

## Newly discovered immune cell type protects against lung infections during chemotherapy

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(From left) Elaine Tuomanen, chair of the St. Jude Department of Infectious Diseases, first author Akinobu Kamei, M.D., a research associate in the Department of Infectious Diseases, and senior author Peter Murray, Ph.D., a member of the St. Jude Department of Infectious Diseases and Department of Immunology. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital investigators have identified a new form of an immune cell that protected mice from life-threatening lung



infections under conditions that mimic cancer chemotherapy. The research appears online today in the scientific journal *Proceedings of the National Academy of Sciences (PNAS)*.

"We have identified a new form of housekeeping macrophage in mice that may in future be harnessed to protect against lung infections like bacterial pneumonia that remain one of the greatest threats to survival of cancer patients during <u>chemotherapy</u>," said senior and corresponding author Peter Murray, Ph.D., a member of the St. Jude Department of Infectious Diseases and Department of Immunology.

Macrophages are a type of white blood cell that engulf and digest bacteria and other foreign invaders as well as remove dead cells. Normal mammalian lung function requires two types of macrophages—alveolar and interstitial.

Chemotherapy drugs kill dividing cells, including cells in the bone marrow that give rise to different immune cells. That can lead to a dramatic reduction in <u>white blood cells</u>, including the neutrophils that play a central role in combating bacterial and other infections that are a common complication of <u>cancer chemotherapy</u>.

Researchers showed the macrophages identified in this study were produced in the lungs following vaccination rather than the bone marrow. Researchers called the newly recognized cell type vaccineinduced macrophages (ViMs). Once generated, ViMs were maintained in the lungs by cell division. Importantly, unlike other immune cells types, the size of the ViMs population remained stable during chemotherapy. This newly recognized cell type also showed enhanced anti-bacterial activity in mice that lacked neutrophils due to chemotherapy.

"Also serving as an <u>infectious diseases</u> physician at the bedside, I have witnessed how complications due to infection disrupt cancer treatment



and threaten patient survival," said first and co-corresponding author Akinobu Kamei, M.D., a research associate in the Department of Infectious Diseases. "The challenge has been how to create protective immunity in patients whose neutrophils have been severely depleted by chemotherapy. This study suggests a possible framework for developing new strategies."

Working in a mouse model that mimics infection in chemotherapytreated patients, the researchers were surprised to find that vaccination protected mice from lethal Pseudomonas aeruginosa pneumonia. Pseudomonas is the leading cause of bacterial pneumonia in cancer patients with depleted blood neutrophils. The quest to understand how such protection was possible in the absence of neutrophils led investigators to ViMs.

"All lines of cellular and molecular evidence in this study point to alveolar macrophages as the source of ViMs," Murray said. Alveolar macrophages originate in the embryo, reside in the air-exposed surfaces of alveoli and are self-maintained in adults. In contrast, interstitial macrophages are derived from the <u>bone marrow</u> and populate the lung interstitial space between alveoli.

Once activated, ViMs persisted in the lungs for at least one month. When ViMs were transferred to unvaccinated mice with chemotherapydepleted neutrophils, they were protected from lethal Pseudomonas infections.

Researchers are not sure how ViMs survive chemotherapy, but investigators ruled out mechanisms other cells use to resist radiation or certain <u>chemotherapy drugs</u>.

"We now know that increasing the number of ViMs in the tissue can compensate for the immune deficit caused by chemotherapy," Kamei



said. "In this study, we relied on vaccination prior to chemotherapy. Going forward we will explore other, more practical methods for use at the bedside to effectively induce tissue resident macrophages like ViMs." The possible approaches include using drugs or signaling molecules called cytokines to induce protection in the immunecompromised host.

The other study authors are Geli Gao, Geoffrey Neale, Lip Nam Loh, Peter Vogel, Paul Thomas and Elaine Tuomanen, all of St. Jude.

Provided by St. Jude Children's Research Hospital

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