Anti-CCL2: building a reservoir or opening the floodgates to metastasis?

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understanding, many aspects of the story, particularly in immunological terms, remain unclear.

The immune system must have the ability to detect foreign antigen and respond in an appropriate and timely manner, but must also be adequately desensitized to avoid unnecessary response to self. The majority of studies into CCL2 signalling describe its tumorigenic features, but CCL2 is also known to provide protection, for example, by recruiting anti-tumorigenic T cell subsets to the tumour microenvironment [9]. Therefore, it is plausible that CCL2 signalling may have dual context-dependent effects in tumourigenesis: promoting metastasis of established primary tumours, but performing tumour immune-surveillance in neo-transformed animals [10]. Cancer generally establishes an immune-tolerant environment in which it thrives [1], and this may be key to the observations described by Bonapace et al. Withdrawing CCL2-neutralisation in a tolerogenic environment may favour different outcomes to withdrawing treatment during an immunogenic period.

To determine this hypothesis, further clarification is required to understand the extent to which monocytes are sequestered in the bone marrow during CCL2 neutralisation. It is difficult to interpret the distribution of these cells without appropriate data outlining their localisation and abundance in a resting mouse. This is exacerbated by differing patterns in monocyte distribution between experimental cell lines. Future studies must address bone marrow output during treatment to fully decipher whether monocytes are sequestered here. It is acknowledged that cancer patients often have augmented production of immature cells [11]; therefore some indication as to the functionality of monocytes and their ability to differentiate in the context of CCL2 neutralisation would be useful.

CCL2 neutralisation has shown positive outcomes in several murine models of mammary, prostate and lung cancers [3,12-14]. Despite this, the lack of studies into long-term CCL2 neutralisation and the associated consequences of compromised immunosurveillance, which have been acknowledged in the past [10], are only beginning to be addressed. The work by Bonapace and colleagues has highlighted the necessity of long-term strategies becomes increasingly resonant in an era where the expense of immunotherapy plays a prominent role in therapeutic options.

Abbreviations
CCL2: Chemoattractant C-C chemokine ligand 2; STAT3: Signal transducer and activator of transcription 3; VEGF-A: Vascular endothelial growth factor-A.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JRH drafted the manuscript and revised it critically for intellectual content; CJW made substantial intellectual contribution to the revision of the manuscript. Both authors read and approved the final manuscript.

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