Reply to 'Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies'

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We thank Pietro Enea Lazzerini, Franco Laghi-Pasini, Mohamed Boutjdir and Pier Leopoldo Capecchi for their correspondence on our Review (Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat. Rev. Immunol.* **18**, 733–744 (2018))[1], which highlights the emerging interactions between inflammation and cardiac conduction disorders (Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-018-0098-z (2018))[2].

Owing to the broader scope of our Review[1] on general cardioimmunology and to space restrictions, we limited our discussion to emerging mechanisms related to the participation of immune cells and the effects of cytokines in conduction disorders. In their response, Lazzerini and colleagues mention that rhythm disorders may also occur as a result of autoimmunity, as autoreactive antibodies can target ion channels in cardiomyocytes[2]. We appreciate this comment and would like to add several further areas that equally deserve attention.

These include atrioventricular block in patients with Lyme disease[3], Chagas disease[4] or cardiac sarcoidosis[5], and in patients who are receiving immune checkpoint inhibitors for immunotherapy of cancer[6]. In addition, conduction disorders such as atrioventricular block often occur in the elderly; in Lev's disease, this is referred to as idiopathic atrioventricular block and is thought to be caused by fibrosis[7]. Interestingly, macrophages are well known to regulate turnover of the extracellular matrix in the heart, and the phenotype, activities and source of these macrophages might change as a function of ageing[8]. Hypothetically, such changes in phenotype could compromise the participation of macrophages in steady-state electrical conduction in the heart[9]. Another interesting observation, with unclear pathophysiology but perhaps related to involvement of the immune system, is the frequent incidence of atrial fibrillation in patients with sepsis[10].

These clinical observations could be useful for generating new hypotheses regarding how inflammation can affect cardiac conduction. Taking the results together, we believe that work in this exciting new area of interdisciplinary science may lead to much needed solutions for the pressing clinical problems in many patients with cardiovascular disease.

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Competing interests
The authors declare no competing interests.