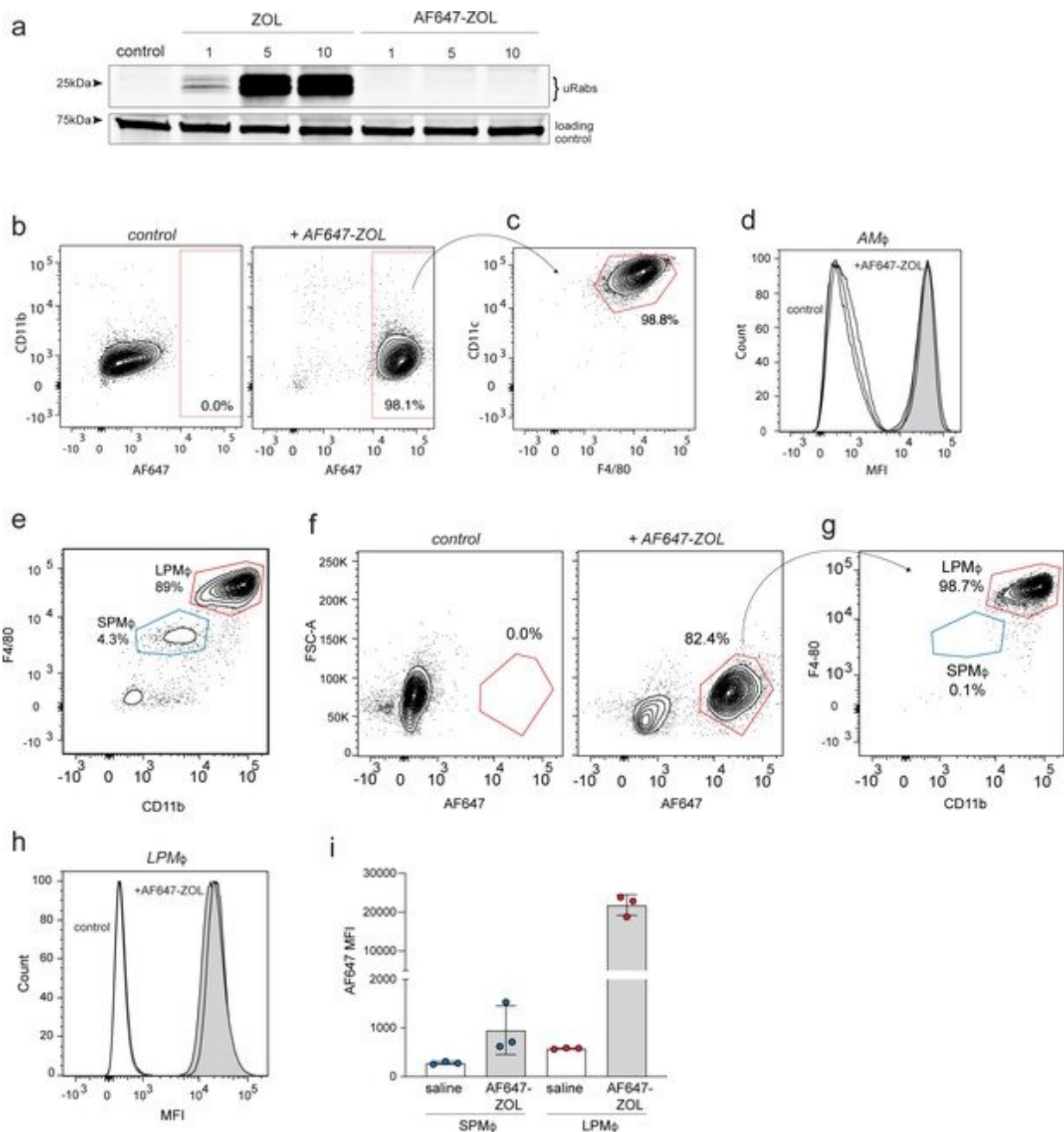


# Common osteoporosis medication boosts immune response in lungs

January 6 2022



Bisphosphonate is internalized by alveolar and peritoneal macrophages in vivo. (a) An in vitro prenylation assay detects unprenylated Rab GTPases (uRabs) in bone marrow-derived macrophages after culture for 24 hr with 1, 5, or 10  $\mu\text{M}$  zoledronic acid (ZOL) compared to 1, 5, or 10  $\mu\text{M}$  AF647-ZOL. (b) FACS plots showing the percentage of labeled single cells in bronchoalveolar lavage (BAL) samples after one intravenous (i.v.) dose of AF647-ZOL compared to saline-treated mice. (c) AF647-ZOL-positive cells were predominantly alveolar macrophages (AM $\Phi$ ), that is, B220-TCRb-, CD11c+F4/80+ singlets. (d) Histograms show AF647-ZOL mean fluorescence intensity (MFI) of AM $\Phi$  in BAL samples from  $n = 3$  control mice (white) and  $n = 3$  AF647-ZOL-treated mice (gray). (e) FACS plot illustrating the percentages of small peritoneal macrophages/SPM $\Phi$  (B220-TCRb- singlets, CD11b<sup>int</sup>F4/80<sup>int</sup>) and large peritoneal macrophages/LPM $\Phi$  (B220-TCRb- singlets, CD11b<sup>hi</sup>F4/80<sup>hi</sup>) in peritoneal lavage. (f) Percentage of labeled peritoneal cells 4 hr after one i.v. injection of saline (left) or AF647-ZOL (right). (g) The labeled cell population (AF647-ZOL+, 82.4%) in (f) consists predominantly of CD11b<sup>hi</sup>F4/80<sup>hi</sup> LPM $\Phi$ . (h) Histograms show the MFI of LPM $\Phi$  from saline- (white) and AF647-ZOL-treated (gray) mice. (i) MFI (AF647 MFI) values from SPM $\Phi$  and LPM $\Phi$  isolated from saline- or AF647-ZOL-treated animals. Bars represent mean  $\pm$  SD ( $n = 3$  mice per group in (h, i); each symbol represents the measurement from an individual mouse). FACS plots in (b, c, e–g) are representative of three mice per group. Credit: DOI: 10.7554/eLife.72430

Researchers at the Garvan Institute of Medical Research have revealed that a common osteoporosis treatment boosts immune cells in the lung that form one of the first lines of defense against pathogens.

In experimental models, bisphosphonate [treatment](#) stimulated [lung macrophages](#) to mount a stronger response against an immune challenge. The findings published in *eLife* follow observations made in previous [clinical trials](#) that individuals who took bisphosphonates had a reduced

risk of pneumonia.

"Bisphosphonates are a safe and effective class of osteoporosis medication that have been the standard-of-care since the 1990s to prevent loss of [bone](#) and reduce the risk of fractures," says senior author Professor Mike Rogers, who heads the Bone Therapeutics Lab at the Garvan Institute.

"We have found an added potential benefit for this treatment—it can boost the immune function of lung [cells](#), which may protect against [respiratory infection](#) and pneumonia. Our evidence warrants further investigation that we hope will lead to improved health outcomes in the older population, who are at higher risk of pneumonia and osteoporosis."

## **Boost to immunity**

Respiratory infections, such as acute pneumonia, are a major cause of death from [infection](#) worldwide. They increasingly affect the older population, as our ability to generate protective immune responses against infectious diseases declines with age.

"Previous clinical trials have suggested that bisphosphonate treatment has a beneficial effect in protecting against pneumonia," says Dr. Marcia Munoz, first author of the paper. "In our research we wanted to understand why that is."

The researchers administered a bisphosphonate called zoledronic acid to mouse models and tracked how the medication moved into different cells.

"It was previously thought that bisphosphonates act only in the bones, but we found that they are taken up by macrophages in the lung, which are 'first responder' cells that can recognize, engulf and destroy a

pathogen during an immune response," says Dr. Munoz.

The team then tested their model's immune response by exposing them to LPS, a molecule found on the surface of bacteria, which is commonly used to assess response to infection. They found that even after just one bisphosphonate dose, the activity of macrophages in the lung had increased compared to mice that had not received the treatment.

"In the skeleton, bisphosphonates prevent bone loss by blocking an enzyme needed by the specialized cells that break down bone," says Ph.D. student Emma Fletcher, second author of the paper. "In [immune cells](#) in the lung, we found that the treatment blocked the same enzyme, which in this case enhanced the immune response."

## **Potential impact for health**

"Macrophages are one of the first lines of defense against infection," says Professor Rogers. "If bisphosphonates are ramping up the ability of these cells to respond when they encounter a viral or bacterial infection, a stronger initial immune response may help clear the infection and lead to a better outcome. This is what we will be investigating next."

In Australia alone, 3.7 million individuals aged over 50 have a high fracture risk and are eligible for [bisphosphonate](#) treatment. However, less than 30% of individuals who should be receiving the medication under existing clinical guidelines are currently treated.

"This leaves a large population of individuals who may receive additional benefits," Professor Rogers adds. "Clinical trials are warranted to determine whether bisphosphonates, aside from preventing [bone loss](#), can provide protection against pneumonia infection in vulnerable individuals, for instance, patients in aged care homes."

**More information:** Marcia A Munoz et al, Bisphosphonate drugs have actions in the lung and inhibit the mevalonate pathway in alveolar macrophages, *eLife* (2021). [DOI: 10.7554/eLife.72430](https://doi.org/10.7554/eLife.72430)

Provided by Garvan Institute of Medical Research

Citation: Common osteoporosis medication boosts immune response in lungs (2022, January 6)  
retrieved 2 May 2024 from  
<https://medicalxpress.com/news/2022-01-common-osteoporosis-medication-boosts-immune.html>

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