CASE REPORT

Open Access

Allogenic V γ 9V δ 2 T cell as new potential immunotherapy drug for solid tumor: a case study for cholangiocarcinoma

Mohammed Alnaggar^{1,2†}, Yan Xu^{1†}, Jingxia Li¹, Junyi He¹, Jibing Chen^{2,3}, Man Li¹, Qingling Wu¹, Li Lin¹, Yingqing Liang³, Xiaohua Wang³, Jiawei Li¹, Yi Hu¹, Yan Chen¹, Kecheng Xu^{2,3**}, Yangzhe Wu^{1*†} and Zhinan Yin^{1*†}

Abstract

Background: Cholangiocarcinoma (CCA) is a highly aggressive and fatal tumor. CCA occurs in the epithelial cells of bile ducts. Due to increasing incidences, CCA accounts for 3% of all gastrointestinal malignancies. In addition to comprehensive treatments for cancer, such as surgery, chemotherapy, and radiotherapy, during the past few years, cellular immunotherapy has played an increasingly important role. As a result of our research, we have discovered the $\gamma\delta$ T cell-based immunotherapy for CCA.

Case presentation: A 30-year-old male (<https://www.clinicaltrials.gov/> ID: NCT02425735) was diagnosed with recurrent mediastinal lymph node metastasis after liver transplantation because of Cholangiocarcinoma (stage IV). In the course of his therapy sessions, he only received allogenic $\gamma\delta$ T cell immunotherapy from August, 2017 through February, 2018 (8 infusions in total). $\gamma\delta$ T cells were expanded from peripheral blood mononuclear cells (PBMCs) of healthy donor, and $\sim 4 \times 10^8$ cells were adoptive transferred to the patient.

Conclusion: In the above case report of the Cholangiocarcinoma (stage IV) patient who had received liver transplantation and afterward was diagnosed with recurrent mediastinal lymph node metastasis, we clinically proved that allogenic $\gamma\delta$ T cell treatment had no adverse effects. We observed that allogenic $\gamma\delta$ T cell treatments positively regulated peripheral immune functions of the patient, depleted tumor activity, improved quality of life, and prolonged his life span. After 8 $\gamma\delta$ T cell treatments, the size of lymph nodes was remarkably reduced with activity depletion. This clinical work suggested that allogenic $\gamma\delta$ T cell immunotherapy could be developed into a promising therapy drug for CCA.

Keywords: Gamma delta ($\gamma\delta$) T cells, Immunotherapy, Cholangiocarcinoma, Clinical trial

Introduction

Cholangiocarcinoma (CCA) is the most common malignancy of the biliary tree; it may cause fatal consequences in a short period of time [1–3]. Currently, the pathogenesis of this disease has not yet been clearly defined, although high-risk factors, such as Primary Sclerosing Cholangitis (PSC), fibrous polycystic liver, intrahepatic bile

duct stones, parasitic infections, hepatitis B virus infection, chemical carcinogen exposure, diabetes, and smoking were reported to be probably related to CCA incidences [4, 5]. CCA is highly aggressive and metastatic; statistics have shown an approximate median survival of 24 months [6, 7].

For recurrent CCA, however, the median survival is only 9 months, and the five-year survival is less than 5% [8].

Because of poor efficacy results and prognoses of existing treatments for malignant cancer, the most up-to-date treatments are continually being researched, or under clinical trials. Among new developing therapeutics, immune cell therapy is emerging as an important alternative for malignant cancer treatment, particularly after the success of

* Correspondence: xukc@vip.163.com; tyzwu@jnu.edu.cn; zhinan.yin@yale.edu

[†]Kecheng Xu, Yangzhe Wu and Zhinan Yin contributed equally to this work.

[†]Mohammed Alnaggar and Yan Xu share the first authorship.

²Department of Oncology, Fuda Cancer Hospital, School of Medicine, Jinan University, Guangzhou 510665, Guangdong, People's Republic of China

¹Biomedical Translational Research Institute and The First Affiliated Hospital, Jinan University, 601 W Ave Huangpu, Guangzhou 510632, Guangdong, People's Republic of China

Full list of author information is available at the end of the article

CD19 CAR-T [9, 10]. However, for all existing adoptive immune cell therapy, autologous T cells were applied because of MHC restriction. Until present, there have been no reports concerning allogenic T cell applications regarding clinical safety or efficacy. As for $\gamma\delta$ T cells, all previous reported works only focused on autologous cells (in vitro or in vivo expansion strategy) as well [11–20].

In this report, we applied allogenic $\gamma\delta$ T cells (V γ 9V δ 2 subsets) as a new type of immune cell therapy to treat CCA. To our knowledge, our work provided the first paradigm on using allogenic $\gamma\delta$ T cells to treat cancer. Previously, literatures have demonstrated that $\gamma\delta$ T cells are the “first line of defense” as an antitumor effector cell [21, 22], for instance, $\gamma\delta$ T cells provide an early source of IFN- γ in the tumor microenvironment [23]. Unlike $\alpha\beta$ T cells, $\gamma\delta$ T cells recognize antigens in a non-MHC restriction manner. Molecules like LFA, NKG2D, CD16, and others play key roles in $\gamma\delta$ T cell recognition and killing of cancer cells. Altogether, $\gamma\delta$ T cells could be a promising candidate for cancer immunotherapy [24–26].

In addition, for the first time via this clinical trial study for CCA, we discovered evidence that allogenic $\gamma\delta$ T cells in immunotherapy are clinically safe and risk-free. In this case, the patient only received allogenic $\gamma\delta$ T cell treatments. We did not observe any side effects after cell infusions, and more strikingly, peritoneal lymph node metastasis was depleted. Currently, the patient's condition is completely released and stable. The Regional Ethics Committee of Guangzhou Fuda Cancer Hospital approved the study protocol (Approval ID 2017–02). Written informed consent was obtained from the participant, in accordance with the *Declaration of Helsinki*. And [ClinicalTrials.gov](https://clinicaltrials.gov) ID: NCT02425735.

Case report and methods

A 30-year-old man was diagnosed as Cholangiocarcinoma with mediastinal lymph node metastasis stage IV. In July 2013, he received treatment at a local hospital for Crohn's disease. In Nov. 2014, he received a liver transplantation; a huge tumor at hepatic portal

was intraoperatively resected. The postoperative pathology report revealed a liver and hepatic portal poorly-differentiated adenocarcinoma with unresectable Cholangiocarcinoma metastasized to lymph nodes.

The MRI scan performed on Feb. 24th, 2015 showed a lesion in patient's liver, therefore, he received lymph node resection on Apr. 13th, 2015. From Jun. 13th, 2015 to Aug. 14th, 2015, the patient received radiotherapy for hepatic portal and the area adjacent to inferior vena cava, with a total dosage of 45Gy. Afterward, the patient did not receive any further anti-cancer treatments, except follow-up visits. The PET/CT collected on Apr. 15th, 2016, showed lesions in mediastinum and liver. On Jun. 29th, 2016, the patient came to the Fuda Cancer Hospital. Firstly, aspiration biopsy was conducted and 10 1^{125} was seeded into the mediastinal tumor. On June 2017, when the patient came back the Fuda Cancer Hospital for follow-up check-up, biopsy result showed recurrent abdominal lymph node metastasis by experts' consultation, therefore starting from June 2017, the patient only received $\gamma\delta$ T cell immunotherapy to control his lesions, and the first $\gamma\delta$ T cell infusion was scheduled on August 2017.

Immunotherapy

100 ml of blood was donated by a donor who had passed a health examination that included a check

for infectious diseases. Following this procedure, a cell culture formula, which we developed (patent pending) that included zoledronic acid and a variety of interleukin was applied specifically to expand V γ 9V δ 2 T cells in vitro (culture media components and mechanism will be discussed in detail in our preparing article). With this formula, we can generally obtain 300–400 million of V δ 2 T cells at ~12 days. Figure 1 shows a brief illustration on cell expansion and cell quality control as well as cell reinfusion, and Fig. 2 indicates schedules of $\gamma\delta$ T cell treatments and immunophenotypes monitoring (Additional file 1: Figure S1 and S2).

Immunophenotype evaluation

5 mL of peripheral blood was extracted from the patient each time, 1–3 days before receiving V δ 2 T cell treatment. Peripheral blood monocyte cells (PBMC) were isolated using the Ficoll recipe. Then immunofluorescence labeled cells were analyzed using flow cytometry (FACSanto™ II; BD Biosciences, San Jose, CA, USA). The analyzed immune cells mainly included T lymphocytes, NK cells, and $\gamma\delta$ T cells.

Tumor monitoring by MRI imaging and follow-up

During V δ 2 T cell treatment, tumor was routinely evaluated by using MRI imaging to monitor tumor size/area

Fig. 2 **a** Schematic diagram on schedules of $\gamma\delta$ T cell treatments and immunophenotypes monitoring. Patient was enrolled in on June 2017, and received cell treatments starting from August 2017. The patient received 8 treatment courses (3 infusions per treatment course infused within 2 days) of $\gamma\delta$ T cell treatments from August, 2017 through February 2018. As **(a)** showing, infusion was performed every 2 weeks for first six infusions, and then 4 weeks for last two infusions. Moreover, before and after $\gamma\delta$ T cell treatments, immunophenotyping of the patient was checked up each time. **b** Purity phenotype of infused allogeneic V γ 9V δ 2 T cells for each treatment course. It shows > 85% V δ 2 T cells in CD3+ T lymphocytes were intravenously infused. As for phenotypes of infused V δ 2 T cells and non-V δ 2 T cells were attached in Additional file 1: Figures S1 and S2

Fig. 3 Upper abdominal MRI examinations were taken at 3 time points, **a** 2 weeks before treatment, **b** 3 month's clinical effect post treatment and **c** 6 months clinical effect post treatment. In this figure, we show representative MRI images obtained before entry into the clinical trial and after the 8th treatment course

changes by the largest transverse diameter, particularly before and after treatment. The patient received plain and enhanced MRI 2 weeks before treatment, and then scanned periodically at the 3rd and 6th months after treatment.

Results

Firstly, from the MRI images (Fig. 3), we can see that the size of the lymph nodes is markedly reduced, visualizing that lymph nodes metastases of the patient were gradually eliminated with increasing infusion times of

Fig. 4 The changes in immunophenotyping before ('1') and after ('2' - '8') γδ T cell treatments. The results showed that γδ T cell therapy could greatly improve immunity by regulating the immunological functions of peripheral immune cells, as the administration of γδ T cells was associated with an increase of the functional CD3 + CD4 + CD28+ T cells and CD3 + CD8 + CD28+ T cells, and with a decrease of CD3 + CD4 + CD28- T cells and CD3 + CD4 + CD28-CD57+ T cells. In these graphs, checking point '1' means immunophenotyping without γδ T cell treatment, while checking points '2' - '8' stand for immunophenotyping from the first time to the seventh γδ T cell treatments

V δ 2 T cells. Such visual images indicated that the patient greatly benefited from allogeneic V γ 9V δ 2 T cell treatment in this case. Then, the immunophenotypes of the patient before and after $\gamma\delta$ T cell treatment were analyzed (Fig. 4). We evaluated immunophenotype variations of CD4+, CD8+, NK, and $\gamma\delta$ T cells using immunofluorescence labeling and flow cytometry. The results showed that $\gamma\delta$ T cell therapy could greatly improve immunity by regulating the immunological functions of these immune cells, as the administration of $\gamma\delta$ T cells was associated with an increase of the functional CD3 + CD4 + CD28+ T cells and CD3 + CD8 + CD28+ T cells, and decrease of CD3 + CD4 + CD28- T cells and CD3 + CD4 + CD28-CD57+ T cells. It should be mentioned that, the patient was oroling Rapamune 2 mg, Ursofalk 500 mg once a day, these two drugs serve as anti-transplant rejection since the patient received liver transplantation.

Biochemical examination results clearly demonstrated that allogeneic V γ 9V δ 2 T cells were safe for immunotherapeutic application (Fig. 5). We noticed that the expression of tumor marker molecule was maintained at a low level during $\gamma\delta$ T cell treatment, and there was no liver function impairment. This was consistent with the stable physical condition and sound prognosis of the patient. Altogether, this clinical trial study clearly evidenced that there were no observed complications related to $\gamma\delta$ T cell infusion.

Discussion

Because $\gamma\delta$ T cells can bridge the gap between innate and adaptive immune systems and are critical in surveillance and defense of tumorigenesis and infection, $\gamma\delta$ T cell-based immunotherapy could be developed into a promising treatment for tumor control or elimination [24–30], particularly for diseases refractory to traditional treatments (surgery, chemotherapy and radiotherapy). It's known that $\gamma\delta$ T cells can recognize target cells (cancer cells or pathogen-infected cells) in a MHC independent way, which implicates with the immunological mechanism of high allogeneic safety of $\gamma\delta$ T cells [31]. This clinical trial study also clearly evidenced that there were no observed complications related to $\gamma\delta$ T cell infusion.

In this report, we evaluated the safety and efficacy of allogeneic V γ 9V δ 2 T cells for the first time as a new type of immunotherapy to treat a patient (stage IV Cholangiocarcinoma and liver transplanted) with recurrent mediastinal lymph node metastasis. The patient received $\gamma\delta$ T cell treatment every 2 weeks for the first six treatments, and every 4 weeks for the last two treatments (between August, 2017 and February, 2018) (Fig. 2). Clinical results clearly demonstrated that allogeneic V γ 9V δ 2 T cells were safe for immunotherapeutic application, and that allogeneic V γ 9V δ 2 T cell treatment eliminated tumor metastases in this case (Fig. 3). Firstly, from

the MRI images (Fig. 3), we can see that the size of the lymph nodes is markedly reduced, visualizing that lymph nodes metastases of the patient were gradually eliminated with increased infusion times of V δ 2 T cells. Then, the immunophenotypes of the patient before and after $\gamma\delta$ T cell treatment were analyzed (Fig. 4). We evaluated immunophenotypes of CD4+, CD8+, NK, and $\gamma\delta$ T cells using immunofluorescence labeling and flow cytometry. We found that $\gamma\delta$ T cell therapy could greatly improve immunity by regulating $\alpha\beta$ T cells and NK cells. For instance, it could elevate ratio of naïve, functional CD4+, and CD8+ T cells, and reduce exhausted and aged CD4+, CD8+ T cells, and so on (Fig. 4). Previous literatures [21, 26, 32, 33] proposed that $\gamma\delta$ T cells can regulate other immune cells including potentiating functions of CD4+, CD8+ T cells, maturing dendritic cells and activate neutrophils. As a further step, our work here revealed that V δ 2 subpopulation transfer therapy can affect $\alpha\beta$ T cell differentiation and NK maturation, particularly, for example, by reducing exhausted and aged $\alpha\beta$ T cells and elevating functional $\alpha\beta$ T cells. Additionally, according to Fig. 5, we noticed that the expression of tumor marker molecules AFP and CA-199 was maintained at a low lever during $\gamma\delta$ T cell treatment, with no observed impaired liver functions. This is consistent with the stable physical condition and sound prognosis of the patient.

In conclusion, in this case report, we conducted allogenic $\gamma\delta$ T cell immunotherapy of Cholangiocarcinoma for the first time. The clinical outcome evidenced that allogenic $\gamma\delta$ T cell therapy was very safe and displayed reliable efficacy in liver cancer treatment. This exciting trial opened a new window for cancer immunotherapy and could inspire more clinical trial studies, based upon allogenic $\gamma\delta$ T cell. Allogenic $\gamma\delta$ T cells could be developed into a very promising ‘immune drug’ for malignant tumor therapy. Our report will undoubtedly represent the next frontier for immunotherapeutic innovations in cancer research and treatment.

Additional file

Additional file 1: Figure S1. Purity of infused allogenic Vy9V δ 2 T cells of all 8 treatment courses is > 85%. According to flow cytometry data, rest non V δ 2 T cells including V δ 1 T cells, NK cells, B cells, NKT cells, CD8⁺T cells, CD4⁺T cells, CD4⁺CD8⁺T cells, and CD4⁺CD8⁺T cells.

Figure S2. Molecular phenotypes of allogenic Vy9V δ 2 T cells cultured using our developed specific culture formula, showing high expression of killing related molecules (like NKG2D, IFN- γ , TNF- α , CD107a) and low expression of inhibitory molecules like PD-1. (PPTX 255 kb)

Abbreviations

CCA: Cholangiocarcinoma; I¹²⁵: Iodine-125; PBMCs: Peripheral blood mononuclear cells; PSC: Primary Sclerosing Cholangitis; $\gamma\delta$: Gamma delta

Acknowledgements

We thank Mrs. Pipoly Zsafia, a patient's friend who donated blood four times for PBMC isolation and cell culture, and as translator between researchers and the patient.

Funding

The present study was partially supported by: Guangzhou Science and Technology Key Project (201604020006), Scientific and Technological Plan of Guangdong Province (201704KW010), the Key Program of the National Natural Science Foundation of China (31830021), the Major International Joint Research Program of China (31420103901), the ‘111 project’ (B16021), and International Foundation for Sciences of Guangzhou, Fuda Cancer Hospital (Y2016-ZD-007).

Availability of data and materials

No data sets were generated or analyzed for inclusion in this report.

Authors' contributions

Protocol design: ZNY, YZW, KCX, MA, and JBC. Clinical therapy of the patient: KCX, MA, and JBC. Immuno-function testing and statistics analysis: YX, JXL, JYH, QLW, LL, ML, JWL, YC, and YH. Cell culture and quality control: YQL and XHW. Manuscript drafting: MA. Manuscript writing, revision and proof-reading: YZW, ZNY. All authors contributed to results discussion and confirmation of clinical protocol, and approved manuscript submission.

Ethics approval and consent to participate

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital, China. Written informed consent was obtained from participant in accordance with the Declaration of Helsinki, and ClinicalTrials.gov ID: NCT02425735.

Consent for publication

Not applicable.

Competing interests

The IND for allogenic $\gamma\delta$ T cell application in clinical therapy is filling in both PR China and USA.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Biomedical Translational Research Institute and The First Affiliated Hospital, Jinan University, 601 W Ave Huangpu, Guangzhou 510632, Guangdong, People's Republic of China. ²Department of Oncology, Fuda Cancer Hospital, School of Medicine, Jinan University, Guangzhou 510665, Guangdong, People's Republic of China. ³Department of Biological Treatment Center, Fuda Cancer Hospital, School of Medicine, Jinan University, Guangzhou 510665, Guangdong, People's Republic of China.

Received: 3 October 2018 Accepted: 9 January 2019

Published online: 08 February 2019

References

1. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*. 2014;60:1268–89.
2. Banales JM, Cardinale V, Carpino G, Marzoni M, Andersen JB, Invernizzi P, Lind GE, Folseraas T, Forbes SJ, Fouassier L, Geier A, Calvisi DF, Mertens JC, Trauner M, Benedetti A, Maroni L, Vaquero J, Macias RI, Raggi C, Perugorria MJ, Gaudio E, Boberg KM, Marin JJ, Alvaro D. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European network for the study of cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol*. 2016;13:261–80.
3. Washington MK, Berlin J, Branton PA, Burgart LJ, Carter DK, Compton CC, Fitzgibbons PL, Frankel WL, Jessup JM, Kakar S, Minsky B, Nakhleh RE, Vauthey JN. Protocol for the examination of specimens from patients with carcinoma of the distal extrahepatic bile ducts. *Arch Pathol Lab Med*. 2010; 134:e8–13.

4. Lipsett PA, Pitt HA, Colombani PM, Boitnott JK, Cameron JL. Choledochal cyst disease. A changing pattern of presentation. *Ann Surg.* 1994;220:644–52.
5. Bergquist A, Glaumann H, Persson B, Broome U. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case-control study. *Hepatology.* 1998;27:311–6.
6. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. *Nat Rev Gastroenterol Hepatol.* 2011;8:512–22.
7. Bartella I, Dufour JF. Clinical diagnosis and staging of intrahepatic cholangiocarcinoma. *J Gastrointest Liver Dis.* 2015;24:481–9.
8. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis.* 2004;24:115–25.
9. Chavez JC, Locke FL. CAR T cell therapy for B-cell lymphomas. *Best Pract Res Clin Haematol.* 2018;31:135–46.
10. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol.* 2016;13:370–83.
11. Braza MS, Klein B. Anti-tumour immunotherapy with Vgamma9delta2 T lymphocytes: from the bench to the bedside. *Br J Haematol.* 2013;160:123–32.
12. Kobayashi H, Tanaka Y. gammadelta T cell immunotherapy-a review. *Pharmaceuticals (Basel).* 2015;8:40–61.
13. Sakamoto M, Nakajima J, Murakawa T, Fukami T, Yoshida Y, Murayama T, Takamoto S, Matsushita H, Kakimi K. Adoptive immunotherapy for advanced non-small cell lung cancer using zoledronate-expanded gammadeltaTcells: a phase I clinical study. *J Immunother.* 2011;34:202–11.
14. Dieli F, Vermijlen D, Fulfaro F, Caccamo N, Meraviglia S, Cicero G, Roberts A, Buccheri S, D'Asaro M, Gebbia N, Salerno A, Eberl M, Hayday AC. Targeting human {gamma}delta T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer. *Cancer Res.* 2007;67:7450–7457.
15. Bennouna J, Bompas E, Neidhardt EM, Rolland F, Philip I, Galea C, Salot S, Saiagh S, Audrain M, Rimbert M, Lafaye-de Micheaux S, Tiollier J, Negrier S. Phase-I study of Innacell gammadelta, an autologous cell-therapy product highly enriched in gamma9delta2 T lymphocytes, in combination with IL-2, in patients with metastatic renal cell carcinoma. *Cancer Immunol Immunother.* 2008;57:1599–609.
16. Kobayashi H, Tanaka Y, Yagi J, Osaka Y, Nakazawa H, Uchiyama T, Minato N, Toma H. Safety profile and anti-tumor effects of adoptive immunotherapy using gamma-delta T cells against advanced renal cell carcinoma: a pilot study. *Cancer Immunol Immunother.* 2007;56:469–76.
17. Kobayashi H, Tanaka Y, Yagi J, Minato N, Tanabe K. Phase I. II study of adoptive transfer of gammadelta T cells in combination with zoledronic acid and IL-2 to patients with advanced renal cell carcinoma. *Cancer Immunol Immunother.* 2011;60:1075–84.
18. Bryant NL, Suarez-Cuervo C, Gillespie GY, Markert JM, Nabors LB, Meleth S, Lopez RD, Lamb LS Jr. Characterization and immunotherapeutic potential of gammadelta T-cells in patients with glioblastoma. *Neuro-Oncology.* 2009;11:357–67.
19. Li Z, Xu Q, Peng H, Cheng R, Sun Z, Ye Z. IFN-gamma enhances HOS and U2OS cell lines susceptibility to gammadelta T cell-mediated killing through the Fas/Fas ligand pathway. *Int Immunopharmacol.* 2011;11:496–503.
20. Li Z, Peng H, Xu Q, Ye Z. Sensitization of human osteosarcoma cells to Vgamma9delta2 T-cell-mediated cytotoxicity by zoledronate. *J Orthop Res.* 2012;30:824–30.
21. Bonneville M, O'Brien RL, Born WK. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. *Nat Rev Immunol.* 2010;10:467–78.
22. Chien YH, Meyer C, Bonneville M. gammadelta T cells: first line of defense and beyond. *Annu Rev Immunol.* 2014;32:121–55.
23. Gao Y, Yang W, Pan M, Scully E, Girardi M, Augenlicht LH, Craft J, Yin Z. Gamma delta T cells provide an early source of interferon gamma in tumor immunity. *J Exp Med.* 2003;198:433–42.
24. Fisher JP, Heuvelink J, Yan M, Gustafsson K, Anderson J. gammadelta T cells for cancer immunotherapy: a systematic review of clinical trials. *Oncoimmunology.* 2014;3:e27572.
25. Wu YL, Ding YP, Tanaka Y, Shen LW, Wei CH, Minato N, Zhang W. gammadelta T cells and their potential for immunotherapy. *Int J Biol Sci.* 2014;10:119–35.
26. Xiang Z, Tu W. Dual face of Vy9delta2-T cells in tumor immunology: anti-versus pro-tumoral activities. *Front Immunol.* 2017;8:1–13.
27. Nedellec S, Bonneville M, Scotet E. Human Vgamma9delta2 T cells: from signals to functions. *Semin Immunol.* 2010;22:199–206.
28. Paul S, Shilpi, Lal G. Role of gamma-delta (gammadelta) T cells in autoimmunity. *J Leukoc Biol.* 2015;97:259–71.
29. Adams EJ, Gu S, Luoma AM. Human gamma delta T cells: evolution and ligand recognition. *Cell Immunol.* 2015;296:31–40.
30. Khan MW, Eberl M, Moser B. Potential use of gammadelta T cell-based vaccines in cancer immunotherapy. *Front Immunol.* 2014;5:512.
31. Wrobel P, Shojaei H, Schitteck B, Gieseler F, Wollenberg B, Kalthoff H, Kabelitz D, Wesch D. Lysis of a broad range of epithelial tumour cells by human gamma delta T cells: involvement of NKG2D ligands and T-cell receptor-versus NKG2D-dependent recognition. *Scand J Immunol.* 2007;66:320–8.
32. Kabelitz D, Peters C, Wesch D, Oberg HH. Regulatory functions of gammadelta T cells. *Int Immunopharmacol.* 2013;16:382–7.
33. Chitadze G, Oberg HH, Wesch D, Kabelitz D. The ambiguous role of gammadelta T lymphocytes in antitumor immunity. *Trends Immunol.* 2017;38:668–78.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions