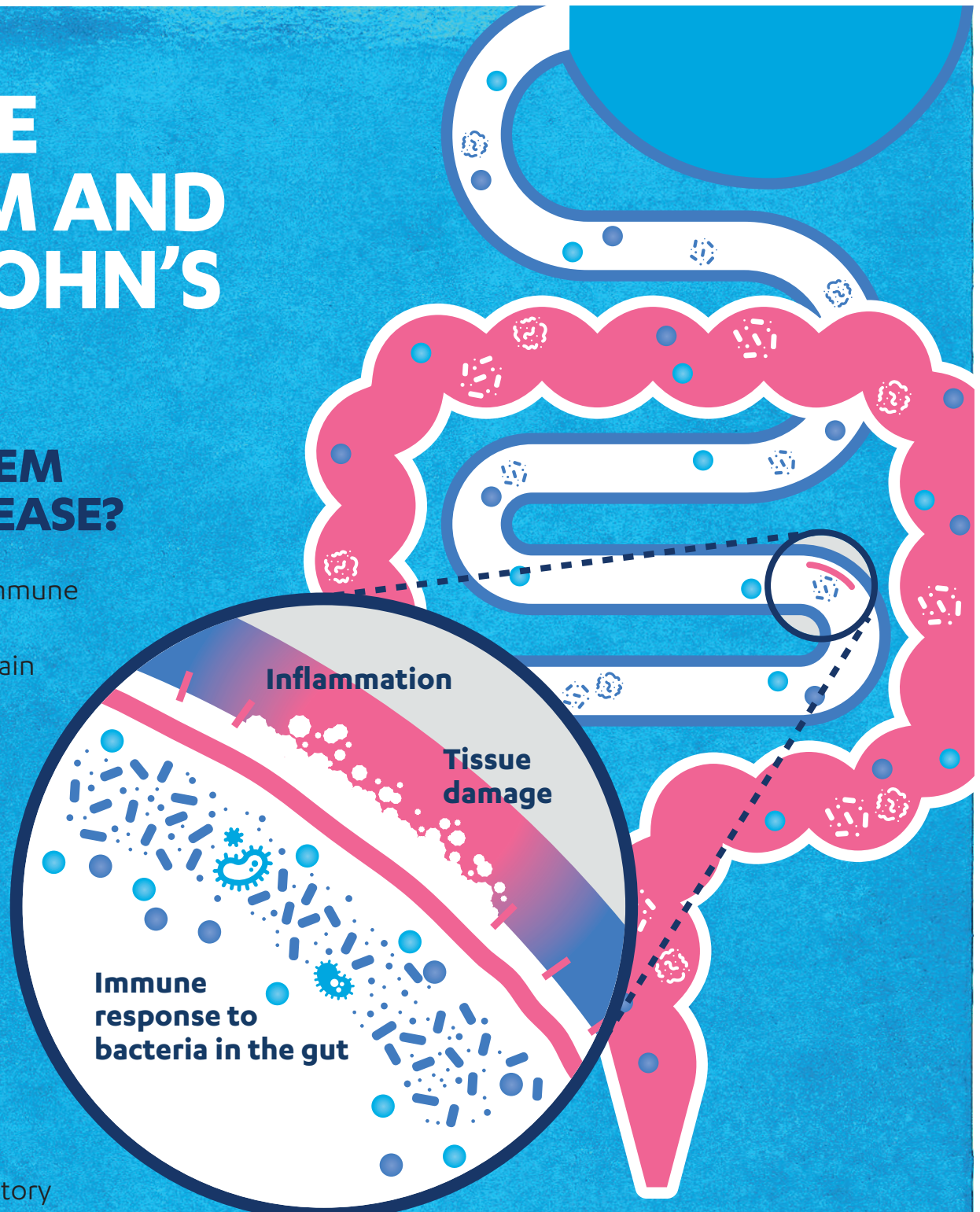
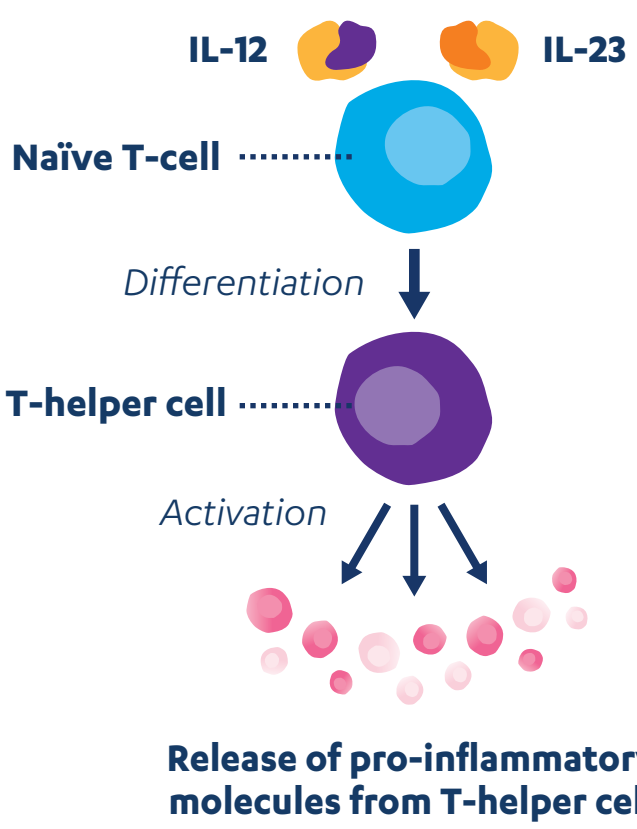
THE ROLE OF THE IMMUNE SYSTEM AND IL-12/IL-23 IN CROHN'S DISEASE

HOW IS THE IMMUNE SYSTEM INVOLVED IN CROHN'S DISEASE?

The intestines are home to a complex mucosal immune system which is thought to interact with bacteria (microbiota) that live in the gut in order to maintain homeostatic balance. When this balance is disrupted, it can make the normally harmonious bacteria in the gut induce a response from the body's own immune system.[1,2]



The immune system's initial first line response, known as the innate immune response, will be activated; however, these short-term inflammatory processes may not be enough to deal with the problem and the adaptive immune response will then be activated. This may result in acute intestinal inflammation which can usually be resolved by the suppression of these pro-inflammatory immune responses by anti-inflammatory mechanisms.[3] However, in Crohn's disease, the inflammation may not be resolved and can, in turn, induce an uncontrolled activation of the mucosal immune system leading to chronic intestinal inflammation. This inflammation can cause further complications such as tissue destruction and ongoing disease activity.[3]



WHAT ARE IL-12 AND IL-23 AND HOW ARE THEY INVOLVED IN CROHN'S DISEASE?

Specific cells that form part of the immune response respond to certain gut bacteria by producing immune signalling molecules known as cytokines. Some cytokines can promote chronic inflammation of the gastrointestinal tract and cause the symptoms of Crohn's disease.[3] Interleukins (IL) -6, 10, 12, 23 and tumour necrosis factor (TNF) are examples of cytokines.[3]

IL-12 and IL-23 help to regulate the adaptive immune response and increased levels are seen in symptomatic Crohn's disease.[4] IL-12 and IL-23 act on naïve T cells to enable them to mature into T-helper (Th) cells and produce pro-inflammatory molecules, which contribute to the uncontrolled chronic intestinal inflammation seen in Crohn's disease.[3,5,6]

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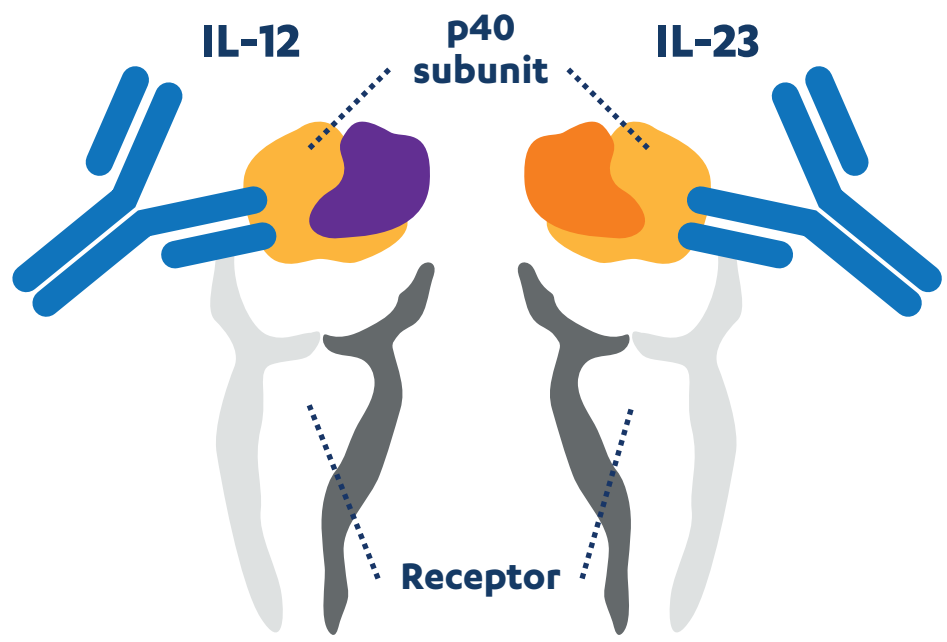
WHY IS IL-12/IL-23 INHIBITION A TARGET FOR THE TREATMENT OF CROHN'S DISEASE?

The IL-12/IL-23 pathway has been shown to have a fundamental role in controlling mucosal inflammation and has therefore been identified as a therapeutic target for autoimmune driven diseases.[7]

Both IL-12 and IL-23 share a common component known as the p40 subunit. This structural similarity inspired the research that led to the development of Stelara® (ustekinumab), a monoclonal antibody that targets the p40 subunit, inhibiting both IL-12 and IL-23 from inducing pro-inflammatory signals.[8]



Stelara® is approved for the treatment of patients with moderately to severely active Crohn's disease who have failed to respond to either conventional therapy or a TNFα antagonist.[8,9]

References

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