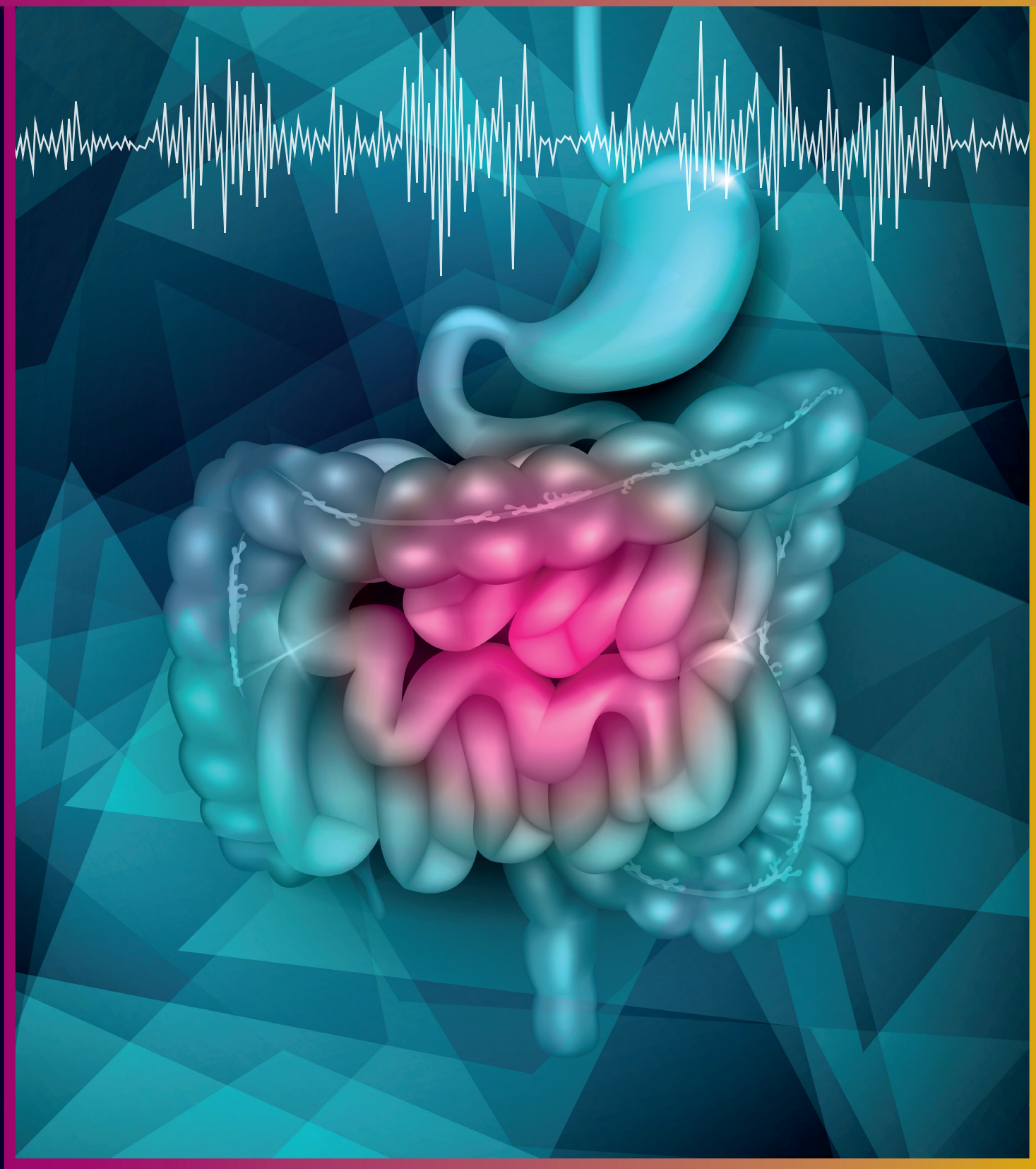
SCIPOD

EMERGING TREATMENT OPTIONS IN INFLAMMATORY BOWEL DISEASE

Dr Benjamin Misselwitz



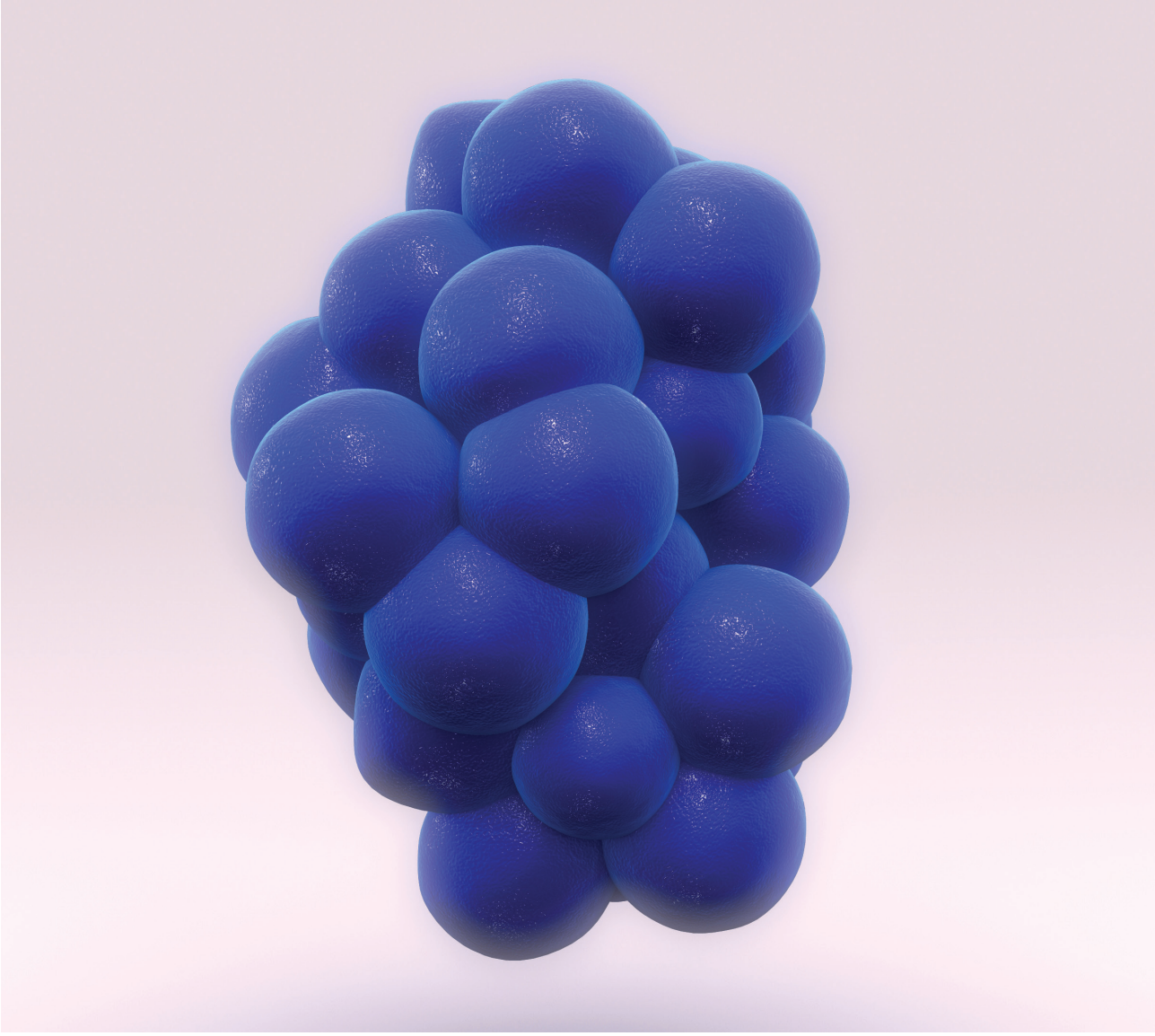
EMERGING TREATMENT OPTIONS IN INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a group of gastrointestinal conditions affecting almost 7 million people globally, and this incidence is rising. While treatments have improved over the last century, many patients do not respond sufficiently, especially those with moderate to severe levels of the disease. Novel drugs that restrain the immune system and reduce inflammation are being developed with the hope of improving patient outcomes.
Dr Benjamin Misselwitz at Island Hospital of Bern and Bern University and his colleagues have conducted a comprehensive review of the emerging therapies and make recommendations for improving treatment for a wider range of patients.

Traditional treatment approaches for patients suffering from inflammatory bowel disease (IBD) have mainly relied on nonspecific immunomodulators that target the immune system to reduce the inflammation that causes IBD symptoms. These broad, immunosuppressive drugs can be less effective and come with more side effects than clinicians would like. The introduction of a new class of drugs that inhibit a molecule called tumor necrosis factor (TNF), represents a significant step forward in treatment for IBD and has granted disease remission for many patients. Unfortunately, a large proportion of patients either do not respond or eventually stop responding to TNF inhibitors. This has been noted by Dr Misselwitz at Inselspital Bern and Bern University and his colleagues to present a critical shortcoming in the provision of effective treatment options.

Newer treatments are becoming more specific in the pathways they target and are rooted in two main mechanisms: the inhibition of cytokines and the inhibition of immune cell trafficking. Cytokines are a type of signaling molecule which recruit immune cells to a location and stimulate an inflammatory response, and TNF is a major cytokine involved in systemic inflammation. Immune cell trafficking is the localization of these cells to their target site, and by targeting these two processes, the overreactive immune response and subsequent inflammation can be reduced.

A problem with typical TNF inhibitors is that they act very broadly and suppress the immune system in the whole body, which can be dangerous for elderly individuals, in particular. AVX-470 is a new type of TNF inhibitor that is specific to the gut. The active component is an antibody which recognizes TNF, binds to it and prevents it from causing inflammation. The new formulation has a delayed release effect, meaning the antibodies only inhibit TNF in the gut



itself. This might make it safer and result in fewer side effects, but large-scale studies are necessary to confirm its enhanced efficacy.

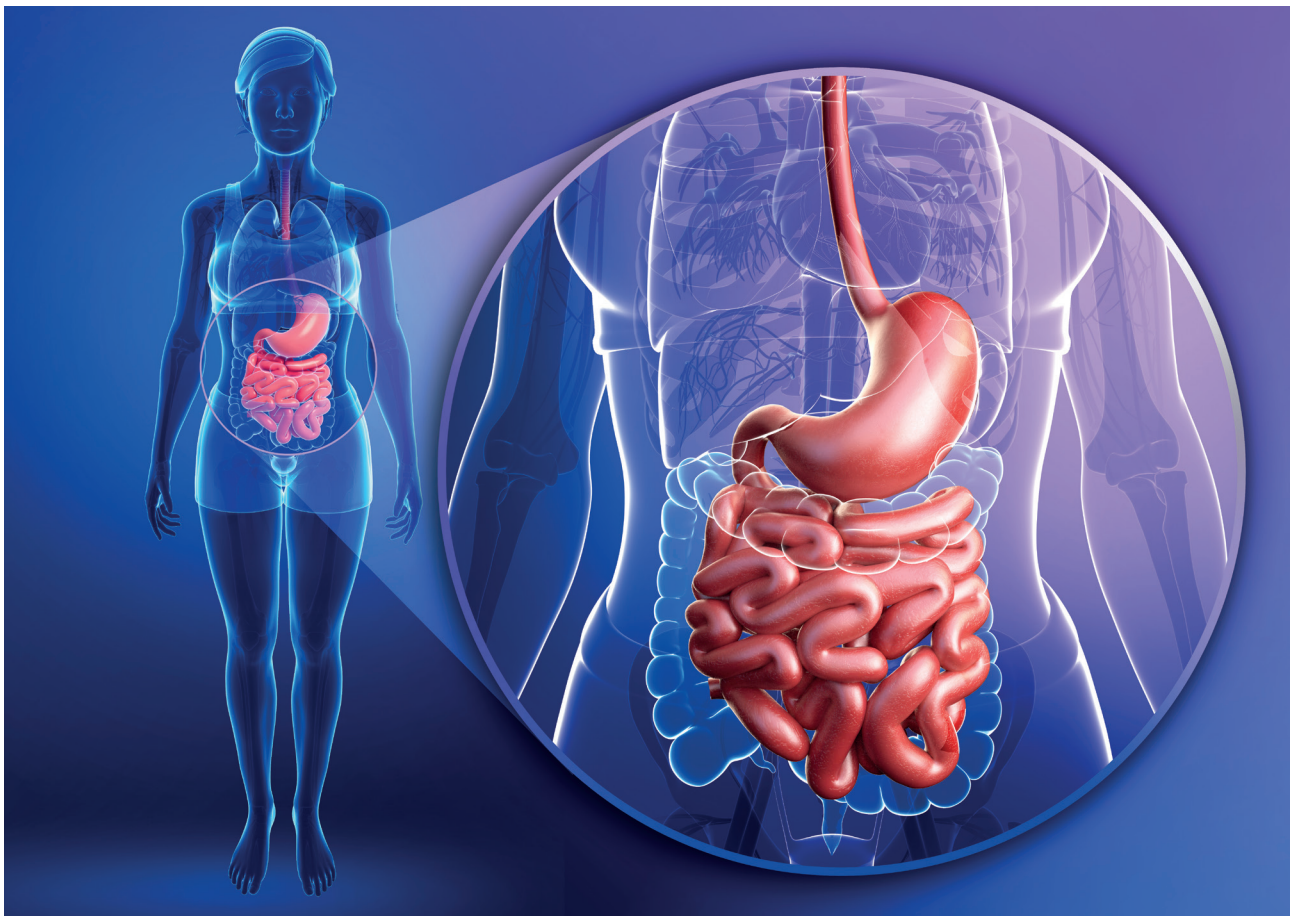
Because of their high level of specificity, antibody therapies are becoming more and more popular as a means to target inflammatory cytokines. Interleukin 23 and interleukin 12 are cytokines which have been recognized in the last few years as being involved in IBD and having inflammatory effects in the intestine. Antibody therapies which have been developed to target these molecules include ustekinumab, briakinumab, and brazikumab. Combining some of these treatments has been shown to be effective for Crohn's Disease (CD), one form of IBD, and the excellent safety profile of these drugs is attractive to clinicians.

Cytokine signaling is an extremely complex process, involving multiple cellular pathways which must be activated at the right times. One of these pathways, known as JAK-STAT, is a promising candidate for inhibitor drugs to prevent cytokines from triggering inflammation. Tofacitinib and filgotinib are antibody inhibitors of JAK-STAT proteins and are a welcome addition to the limited treatment options for IBD. While they may have some efficacy for ulcerative colitis, they may also increase the risk of viral infections such as herpes.

Other experimental drugs that aim to target cytokine signaling include phosphodiesterase inhibitors, such as apremilast. This drug blocks the production of cAMP, an intracellular signaling molecule which activates cytokines. Inhibiting this can reduce the inflammation caused by cytokines such as TNF.

When attempting to inhibit immune cell trafficking, there is the possibility to be highly gut-selective by targeting immune structures in the blood vessels of the intestinal tract. Vedolizumab is an antibody directed against LPAM-1, a type of protein called an integrin, and which is specifically expressed in gut immune tissue. As a long-term treatment, this drug is highly effective for both CD and ulcerative colitis.

A similar drug, etrolizumab has slightly broader specificity for integrins in the gut and granted remission to 21% of patients in



a placebo-controlled trial. These drugs are an effective strategy on the same level as typical TNF inhibition and further study would consolidate their safety profile in IBD patients.

The landscape of IBD treatment is changing rapidly as medicine bears witness to many advancements in other areas. Cell-based therapies are moving into the spotlight as greater insight into their potential use in immune disorders is achieved. Autologous stem cell transplantation is the use of an individual's healthy cells to replace those in the area affected by disease. For patients with severe CD, this treatment indicated some benefits in the long-term but the limited evidence for disease remission remains a concern. Furthermore, as side effects are severe, safer treatment protocols are needed as a priority.

An innovative new treatment called mesenchymal stem cell therapy can have a dual beneficial effect for people with CD. This treatment can have both anti-inflammatory effects and promote wound healing, which is especially helpful for a subset of CD patients where fistulas, small, tunnel-like holes, form in the digestive tract.

Treating IBD is undeniably complex and it remains difficult to find a universal therapy given the wide variety of disease subtypes. Ustekinumab and tofacitinib have recently been approved by regulatory bodies in Europe and the USA and this may pave the way for subsequent developments. However, the efficacy of all IBD treatments assessed here remains only around 15–40% better than placebo, suggesting that no single treatment will provide a cure for all patients.

Dr Misselwitz and his colleagues believe that biomarkers could help the identification of which patients would respond better to specific treatments. This may be of help in the development of 'personalized medicine' for IBD and enable each patient to be treated based on their unique presentation of the condition. With more research and trials leading to a better understanding of the pathological mechanisms of IBD, the future may one day hold a cure.

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