Bristol Myers Squibb®

C-C Motif Chemokine Receptor 8 (CCR8) Immune Pathway

Guided by a deep understanding of causal human biology, scientists at Bristol Myers Squibb study the **tumor microenvironment (TME)**, the protective environment surrounding cancer cells, and work to match the right therapeutic modality to the underlying biological mechanism, an approach applied across the company's broader work in oncology research. With these principles in mind, researchers at Bristol Myers Squibb are **investigating the C-C motif chemokine receptor 8 (CCR8) pathway** to find new ways to treat solid tumors by engaging the body's own immune system.

What You Should Know

CCR8 is a marker found on a type of immune cell called a Treg, short for regulatory T cell. Tregs act as a built-in 'brake' on effector T cells — the immune system's cells responsible for **recognizing and eliminating abnormal cells**, including cancer.

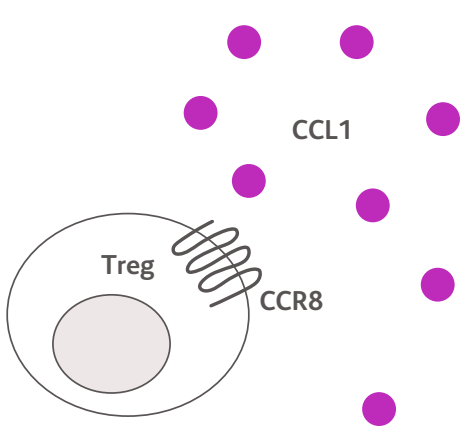
Tumors build up **especially high numbers of CCR8-marked Tregs** within the TME, which is a protective area surrounding cancer cells, and use these Tregs to **limit effector T cell activity** in that space.

Researchers at Bristol Myers Squibb are looking at whether targeting these TME-based Tregs can **restore effector T cell activity against the tumor**.

CCR8 and Its Role in Immune Response

CCR8 is a protein found mainly on the surface of a highly immunosuppressive type of Treg within the TME.[1,2]

Chemokines are signaling molecules that direct immune response by guiding cell movement through the body.[3] CCR8 works with its signaling molecule CC chemokine ligand 1 (CCL1) **to help regulate immune activity, including the immune system's response to cancer**.[3]



CCR8 and Its Role in Cancer

The presence of chemokine receptors influences the recruitment of immune cells to the TME. Tumors then use those cells and mechanisms to **evade or suppress** the body's natural anti-cancer immune response, allowing cancer to grow.[1]

CCR8 expression is elevated on a type of Treg that **helps to suppress the immune system** in multiple cancer types.[4]

CCR8 is found to be **particularly elevated on Tregs in the TME**, while lower levels of these CCR8-expressing Tregs are found in the blood and normal tissues.[4,5]

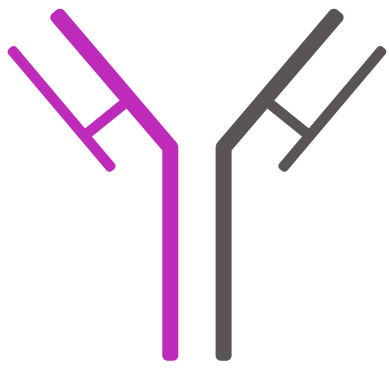
Tregs suppress the immune response in the TME in many ways, including limiting the activity of other immune cells like antigen-presenting cells (APCs), consuming interleukin 2 (IL-2) and releasing signaling molecules that dampen immune function.[2,6]

High levels of Tregs in the TME are **linked with poor prognosis** in multiple cancer types.[1,2,4]

CCR8-expressing Treg Depletion and Research Implications

Targeting CCR8 may provide a more precise way to reduce tumor-promoting Tregs than current approaches.[4,5]

- Early approaches to Treg depletion targeted molecules found on many other cells and locations within the body.
- A highly selective target like CCR8 is needed for the specific depletion of Tregs in the TME, with minimal impact on Tregs in the blood and normal tissues, as well as on other important types of T cells (effector T cells).



Preclinical data suggested that **removing CCR8-expressing Tregs** with antibodies helped **drive an immune response that inhibited tumor growth**.[4,5]

- Researchers are studying anti-CCR8 antibodies that have increased antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity, allowing them to remove CCR8-expressing Tregs while sparing effector T cells.
- This approach is being explored alone as well as in combination with immune checkpoint blockade and chemotherapy.

Bristol Myers Squibb is investigating antibody-mediated Treg depletion targeting CCR8 as part of a science-driven approach to cancer research.

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