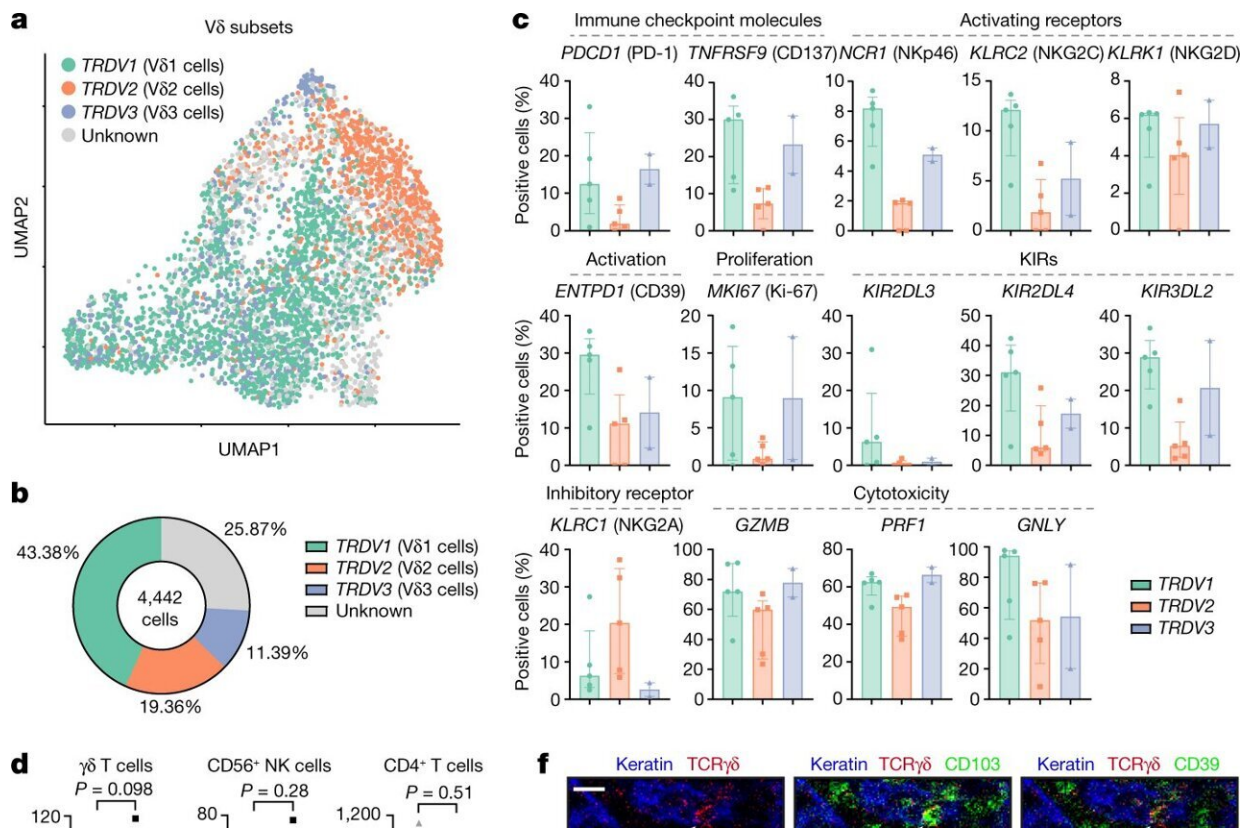


Specialized immune cells carry potential for new cancer immunotherapies

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Tumor-infiltrating V δ 1 and V δ 3 T cell subsets display hallmarks of cytotoxic activity in MMR-d colon cancers. a, UMAP embedding showing the clustering of $\gamma\delta$ T cells (n = 4,442) isolated from MMR-d colon cancers (n = 5) analyzed using scRNA-seq. The colors represent the TCR V δ chain usage. Dots represent single cells. b, The frequencies of TCR V δ chain use of the $\gamma\delta$ T cells (n = 4,442) analyzed using scRNA-seq as a percentage of total $\gamma\delta$ T cells. c, The frequencies of positive cells for selected genes across V δ 1 (n = 1,927), V δ 2 (n = 860) and V δ 3 (n = 506) cells as the percentage of total $\gamma\delta$ T cells from each

MMR-d colon tumor (n = 5) analyzed using scRNA-seq. $\gamma\delta$ T cells were present in two out of five colon cancers. Data are median \pm IQR, with individual samples (dots). d, The frequencies of $\gamma\delta$ T cells, CD56⁺ NK cells, CD4⁺ T cells and CD8⁺ T cells in treatment-naive B2M⁺ (n = 12) and B2M⁻ (n = 5) MMR-d colon cancers. Data are median \pm IQR, with individual samples (dots). P values were calculated using two-sided Wilcoxon rank-sum tests. e, The frequencies of granzyme-B-positive $\gamma\delta$ T cells, CD56⁺ NK cells, CD4⁺ T cells and CD8⁺ T cells in treatment-naive B2M⁻ (n = 5) MMR-d colon cancers. CD56⁺ NK cells were present in four out of five B2M⁻ cancer samples. Data are median \pm IQR, with individual samples (dots). f, Representative images of the detection of tissue-resident (CD103⁺), activated (CD39⁺), cytotoxic (granzyme B⁺), proliferating (Ki-67⁺) and PD-1⁺ $\gamma\delta$ T cells (white arrows) by IMC analysis of a treatment-naive MMR-d colon cancer with B2M defects. Scale bar, 20 μ m. Credit: *Nature* (2023). DOI: 10.1038/s41586-022-05593-1

Scientists from Leiden University Medical Center (LUMC) and Netherlands Cancer Institute (NKI) have discovered how specialized immune cells can detect and remove cancers that are "invisible" to the conventional defense mechanisms of the immune system. Their work has been published in *Nature*. The findings could lead to novel cancer immunotherapies.

Normally, the recognition of abnormal cells in our body is a task for T cells, one of the most important white blood cells of the [immune system](#). These cells can recognize many types of abnormalities, including viral and bacterial infections. But the immune system sometimes has trouble detecting [cancer cells](#). Cancer cells are only recognized by T cells if a specific molecule is attached to their surface. In order to escape immune recognition, some cancers lack such molecule and become 'invisible' to T cells.

Why does immunotherapy work in these patients?

Recently, researchers of the LUMC and NKI stumbled upon a strange phenomenon: some [patients](#) with "invisible" cancers respond very well to cancer immunotherapies. These therapies rely on antibodies that activate or reinvigorate the activity of T cells.

"Since these cancers lack the molecules which enable T cells to identify them, we did not understand why patients responded so well to the therapy," says Noel de Miranda, associate professor at LUMC Department of Pathology.

Back-up in our immune system

Research on cells drawn from patients that were treated at NKI now shows that $\gamma\delta$ T cells—a lesser known, specialized immune type of cell—are capable of detecting cancers that are invisible to conventional T cells.

De Miranda says, "This shows that there is a backup system in our immune system. When the main way of recognizing [tumor cells](#) does not work, we have a second line of defense. Our findings could eventually lead to new treatments for 'invisible' tumors with $\gamma\delta$ T cells."

"We are only beginning to unveil the tremendous potential that $\gamma\delta$ T cells carry for the development of novel cancer immunotherapies," says Emile Voest, professor of medical oncology, group leader at the Netherlands Cancer Institute and Onco Investigator.

"Going forward, we will try to gain a better understanding of how these [immune cells](#) work in the body of cancer patients, and how we can make use of them to develop novel immunotherapies. They will be particularly important to treat cancers that are not susceptible to elimination by 'conventional' T cells."

More information: Natasja L. de Vries et al, $\gamma\delta$ T cells are effectors of immunotherapy in cancers with HLA class I defects, *Nature* (2023).
[DOI: 10.1038/s41586-022-05593-1](https://doi.org/10.1038/s41586-022-05593-1)

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