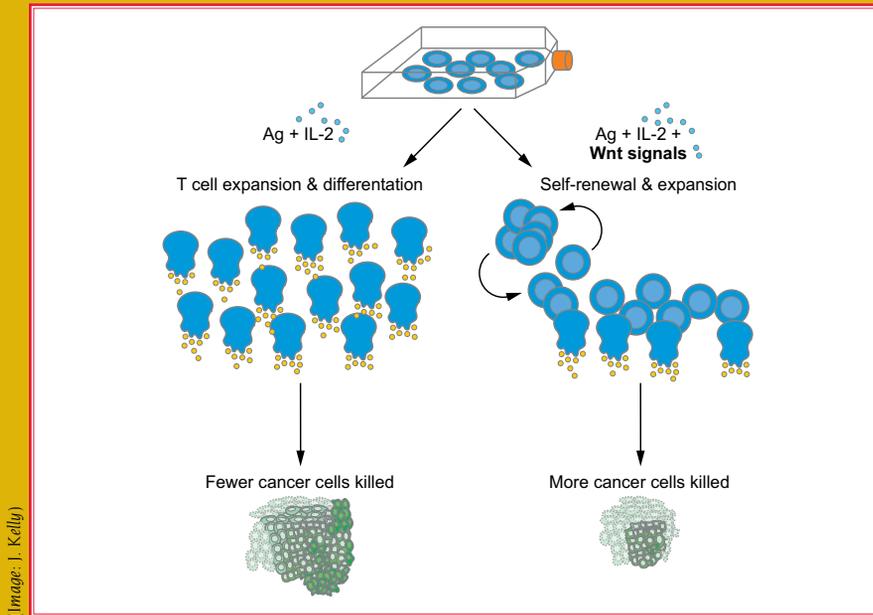


# A Cure for the Incurable?

## Using the Body's Immune System to Treat Metastatic Cancers

*The long fight against cancer has rewarded us with many treatments—chemotherapy, radiotherapy, and surgery—that have improved the prognoses for many types of cancer. Cures for metastatic disease have thus far been less forthcoming; however, recent advances in cancer immunotherapy may lead us in a promising new direction.*



Stimulating antitumor T cells in the presence of drugs that mimicked Wnt signaling suppressed the process of T-cell differentiation, so that the lymphocytes remained in a stem-like state. These T cells could self-renew and differentiate into various CD8<sup>+</sup> memory and killer T cell subsets. When adoptively transferred into a tumor-bearing host, they could kill more tumor cells than non-Wnt-stimulated T cells.

Although the concept of immunotherapy for cancer has been around for over a century, its history has seen alternating cycles of optimism and frustration. Cancer vaccines have thus far proven insufficient by themselves to induce cancer regression reliably. Adoptive immunotherapies in which a patient's immunological components (such as T lymphocytes) are isolated, modified *in vitro*, and then re-infused back into the patient could, in principle, contribute to therapeutic progress. In the July 2009 issue of *Nature Medicine*, Nicholas Restifo, M.D., Senior Investigator in the Tumor Immunology Section at CCR, introduced the adoptive transfer of genetically engineered tumor-specific T memory stem cells (T<sub>SCM</sub>) as an

exciting new strategy towards an effective cancer therapy.

Previous experiments using the adoptive transfer of naturally occurring T lymphocytes have given variable results. The transplanted cells do not always induce optimal anti-tumor responses, and as they are already terminally differentiated into CD8<sup>+</sup> killer T cells, their therapeutic effects are relatively short-lived. Restifo and colleagues wanted to limit the differentiation so as to maximize proliferation *in vivo* after transfer, and they did this by pharmacologically generating stem-like T cells with an enhanced ability to renew themselves and proliferate—qualities most associated with anti-tumor effectiveness.

Using a mouse model, the researchers isolated young T lymphocytes and, *in vitro*, stimulated anti-tumor T cells in the presence of drugs that mimicked Wnt signaling. Wnts control developmental programs that are important for embryogenesis and development, including T lymphocyte development. The researchers found that Wnt signaling plays a key role in the maintenance of “stemness” in mature CD8<sup>+</sup> memory T cells. Stimulating Wnt signaling suppressed the process of T cell differentiation so that the lymphocytes remained in a young, stem-like state with a high proliferative potential. This new class of T<sub>SCM</sub> cells could self-renew and differentiate into various CD8<sup>+</sup> memory and killer T cell subsets following adoptive transfer back into the tumor-bearing mice.

The ability to pharmacologically induce T<sub>SCM</sub> cells has considerable implications for adoptive immunotherapies and the design of new vaccine strategies. Because of their increased proliferative responses, enhanced survival capacity, and superior anti-tumor activity, only a small number of T<sub>SCM</sub> cells, together with a recombinant cancer vaccine and interleukin-2, were sufficient to trigger the destruction of large tumors in mice.

“Using the immune system to cause rejection of cancer was once considered a radically alternative, futuristic approach,” said Dr. Restifo. “But the adoptive transfer of young T cells derived from naturally occurring or genetically-engineered tumor-specific cells is a reality. For some patients with metastatic cancer, immunotherapies based on the adoptive transfer of T lymphocytes can be curative.”

To learn more about Dr. Restifo's research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?profileid=5762>.