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# Double-negative T cells: a promising avenue of adoptive cell therapy in transplant oncology

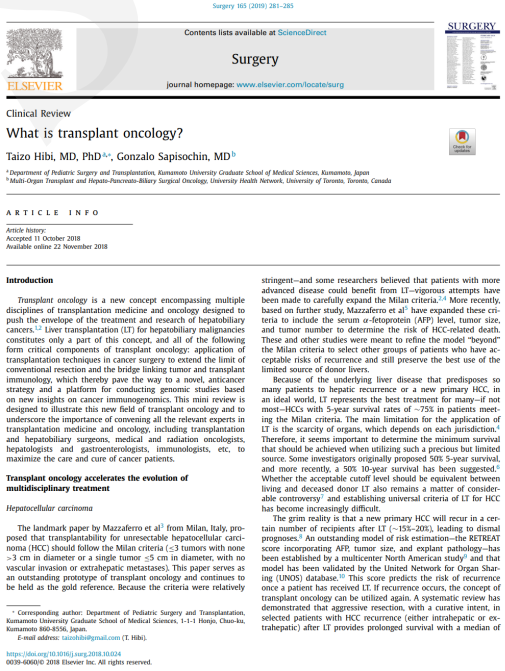
**Key words:** Double negative T cell (DNT), Adoptive cell therapy (ACT), Liver cancer, Liver transplantation, Oncology

# Research Background

**Transplant oncology is a synthetic field consisting of multiple disciplines.**

**Thereinto, a common and life-threatening issue is that immunosuppression regimen after transplantation can promote the recurrence and metastasis of liver cancer.**


**The 4 E-pillars of transplant oncology.**



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Clinical Review

What is transplant oncology?

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**Introduction**

*Transplant oncology* is a new concept encompassing multiple disciplines of transplantation medicine and oncology designed to push the envelope of the treatment and research of hepatobiliary cancers.[1,2] Liver transplantation (LT) for hepatobiliary malignancies constitutes only a part of this concept, and all of the following form critical components of transplant oncology: application of transplantation techniques in cancer surgery to extend the limit of conventional resection and the bridge linking tumor and transplant immunology, which thereby pave the way to a novel, anticancer strategy and a platform for conducting genomic studies based on new insights on cancer immunogenomics. This mini review is designed to illustrate this new field of transplant oncology and to underscore the importance of convening all the relevant experts in transplantation medicine and oncology, including transplantation and hepatobiliary surgeons, medical and radiation oncologists, hepatologists and gastroenterologists, immunologists, etc, to maximize the care and cure of cancer patients.

**Transplant oncology accelerates the evolution of multidisciplinary treatment**

*Hepatocellular carcinoma*

The landmark paper by Mazzaferro et al[3] from Milan, Italy, proposed that transplantability for unresectable hepatocellular carcinoma (HCC) should follow the Milan criteria (≤3 tumors with none >3 cm in diameter or a single tumor ≤5 cm in diameter, with no vascular invasion or extrahepatic metastases). This paper serves as an outstanding prototype of transplant oncology and continues to be held as the gold reference. Because the criteria were relatively stringent—and some researchers believed that patients with more advanced disease could benefit from LT—vigorous attempts have been made to carefully expand the Milan criteria.[2,3] More recently, based on further study, Mazzaferro et al[3] have expanded these criteria to include the serum α-fetoprotein (AFP) level, tumor size, and tumor number to determine the risk of HCC-related death. These and other studies were meant to refine the model "beyond" the Milan criteria to select other groups of patients who have acceptable risks of recurrence and still preserve the best use of the limited source of donor livers.

Because of the underlying liver disease that predisposes so many patients to hepatic recurrence or a new primary HCC, in an ideal world, LT represents the best treatment for many—if not most—HCCs with 5-year survival rates of ~75% in patients meeting the Milan criteria. The main limitation for the application of LT is the scarcity of organs, which depends on each jurisdiction.[4] Therefore, it seems important to determine the minimum survival that should be achieved when utilizing such a precious but limited source. Some investigators originally proposed 50% 5-year survival, and more recently, a 50% 10-year survival has been suggested.[5] Whether the acceptable cutoff level should be equivalent between living and deceased donor LT also remains a matter of considerable controversy[7] and establishing universal criteria of LT for HCC has become increasingly difficult.

The grim reality is that a new primary HCC will recur in a certain number of recipients after LT (~15%–20%), leading to dismal prognoses.[8] An outstanding model of risk estimation—the RETREAT score incorporating AFP, tumor size, and explant pathology—has been established by a multicenter North American study[9] and that model has been validated by the United Network for Organ Sharing (UNOS) database.[10] This score predicts the risk of recurrence once a patient has received LT. If recurrence occurs, the concept of transplant oncology can be utilized again. A systematic review has demonstrated that aggressive resection, with a curative intent, in selected patients with HCC recurrence (either intrahepatic or extrahepatic) after LT provides prolonged survival with a median of

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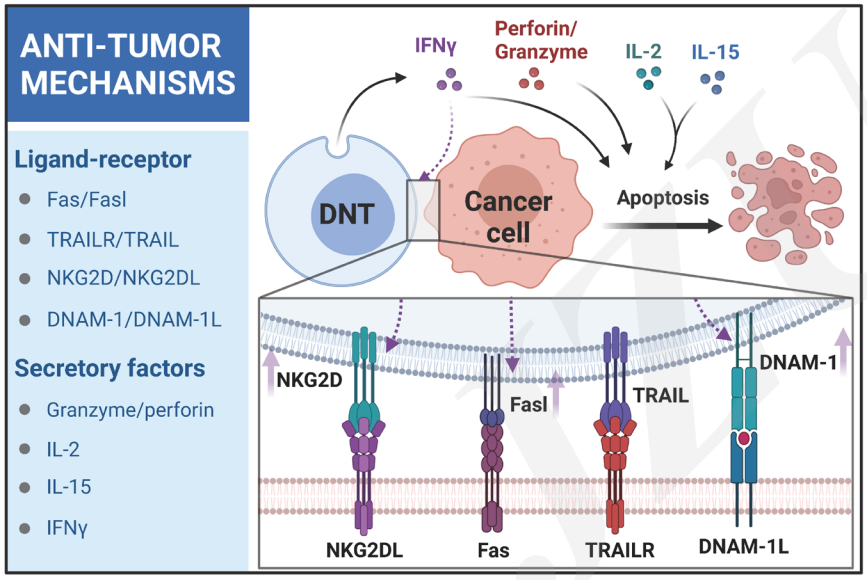
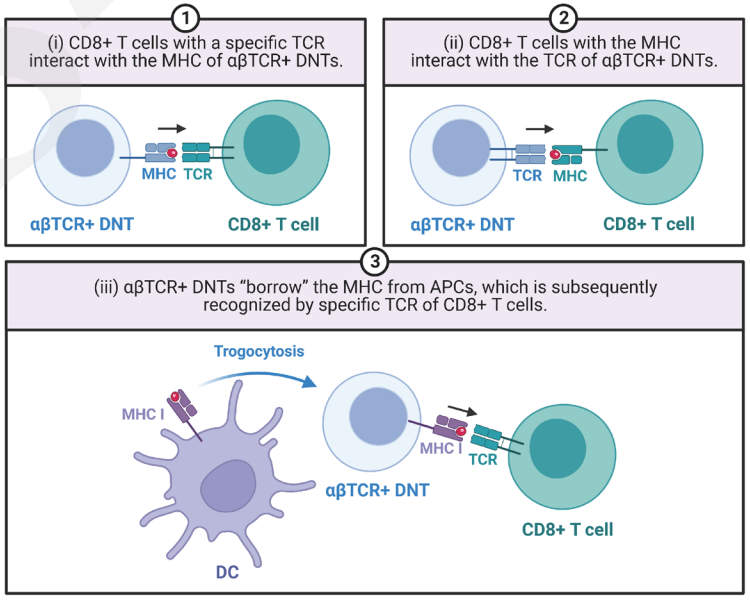
# Research Summary

**This review discussed the dual roles of double negative T cells in the fields of oncology and transplantation. This novel adoptive cell therapy is promising to act as both 'fighters' and 'peacemakers' in transplant oncology.**




**Anti-tumor activity**

**Immune regulation**

# *Innovation points*

- **Introduction** of DNT, an emerging T cell therapy to treat malignancies without increasing the immune burden.

- **Summary** of the recent updated research progress about DNT in oncology and immunology.

- **Emphasis** of the potential adoptive T cell therapy in transplant oncology.