Response to: 'Potential roles for tenascin in (very) early diagnosis and treatment of rheumatoid arthritis' by Cutolo *et al*

We thank the authors for their commentary[1] on our article which was recently published in the *Annals of Rheumatic Diseases*.[2] Cutolo *et al* write an extended discussion of the study, in which we describe the development of therapeutic monoclonal antibodies that block the pro-inflammatory activity of the fibrinogen-like globe (FBG) domain of tenascin-C, and the efficacy of these antibodies in preventing disease progression in preclinical models of rheumatoid arthritis (RA). The commentary includes a detailed summary of the autoantibody response to a citrullinated epitope (cTNC5) within the FBG domain of tenascin-C which arises very early during the development of RA, and which can also be detected in around one in five people at risk of developing RA. As highlighted by the authors, the questions around how the response to modified components of the extracellular matrix evolves during the development of RA, and whether or not this autoantibody response contributes to disease pathogenesis, are an area of ongoing research. We also agree that detection of anticitrullinated peptide antibodies recognising cTNC5 in people with RA, or who will go on to develop RA, should be explored as a potential companion diagnostic with which to identify individuals who may benefit from treatment with therapies directed against the FBG domain of tenascin-C. If this hypothesis holds true, then we may well be able to stratify patients in whom we can intervene to stop disease progression from an extremely early stage. Following the seminal paper by Cutolo *et al* in 1992,[3] there has been enormous progress worldwide in the field of tenascin-C and joint pathology. Although there remains much work still to be done, not least in assessing the potential benefits of targeting tenascin-C as a means to treat people with RA in the clinic, as well as discovering more about whether a direct link exists between the pathogenic action of the FBG domain as a modulator of Toll-like receptor 4-mediated inflammation with its role in adaptive immunity in this disease, these are challenges that we look forward to facing.

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