Commentary

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# "*Matters Arising*" on a Recent Biologic (Ab-IPL-IL-17™) for IL-17-Mediated Diseases

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The following *Matters Arising* on a recent biologic (Ab-IPL-IL-17™) for interleukin (IL)-17-mediated diseases represents particularly timely scientific comments and clarifications on the original research paper titled "New biologic (Ab-IPL-IL-17™) for IL-17-mediated diseases: Identification of the bioactive sequence (nIL-17™) for IL-17A/F function" published by Saviano A. *et al.* [1] in Ann Rheum Dis. on 2023. The article under discussion, along with the most recent literature, support the hypothesis that IL-17 cytokines are pivotal in the pathogenesis of chronic inflammation and likely contribute to the homeostatic dysregulation observed in patients with immune-mediated inflammatory diseases (IMIDs). However, it remains to be ascertained whether the findings from *in vitro* experiments, animal models, and limited *ex vivo* (and possibly clinical) studies will enhance our understanding of the biology, and future clinical application, of IL-17 homodimers and heterodimers and related targeted-therapies.

IL-17 is a pro-inflammatory cytokine involved in the immune response. The IL-17 family consists of six members, IL-17A through IL-17F. Among these, IL-17A and IL-17F are the most closely related and can form not only homodimers (IL-17A and IL-17F) but also a heterodimer (IL-17A/F) [2,3]. IL-17 cytokines play crucial roles in immune responses, particularly in inflammation and host defence against pathogens. These cytokines are mainly produced by a subset of T cells known as T helper (Th)17 and Th1-like Th17 cells, as well as by other immune populations, including gamma delta ($\gamma\delta$) T cells, natural killer (NK) cells, and certain innate lymphoid cells [3,4]. Overproduction or dysregulation of IL-17A, IL-17F and IL-17A/F are implicated in several autoimmune diseases, including psoriasis (PsO), rheumatoid arthritis (RA), and multiple sclerosis. They are also involved in chronic inflammatory conditions like inflammatory bowel disease (IBD) and chronic obstructive pulmonary disease (COPD), primarily due to their intrinsic ability to amplify rather than merely induce inflammation [5–9].

The role of these cytokines in promoting inflammation and tissue damage, through a cascade of molecular, including nuclear factor kappa B (NF-$\kappa$B) activator 1 (Act-1) and tumor necrosis factor receptor-associated factors (TRAFs) signals, culminates in NF-$\kappa$B translocation and (over)expression. This makes them key targets for therapeutic intervention in various IMIDs [10]. Currently, targeted therapies against IL-17A, IL-17F, and their heterodimer IL-17A/F (or their receptors IL-17Rs), have been developed and are used in clinical practice to treat conditions such as psoriasis and ankylosing spondylitis. However, ongoing research is focused on refining these therapies and exploring new applications and/or drug (-therapy) repurposing [11].

As reported in a recent "Research Highlight" published in Nat Rev Rheumatol [12], on an article from our research group titled "New biologic (Ab-IPL-IL-17™) for IL-17-mediated diseases: Identification of the bioactive sequence (nIL-17™) for both IL-17A and IL-17F function" [1], we designed a series of peptides based on IL-17A/F and tested their ability to mimic the actions of the full proteins *in vitro*. We found a unique sequence of 20 amino acids long, named nIL-17™, which was responsible for IL-17's biological activity in both mice and humans. We then determined the 3D structure of this AA sequence and conducted studies that showed, at an atomic level, how the sequence 'docks' onto receptors that are known to trigger an inflammatory response.

We demonstrated that this short sequence was a potent activator of the inflammatory response, stimulating the release of cyto-chemokines (and inflammatory mediators), to the same extent as full-length IL-17 proteins, and driving immune cell migration to an even greater extent than the parent molecules. Moreover, nIL-17™ modulated

Act-1/TRAFs/NF-$\kappa$B expression more effectively than the parental protein. The results from these cellular *in vitro* experiments were confirmed in animal models, which showed that nIL-17™ truly represents the most biologically active sequence of IL-17.

Based on this evidence, we generated the novel antibody Ab-IPL-IL-17™ to target this sequence [12]. Further studies reported in the paper evaluated Ab-IPL-IL-17™. In detail, in cell studies, Ab-IPL-IL-17™ showed potent activity, significantly decreasing the production of cytochemokines and reducing white blood cell migration in tissues primed for inflammation. Mouse studies evaluating the activity of Ab-IPL-IL-17™ against existing anti-IL-17 therapies (secukinumab, an anti-IL-17A; and bimekizumab, an anti-IL-17A and IL-17F) showed that Ab-IPL-IL-17™ did not trigger unwanted immune responses, reduce circulating platelet, or increase circulating lymphocytes. Further studies in mouse models of arthritis showed that therapeutic administration of Ab-IPL-IL-17™ was as effective at halting disease progression and triggering resolution as the current gold-standard treatment for RA, infliximab.

Finally, we conducted proof-of-concept studies that tested the response of tissues donated by patients with RA and IBD to Ab-IPL-IL-17™. In this context, we found that Ab-IPL-IL-17™ was able to reduce the pathological symptoms of disease. In RA, where we examined fibroblasts (connective tissue cells), the results strongly suggested that Ab-IPL-IL-17™ specifically inhibits the pro-inflammatory actions of chronically inflamed fibroblasts within the rheumatoid joint. In IBD, Ab-IPL-IL-17™ was shown to deplete plasma IL-17A in samples obtained from treatment naïve IBD patients, indicating its potential to alleviate pathological pro-inflammatory changes in this disease.

Further research is needed to determine how these findings will enhance our understanding of IL-17 homodimers and heterodimers and if they can be translated into clinical practice. Our "matter arising" is based on the evidence that IL-17A and IL-17F are relatively modest activators in terms of their pro-inflammatory potency when acting alone [13,14], but they can dramatically amplify their signal by synergizing with other pro-inflammatory molecules, such as tumor necrosis factor-alpha (TNF-$\alpha$), transforming growth factor-beta (TGF-$\beta$), IL-1$\beta$, and IL-22 in a "tissue-dependent" and "tissue-specific" manner [15]. Moreover, although IL-17A has a more potent pro-inflammatory effect, IL-17F is found at higher levels (up to 30-fold) in lesional skin and serum of patients with PsO [16] and, to a lesser extent, in other IMIDs [17–19]. Our vision and experimental *mission,* aim to precisely determine the temporal and spatial expression of IL-17A, IL-17F, and IL-17A/F and their pathological contributions to the onset and progression of certain autoimmune diseases, particularly psoriasis and psoriatic syndromes. Our experimental hypothesis could be corroborated by evaluating sera from PsO patients and testing the efficacy of neutralizing Ab. These findings will be instrumental in developing novel therapeutic strategies and translating these insights into clinical practice.

## Availability of Data and Materials

Not applicable.

## Author Contributions

AS and AAM contributed to literature review and analysis. PG, AJI and FM provided expertise, drafted and revised the manuscript for intellectual content. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

This article has been conducted and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors AS, PG, AJI. and FM, hold patents for the diagnostic and therapeutic use of nIL-17™ and Ab-IPL-IL17™ (IT patent No. 102022000016722; IN patent No. WO2024/028436 A1) in autoimmune disease, chronic inflammatory disease and other diseases in which IL-17 producing cells contribute to pathogenesis. Francesco Maione is serving as one of the Editorial Board Members (Deputy Editor-in-Chief) of this journal. The Journal declares that

Francesco Maione had no involvement in the peer review of this article and has no access to information regarding its peer review.

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