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Failed treatment for chikungunya highlights the need for extreme caution when manipulating the immune system

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A*STAR researchers found that a treatment they developed for chikungunya, a disease causing painful joint inflammation, was successful when administered closely preceding an infection, but made things much worse if subjects—in this case, mice—were already in the grip of the virus.

Lisa F. P. Ng, who has studied chikungunya virus immunity and infection for the past decade, and her team from A*STAR's Singapore Immunology Network (SIgN) had previously shown a specific antibody complex, IL-2/JES6-1, could prevent chikungunya virus-mediated inflammation when administered before infection.

As it is not always feasible to predict an infection and administer prophylaxis, Ng and the team went on to test the treatment on mice already infected with the chikungunya virus.

"We hoped to see a similar improvement, but unfortunately the contrary happened. It didn't protect the mice - it made them worse," says Ng.

The antibody complex stimulated the production of regulatory white blood cells called Tregs. Ng and her team, in collaboration with Olaf Rotzschke, a Tregs expert, and Laurent Rénia, an expert in CD4+ T cells, found that, in healthy animals, these cells protected against virus-induced inflammation. If the host was already infected, however, the

body had already generated high levels of activated immune cells and adding more Tregs to the mix initiated a cascade that led to hyper-inflammation.

Ng cites another example of immunotherapy gone awry—the 2006 TeGenero/PAREXEL clinical trial disaster which ravaged the organs of its six healthy volunteers, caused loss of limb and left some participants with lasting damage to their immune systems. "It was terrifying," Ng recalls. "By the time they got to injecting the final participant, the first one had already collapsed."

The ramifications of the SIgN study are clear. "The impact of this research—the take-home message? It's a word of caution," warns Ng. "We've shown here, down to the mechanism of action, why this line of research is dangerous."

She adds, "Modulating the immune system can yield treatment options, but scientists need to take heed: these approaches can have serious adverse effects."

Chikungunya emerged in the 1950s; however, despite decades of reports of sporadic infection in Africa and South-East Asia, it was only thrust into the global research spotlight after a 2005 outbreak in the French territory of Reunion Island. "It's a rarely fatal disease, so priorities were elsewhere for a long time," says Ng.

More information: Wendy W. L. Lee et al. Virus infection drives IL-2 antibody complexes into pro-inflammatory agonists in mice, *Scientific Reports* (2016). DOI: 10.1038/srep37603

Wendy W. L. Lee et al. Expanding Regulatory T Cells Alleviates Chikungunya Virus-Induced Pathology in Mice, *Journal of Virology* (2015). DOI: 10.1128/JVI.00998-15

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