needed for CD8+ T cell memory forma-
tion, as shown to have 10 years earlier.1 The granzyme B– cells did not make TCF1; these subsets were not overlapping.
We wondered whether the non-
killer, TCF1-expressing subset of cells that multiplies in response to PD-1 blockade (Fig. 2). In additional mouse experiments, we showed that the presence of PD-1·TCF1·
CD8+· T cells was essential to increasing the abundance of T cells during check-
point blockade immunotherapy and to controlling tumors.2
As PD-1·TCF1·CD8+·T cells expanded, most of the offspring cells transitioned from one subtype to the other: TCF1 expression is self-enhancing. These cells can divide, while granzyme B expression increased. The T cells gained the potential to kill cancer cells. Some of the offspring maintained TCF1 expression, however, ensuring they maintained the potential for continued multiplication and killer cell production.3
These capacities of a subset of tumor-
resident PD-1·CD8+· T cells—to multiply, differentiate, and self-renew—mirror those of memory CD8+ T cells and tissue-specific stem cells. The tumor environ-
ment therefore contains stem cell–like

ADOPTIVE CELL THERAPY AND STEM CELL–LIKE T CELLS
In patients with metastatic disease, tumor tissue can be surgically removed and immune cells extracted from it. The T cells, which include the cells that can fight the tumor and cells that cannot, are cultured with specific growth factors to increase their number and restore the functionality of cells that have become exhausted and thus less effective. This T cell mixture is then reinfused into the patient, with the aim of increasing the number of functional cells that can kill tumor cells and that will persist in the patient. The number of stem-like CD8+ T cells—which sustain the production of killer CD8+ T cells—that make it back into the patient is currently unclear. But the importance of these cells to sustain tumor-fighting in response to checkpoint blockade raises the possibility that the conditions used to expand cells for infusion can be further optimized to favor higher proportions of stem-like CD8+ T cells.

The T cells, which include both cells that can fight the tumor (killer T cells) and cells that cannot, are cultured with specific growth factors to increase their number and restore the functionality of cells that have become exhausted and thus less effective. This T cell mixture is then reinfused into the patient, with the aim of increasing the number of functional cells that can kill tumor cells and that will persist in the patient. The number of stem-like CD8+ T cells—which sustain the production of killer CD8+ T cells—that make it back into the patient is currently unclear. But the importance of these cells to sustain tumor-fighting in response to checkpoint blockade raises the possibility that the conditions used to expand cells for infusion can be further optimized to favor higher proportions of stem-like CD8+ T cells.

Optimal culture population (homogeneous)
Current culture capability (heterogeneous)

The cultured T cells are infused into the patient with the aim of increasing the number of tumor-fighting T cells that the patient can produce.

In patients with metastatic disease, immune cells (T cells) can be cultured with specific growth factors to increase their number and restore the functionality of cells that have become exhausted and thus less effective. This T cell mixture is then reinfused into the patient, with the aim of increasing the number of functional cells that can kill tumor cells and that will persist in the patient. The number of stem-like CD8+ T cells—which sustain the production of killer CD8+ T cells—that make it back into the patient is currently unclear. But the importance of these cells to sustain tumor-fighting in response to checkpoint blockade raises the possibility that the conditions used to expand cells for infusion can be further optimized to favor higher proportions of stem-like CD8+ T cells.

Stem-like T cells help sustain tumor-
fighting in response to checkpoint blockade in two ways: they can differentiate into killer T cells that can kill cancer cells and also proliferate into more stem cells. This raises the possibility that the conditions used to expand cells for infusion should be further optimized to favor higher proportions of stem-like T cells.

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References
10. It is likely that current immunotherapy approaches do not fully unleash the functional potential of stem-like CD8+ T cells.

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