets of NK cells. K562 cells ectopically expressing NK cell genes (co-stimulatory molecules and cytokines) effectively propagate both NK cells and T cells. Therefore, K562-derived aAPCs serve as excellent stimulators of NK cells [3].

aAPCs for NK cell expansion

K562-based aAPCs were initially manipulated to generate tumour-specific T cells for the treatment of haematological cancers [64,65]. The cells were transduced with genes encoding various molecules allowing them to simulate professional APCs during T cell activation61. Several preclinical studies of haematological malignancies showed that NK cells facilitated engraftment and augmented GVL without mediating GVHD [64,66]; aAPCs have also been utilised in NK cell adoptive therapy to expand the numbers of clinical-grade NK cells (Table 2) [67-71].

Fujisaki H et al. were the first to transduce K562 cells with membrane-bound IL-15 and 4-1BB in an effort to stimulate PBMCs toward the creation of large numbers of NK cells *in vitro* [71]. Highly

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Table 2: Expansion of NK cells *in vitro* for clinical use.

Source of NK cell	K562-based aAPC	Additional cytokines	Mean fold proliferation	Purity	Phenotype	Reference
$CD3^-CD56^+$ cells from PBMCs	K562-mb15-41BBL	IL-2	90.5 in 7 days	83%	$CD3^-$, $CD56^+$ $NKG2D^+$,$NCRs^+$	[67]
PBMCs	K562-mb15-41BBL	IL-2	209 in 8–10 days	61%	$CD3^-$, $CD56^+$	[68]
PBMCs	K562-mb21-41BBL	IL-2	4,7967 in 21 days	78%	$CD3^-$, $CD56^+$, $CD16^+$ $NKG2D^+$, $NCRs^+$ $CD160^+$	[69]
PBMCs	K562-mb15-MICA-41BBL	None	550 in 24 days	86%	$CD3^-$, $CD56^+$, $CD16^+$ $CD27^+$, $NKG2D^+$, $NKP46^+$, $CXCR3^+$	[70]
$CD3^-$cells from UCB mononuclear cells	K562-mb21-41BBL	IL-2	1848 in 14 days	> 95%	$CD3^-$, $CD56^+$, $CD16^+$ $NKG2D^+$, $NCRs^+$	[71]

† PBMCs: peripheral blood mononuclear cell
‡ UCB: umbilical cord blood

cytotoxic NK cells underwent up to 30 doublings; expansion was probably limited by telomere attrition, as suggested by the extent of immortalisation of TERT-transduced NK cells [71]. A pre-clinical study showed that NK cells expanded by K562-mb15-41BBL cells effectively killed primary acute myeloid leukaemia (AML) cells from AML patients, and AML cell lines *in vitro*. Furthermore, in a xenogeneic AML model, the expanded NK cells effectively suppressed the growth of leukaemic cells and remained detectable even to day 31 after the systemic administration of a high dose of IL-2 [56]. Pre-clinical studies of paediatric patients with solid tumours showed that NK cells expanded by K562-mb15-41BBL cells effectively killed Ewing sarcoma (EWS) and rhabdomyosarcoma cell lines, and eradicated EWS cells engrafted into mice that were not obese but were both diabetic and exhibited severe IL-2 immunodeficiency (the IL-2Rγ^{null} mouse line) [72]. Theoretical and practical bases for the large-scale *ex vivo* expansion of NK cells via aAPCs have thus been established.

The findings of Fujisaki H et al. have been further confirmed; Zhang H et al. utilized aAPCs expressing CD137L and IL-15Rα to activate and expand peripheral blood NK cell populations (CD137L/IL-15 NK cells) by up to 1,000-fold in 3 weeks, expanded NK cells by these aAPCs exhibited an evident increase in the expression levels of KIRs and normal cytotoxicity receptors (NCRs: NKp30, NKp44, and NKp46) that have been suggested to be promising biomarkers of the potency of NK cells [71,73]. Additionally, K562-MICA-4-1BBL-IL-15 expressing aAPC stimulated NK cells to expand by a mean of 550-fold over approximately 3 weeks, and they promoted NK cell activation, proliferation, and cytotoxicity [69].

To deal with the fact that telomere shortening in K562-mb15-41BBL-expanded NK cells limited cellular propagation, Singh H et al. transduced mbIL-21 into K562 cells expressing CD64, CD86, 4-1BBL, and truncated CD19 (Clone9.mbIL21). Compared to cells expressing mbIL-15, mbIL-21-expressing aAPCs more potently promoted NK cell expansion in the absence of any sign of cellular demise [74]. NK cells expanded using mbIL-21 were phenotypically similar to those expanded using mbIL-15, but secreted more cytokines. The enhanced killing exhibited by mbIL-21-expanded NK cells was primarily attributable to ADCC [3,69,75].

Conclusion

Chimeric antigen receptor-modified T cells have been successfully used to treat B cell malignancies and a number of solid tumours, highlighting the utility of cellular immunotherapy for cancers. Apart from T cells, NK cells that recognise and kill malignant transformed cells in the absence of prior sensitization are optimal candidates for adoptive cellular immunotherapy. Allogeneic stem cell transplantation after the transfusion of KIR-mismatched NK cells is effective for the treatment of patients with haematological cancers. Studies of the NK cell biology underlying the regulation of phenotype and function have yielded inspiring results; it is now possible to manipulate optimal subsets of NK cells for the purpose of adoptive immunotherapy. It is encouraging that only 5 years have elapsed from the discovery of cytokine induced memory-like NK cells to translational clinical testing of their efficacy and safety in humans.

The *in vitro* preparation of appropriately activated and expanded NK cell populations is difficult but important (Figure 2). K562-derived aAPCs can be used to generate NK cells in numbers adequate to meet clinical demands. Also, this approach facilitates the *ex vivo* study of NK cell development. However, caution should be taken when analyzing aAPC-derived data. During NK cell expansion, phenotypic and functional changes may significantly influence the ultimate efficacy of NK cell adoptive immunotherapy, even though the aAPC approach creates high numbers of activated NK cells. For example, NK cells expanded by K562-mb15-41 BBL aAPCs exhibited replicative demise (a sign of senescence); such cells may be compromised *in vivo* despite the fact that they efficiently lysed tumour targets *in vitro*. Therefore, younger NK cells may exhibit better anti-tumour potential than cells subjected to long-term culture and expansion.

In conclusion, as our understanding of human NK cell biology increases, the clinical indications for, and the spectrum of cancers treatable by, NK cells will increase. We expect that advances in our understanding of NK cell biology will create new strategies allowing us to win the battle against cancer.

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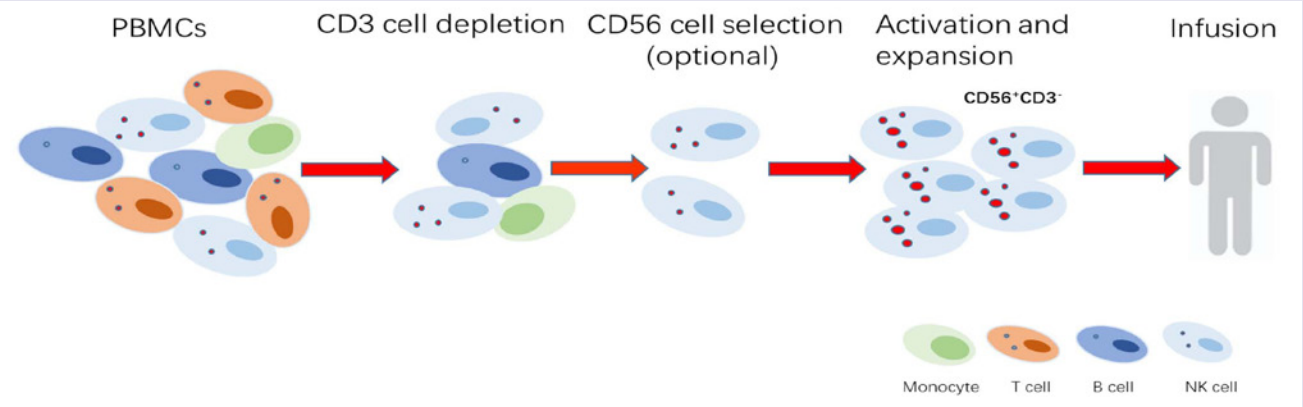

Figure 2: *Ex vivo* production of NK cells for use in adoptive immunotherapy. Peripheral blood is the principal source of NK cells. NK cells may be enriched by apheresis of PBMCs followed by the depletion of $CD3^+$ T cells. Further secondary selection of $CD56^+$ cells ensures a purer NK cell population. After *in vitro* activation and expansion, NK cells can be infused into patients undergoing adoptive immunotherapy.

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