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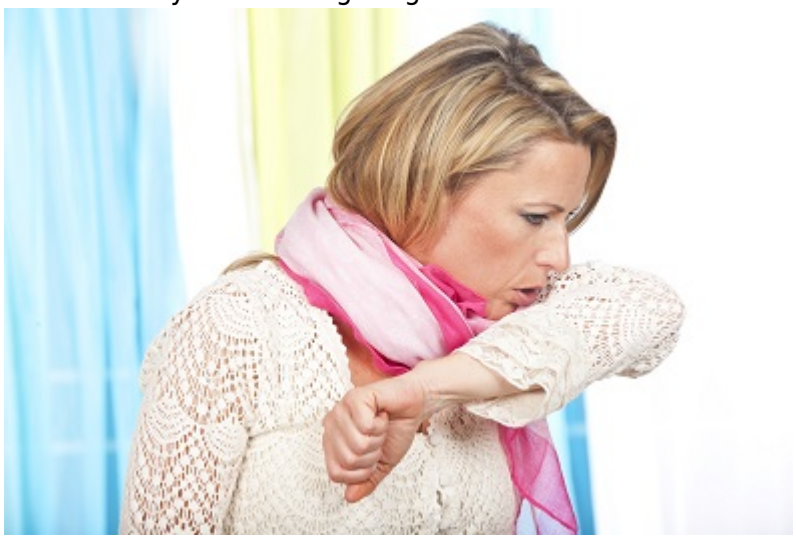
Inflammation is not your enemy. It's a mechanism the body uses to keep us healthy, e.g. to fight invading pathogens. But sometimes, the immune system doesn't know when to stop, say EU-funded researchers. They are learning how to get the message across, in a bid to help tackle diseases caused when our tiny defenders go rogue.


[1]

Helping inflammation to resolve would be more effective than current treatments, which focus on stopping the process, say the partners in the Timer project. They are identifying and testing natural compounds that could help to provide our immune systems with such closure.

New drugs based on these molecules could reduce the burden of chronic inflammation, a condition that can cause a variety of serious illnesses. Timer has found several promising compounds, and three clinical trials are already under way.

How does the immune system know...

“Inflammation is like fire,” says project coordinator Alberto Mantovani of Fondazione Humanitas per la Ricerca, Italy. “But this fire does not abate simply because there is no more fuel to burn; there are actual ‘fire extinguishers’. Identifying more of those is a major thrust of our project [2].”

To explain, Mantovani points to the example of chemokines, molecules that recruit white blood cells to deal with agitators such as a pathogen, a damaged cell or an irritant. Once the disturbance has been quelled, the chemokines are eliminated by other molecules, which thus tell the immune system that it is safe to stand down.

Unless our personal army receives such all-clear signals, it remains on full alert, spoiling for a fight and causing trouble. If we could mimic or manipulate these signals, we would be better equipped to deal with inflammation.

We wouldn’t be the first species to do so. The humble tick is quite adept at lulling mammalian immune systems into a false sense of security.

This trick relies on substances in their saliva. “Ticks have to block immunity and inflammation, because otherwise they would be rejected immediately and wouldn’t get any blood,” Mantovani explains. Timer research has also created new knowledge about these compounds.

...when it's time to calm down?

“In general the immune system works by using accelerators and brakes,” says Mantovani. “There is always a balance between accelerators and brakes. Usually, at the beginning of a reaction, you have a prevalence of accelerators, and then the brakes come in.”

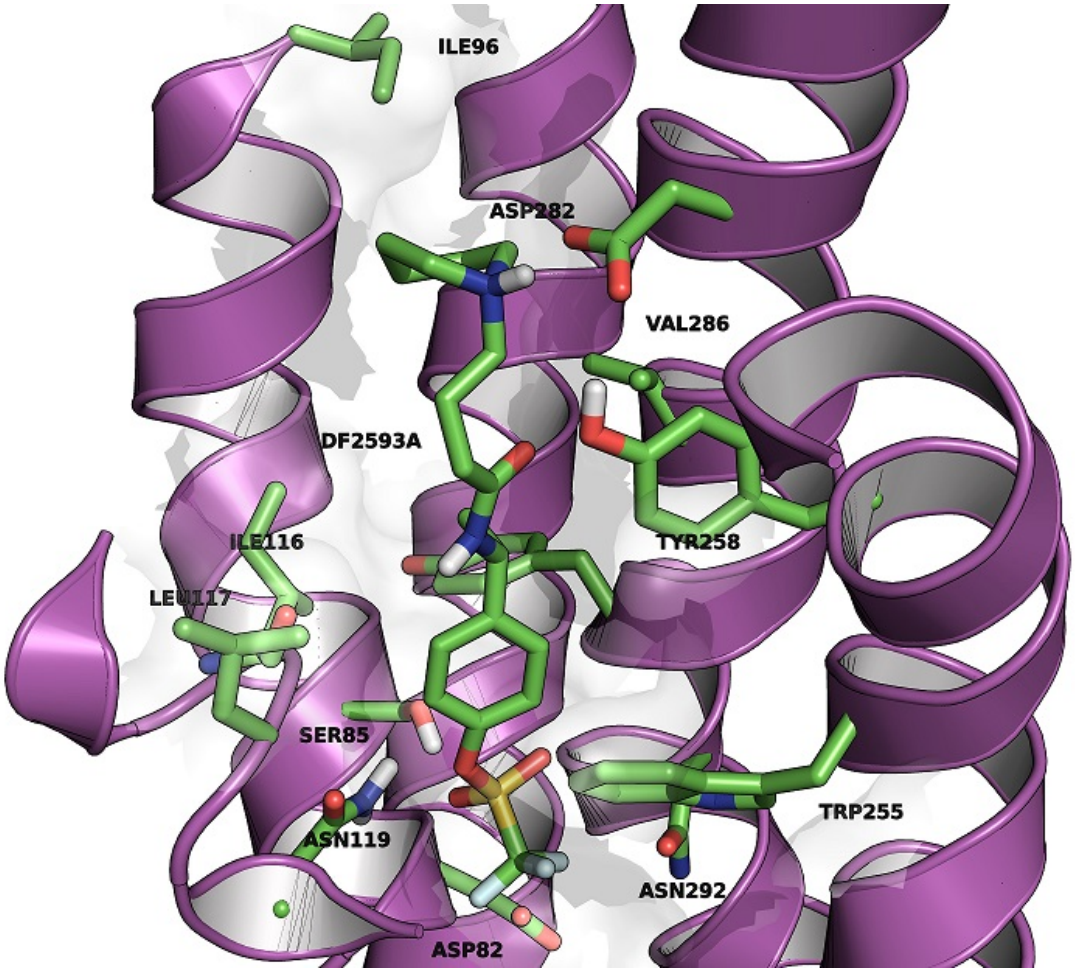
If the brakes don't work, he adds, the inflammation can become chronic, causing the degenerative pathologies that have become a major burden in Western societies. Inflammatory processes are involved in illnesses as varied as cancer, heart disease and arthritis. They may also play a role in the onset of depression.

At the moment, inflammation is primarily treated with non-steroidal anti-inflammatory drugs — aspirin, for instance, says Mantovani. These drugs, he notes, work for just one of the many activators at play, which they block rather than clear.

Timer has identified three candidate compounds — or maybe even four, depending on how you classify them, Mantovani reports. “Our Brazilian colleagues have access to a large collection of natural molecules, and they are very good at testing the potential of these molecules in *in vivo* systems,” he explains. This contribution combines with research capacity and expertise from Ireland, Italy, Switzerland and the United Kingdom.

Together, the partners have taken promising molecules from the lab to the bedside, Mantovani reports. Preliminary clinical trials have been launched for three compounds, which are being tested for safety in the treatment of specific liver, skin and bladder conditions. Further trials will have to confirm that these compounds are effective before they can be developed into licensed drugs.

Mantovani expects the process to take another decade or so. “Timer will not end with the end of dedicated European funding in December 2015,” he concludes. “The legacy of the EU-funded project will endure in the pre-clinical work, in the clinical trials that have been initiated or for which the foundations have been laid, and in the collaboration that has been fostered.”



"Targeting the minor pocket of C5aR for the rational design of an oral allosteric inhibitor for inflammatory and neuropathic pain relief" by: Moriconi A, Cunha TM, Souza GR, Lopes AH, Cunha FQ, Carneiro VL, Pinto LG, Brandolini L, Aramini A, Bizzarri C, Bianchini G, Beccari AR, Fanton M, Bruno A, Costantino G, Bertini R, Galliera E, Locati M, Ferreira SH, Teixeira MM, Allegretti M.

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See also:
CORDIS [3]
Project:
Targeting novel mechanisms of resolution in inflammation
Project Acronym:
TIMER
Project website:
http://www.eumbrella.org/timer.html [2]

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