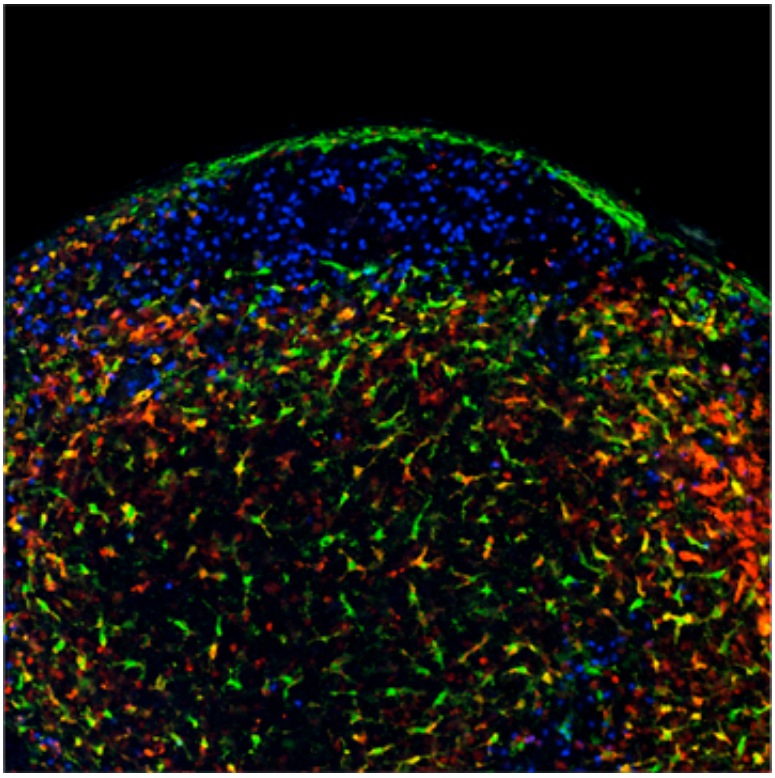
Immune turbocharger: In mice, bone-loss drugs boosted the power of vaccines

November 4 2013, by Elizabeth Cooney



A micrograph section through a lymph node shows different cell types involved in immune response: The green cells in the periphery are macrophages, B cells are blue; dendritic cells are yellow/orange, and the small red cells reflect a subset of memory T cells. Credit: von Andrian Lab

(Medical Xpress)—Could a drug commonly prescribed to prevent bone loss boost the power of vaccines?

New research from Harvard Medical School shows that adding compounds known as bisphosphonates to both commercial and experimental vaccines enhances their effectiveness in mice, raising hopes they could help people mount a more robust immune response.

"Here you have this group of drugs that are approved for millions of people, mostly menopausal women but also others, where there is an extensive database of safety data and a lot of clinical experience. And they have this previously unrecognized enhancing effect on immune responses," said Ulrich von Andrian, HMS Edward Mallinckrodt Jr. Professor of Immunopathology.

"Perhaps down the line it would be possible to use bisphosphonates in combination with existing vaccines, at least in specific groups of patients who are at particular risk of acquiring disease or at risk of not responding well to a conventional vaccine," he said.

These findings are published in *Cell Reports*.

Traditional vaccines include small amounts, weakened versions or components of a given pathogen to induce creation of antibodies without causing disease. The addition of compounds called adjuvants makes vaccines more effective, but elderly people and others with weakened immune systems still don't gain as much protection from a vaccine as healthier people do.

"Oftentimes those groups of individuals who are in the greatest need of the protection afforded by vaccines are the ones who don't respond well," said von Andrian. "If you could make a more potent vaccine that has a more vigorous adjuvant effect, perhaps more of these patients would actually develop protective immune response that would ultimately be beneficial."

Clodronate conundrum

Von Andrian's team established the bisphosphonate-vaccine connection while exploring a well known—but not well understood—phenomenon involving players in the immune system called macrophages. Strategically positioned within lymph nodes, these highly specialized molecules capture viruses ferried from the lymphatic system.

In a paper published in *Nature* in 2007, von Andrian and his colleagues reported that these macrophages do more than simply consume viruses; they also play a key role in spurring antibody production by presenting viral material—the antigen—to B cells that prepare an antibody in response to the threat. The next time the antigen is encountered, the immune system recognizes it and mounts an enhanced attack.

Secondary to that discovery was a puzzling revelation associated with the experimental use of bisphosphonates, which are widely used in people to slow the bone thinning that can accompany age or disease. One particular form, clodronate, is a handy laboratory tool for interfering with macrophages. Packaged inside lipid vesicles, clodronate is appetizing but fatal to macrophages.

Von Andrian and Matteo Iannacone, a former postdoctoral fellow and senior author of the current paper, faced a conundrum: Although their results showed that lymph node macrophages promote B cell activation, the presence of clodronate and other bone-loss drugs revved up B cell-dependent antibody production even after the macrophages were destroyed.

To understand this, the scientists tested a variety of cells and molecular pathways involved in the intricate immune response. They used advanced microscopy to look at cells interacting with one another, capturing viral infections in real time with fluorescence-based imaging

techniques.

One clue came from experiments showing that immune responses were not enhanced when macrophages were eliminated without bisphosphonates. This suggested that bisphosphonates boost vaccines by a novel mechanism that does not depend on macrophage depletion.

Experiments in mice ruled out multiple other immune system cells and key pathways that could conceivably be boosting antibody production. Bisphosphonates stood alone, increasing antibody responses to live and inactive viruses, proteins, helper molecules called haptens and an existing vaccine against hepatitis B. The scientists concluded that they work by directly targeting B cells and enhancing their expansion and antibody production.

'Overdrive'

"The activity these bisphosphonates had was strikingly similar to what you like to have when you use a vaccine adjuvant," von Andrian said. "You take an antigen, you add a second compound to it, whereby that second compound is not seen as an antigen but enhances the response to whatever antigen you combine it with. Clinically there are just a handful of compounds approved for that."

Further cementing the role of bisphosphonates was a boost in the number of antibodies found in blood drawn from 20 patients taking bisphosphonates after cancer had spread to their bones.

"It appears that systemic treatment with bisphosphonate somehow put this entire system in overdrive," von Andrian said.

In another experiment, the scientists gave mice a low dose of a hepatitis B vaccine along with a bisphosphonate and compared them to mice

given the vaccine alone.

"We showed that this commercial vaccine, one that's given to people every day, when combined with bisphosphonate would actually have a turbocharged effect," von Andrian said.

The next step would be to find out if these results can be applied to people.

"We wouldn't do this ourselves but I would be delighted if that was the outcome," he said. "Of course, humans are not mice, so one needs to do the proper research to see whether it will be useful and how useful it would be, based on the benefit relative to any risk."

Long-term use of bisphosphonates has been associated with a jaw disease called mandibular necrosis, but von Andrian said he is not aware of any reports of side effects with single doses.

More information: www.cell.com/cell-reports/abstract/S2211-1247%2813%2900512-3

Provided by Harvard Medical School