Corticosteroid receptors, macrophages and cardiovascular disease

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Abstract

The mineralocorticoid receptor (MR) and glucocorticoid receptor are ligand-activated transcription factors that have important physiological and pathophysiological actions in a broad range of cell types including monocytes and macrophages. While the glucocorticoids cortisol and corticosterone have well-described anti-inflammatory actions on both recruited and tissue resident macrophages, a role for the mineralocorticoid aldosterone in these cells is largely undefined. Emerging evidence, however, suggests that MR signalling may promote pro-inflammatory effects. This review will discuss the current understanding of the role of corticosteroid receptors in macrophages and their effect on diseases involving inflammation, with a particular focus on cardiovascular disease.

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Introduction

Monocytes/macrophages are a diverse and versatile population of cells. Derived from bone marrow, monocytes exit the peripheral circulation and enter tissues where they differentiate into macrophages. Macrophages are recruited to tissues to restore resident populations or respond to an inflammatory stimulus (Fig. 1). The properties exhibited by the differentiated macrophage reflect the recruitment signal and local microenvironment. A number of inflammatory and fibrogenic pathways induced by macrophage activation are central to the pathogenesis of disease states such as cardiovascular disease (Yan & Hansson 2007), cancer (Coussens & Werb 2002) and metabolic syndrome (Zeyda & Stulnig 2007). Furthermore, emerging evidence suggests that nuclear receptor signalling in macrophages may play an important role in the pathology of these conditions (Harkonen & Vaananen 2006, Desvergne 2008).

Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) have well-described roles in a range of pathologies (Walker 2007, Young 2008). The particular focus of the current review is that recent data suggest that MR and GR signalling in macrophages plays a key role in the pathogenesis of disease. This review will summarise the current understanding of the role of corticosteroid receptors in macrophages and their effect on corticosteroid-associated diseases such as atherosclerosis, osteoporosis, hypertension, metabolic syndrome and tissue remodelling.

Corticosteroid receptors

The corticosteroid hormones (glucocorticoids, mineralocorticoids) are synthesised from cholesterol in the adrenal cortex and exert their effects by binding cytoplasmic GR and MR (Rousseau et al. 1972, Sheppard & Funder 1987; Fig. 2). Upon ligand-induced activation, the receptors undergo a conformational change, dissociate from heat shock proteins and translocate to the nucleus. Once in the nucleus they initiate transcription of specific genes by interacting with transcription co-activators and binding to hormone-response elements (HRE; McKenna & O’Malley 2002). The human MR cDNA encodes a polypeptide that is highly homologous to the human GR, with 57% homology in the ligand binding domain and 94% in the DNA binding domain (Arriza et al. 1987). As a consequence of this sequence homology, cross-reactions with ligands and HRE are to be expected for MR and GR.

In vivo, endogenous glucocorticoids (cortisol in human and corticosterone in rats and mice) bind both MR and GR, while the mineralocorticoid...
aldosterone specifically binds MR (Fig. 2). Given that aldosterone and cortisol have equivalent high affinity for the MR (Krozowski & Funder 1983, Arriza et al. 1987) and that glucocorticoids circulate at much higher concentrations than aldosterone, under normal circumstances MR are largely occupied by cortisol. Aldosterone specificity of MR in epithelial tissues and vascular smooth muscle cells (VSMC) is thus conferred by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2; Edwards et al. 1988, Funder et al. 1988).

**11β-hydroxysteroid dehydrogenase enzymes**

11βHSD enzymes catalyse the interconversion of active and inactive glucocorticoids. Two isoenzymes, 11βHSD1 and 11βHSD2, have been identified (Agarwal et al. 1995). 11βHSD1 is NADP⁺-preferring and has bidirectional activity, catalysing the reduction or dehydrogenation of glucocorticoids (Lakshmi & Monder 1988). It is widely expressed in many tissues such as the liver, lung, adipose tissue and the central nervous system (Monder 1993). On the other hand, 11βHSD2 is NAD⁺-dependent and confers aldosterone specificity on MR by metabolising cortisol and corticosterone to their inactive metabolites cortisone and 11-dehydrocorticosterone respectively (Edwards et al. 1988, Funder et al. 1988). These metabolites have negligible affinity for the MR. 11βHSD2 expression is high in physiological aldosterone target tissues such as the kidney and colon (Albiston et al. 1994, Takeda et al. 1995) and is also present in the blood vessel wall, regulating activation of the MR in the same manner as in epithelial tissues (Funder et al. 1989, Alzamora et al. 2000).
Recent studies have demonstrated the presence of \(11\beta\text{HSD1}\) but not \(11\beta\text{HSD2}\) in differentiated macrophages (Thieringer et al. 2001, Chapman et al. 2006, Lim et al. 2007; Fig. 2). Interestingly, \(11\beta\text{HSD1}\) is not present in circulating monocytes and its expression appears to be induced by macrophage differentiation and activation (Chapman et al. 2006).

Properties and functions of monocytes/macrophages

Macrophages, once considered merely the cellular garbage bins of the body, have emerged as key regulators in the initiation and progression of a number of pathologies. They belong to the mononuclear phagocyte system, which is a group of functionally distinct cell types that include polymorphonuclear cells (neutrophils, basophils and eosinophils), monocytes, macrophages, erythrocytes, megakaryocytes and mast cells.

Bone marrow-derived monocytes enter peripheral blood and circulate for several days in an inert state before entering tissues and differentiating into tissue resident macrophages (Vollman & Gowans 1965). Tissue resident macrophages include those in bone (osteoclasts), connective tissue (histiocytes), liver (Kupffer cells), lung (alveolar macrophages) and nervous system (microglia; Gordon 1995; Fig. 1).

The diverse and often opposing roles macrophages display can in part be explained by their functional plasticity. Signals from the microenvironment in which they reside dictate the polarised phenotype macrophages acquire; broadly defined as ‘classically’ and ‘alternatively activated’ macrophages (Goerdt et al. 1999, Gordon 2003, Martinez et al. 2008; Fig. 3). ‘Classical activation’ refers to stimulation by interferon-\(\gamma\) (INF-\(\gamma\)) and microbial products such as lipopolysaccharide (LPS; Adams 1989, Dalton et al. 1993). In contrast, activation by factors such as IL-4 or IL-13, immune complexes, IL-10, transforming growth factor (TGF)-\(\beta\) or glucocorticoids is known as ‘alternative activation’ (Stein et al. 1992, Goerdt & Orfanos 1999).

Classically activated macrophages produce and secrete pro-inflammatory cytokines (IL-1\(\beta\), IL-15, IL-18, tumour necrosis factor (TNF)\(\alpha\) and IL-12), chemokines (CCL15, CCL20, CXCL13, CXCL9, CXCL10 and CXCL11) and oxidative intermediates (nitric oxide and reactive oxygen species (ROS); Goerdt et al. 1999, Mosser 2003, Mantovani et al. 2004, Martinez et al. 2008). Consistent with this profile, classically activated macrophages play important roles in type I inflammation, destruction of tissue

![Diagram]

Figure 3 Classical and alternative activation of macrophages. Polarised phenotypes of macrophages are broadly defined as classically and alternatively activated. Classically activated macrophages respond to interferon-\(\gamma\) (INF-\(\gamma\)) and lipopolysaccharide (LPS) and play important roles in type I inflammation, destruction of tissue, killing of intracellular parasites and tumour resistance. In contrast, alternatively activated macrophages respond to factors such as IL-4 or IL-3, immune complexes, IL-10, TGF-\(\beta\) and glucocorticoids and contribute to type II inflammation, tissue remodelling, angiogenesis, parasite encapsulation and tumour progression.
Macrophages in pathology

Inflammation

Monocytes/macrophages play an integral role in the immune system and can enhance or suppress inflammatory processes depending on their differentiation phenotype or activation state (Hume et al. 2002, Gordon 2003, Mosser 2003). While activated macrophages are a characteristic feature of both acute and chronic inflammatory responses, accumulating evidence suggests that the phenotypic profile and hence the response they elicit varies greatly (Mantovani et al. 2004). In the case of chronic inflammation, pro-inflammatory cytokines secreted by macrophages may perpetuate the inflammatory responses responsible for end organ damage in disease states such as rheumatoid arthritis (Szekanecz & Koch 2007), atherosclerosis (Libby 2002) and inflammatory bowel disease (Zhang & Mosser 2008).

Oxidative burst

An important component of the macrophage phagocytic action is the ‘respiratory burst’ or the production of ROS by the NADPH oxidase system (Babior et al. 1973). Early studies investigating redox signalling in macrophages focused on its role in terms of phagocyte killing, while recent studies have suggested that it may be important for cytokine production and orchestration of the inflammatory response (Kirkham 2007).

Tissue remodelling

In addition to their critical role in the control of immune responses, macrophages can directly influence disease progression in end organs by altering the balance between matrix synthesis and degradation through protease and cytokine secretion (Lupher & Gallatin 2006, Wynn 2008). Importantly, macrophage depletion has been shown to reduce tissue remodelling and fibrosis in a number of experimental models (Duffield et al. 2005). This study demonstrated in transgenic mice, in which macrophage depletion is temporally regulated, that macrophage depletion during active remodelling reduced matrix deposition, whereas their removal during resolution phase exacerbated matrix deposition (Duffield et al. 2005).

The specific roles of macrophage GR and MR signalling in pathological states associated with inflammation are discussed in detail below.

Corticosteroid receptor expression in macrophages

A recent study by Barish et al. (2005) has demonstrated that 28 of 49 known nuclear receptors in mice are expressed in macrophages. They showed that this repertoire of nuclear receptors was identical in primary bone marrow-derived and RAW 264.7 macrophages, suggesting that expression profile may exist in all macrophages. The nuclear receptor expression profile included 9 of 12 known endocrine receptors including GR, MR, oestrogen receptor, vitamin D receptor, thyroid receptors α and β, and retinoic acid receptors α and γ (Barish et al. 2005). Furthermore, the classical macrophage activators LPS or IFN-γ induced a distinct temporal gene expression profile for each of the nuclear receptors in macrophages.

The corticosteroid receptors MR and GR are expressed in a number of immune cells and tissues. The localisation profile of each of the receptors in the immune system is distinct, reflecting their specific and often opposing roles in regulating immune responses (Armanini et al. 1985b, Lowy 1989, Miller et al. 1990, 1993). For example, the thymus contains one of the highest concentrations of GR in the body, whereas it does not express MR. On the other hand, both corticosteroid receptors are expressed in the spleen (Miller et al. 1993), although MR levels are very low. This distinct pattern of expression displayed by corticosteroid receptors may dictate the varied response/sensitivity immune cells/tissues have to corticosteroid hormones (Miller et al. 1994).

LPS and IFN-γ are potent, well-characterised mediators of macrophage activation (Adams 1989, Dalton et al. 1993). LPS is a major constituent of the cell wall of gram-negative bacteria that triggers the production and release of pro- and anti-inflammatory cytokines from macrophages (Boldrick et al. 2002, Nau et al. 2002). The cytokine IFN-γ is secreted by activated T cells and natural killer cells and activates macrophages through the Janus kinase–STAT signalling pathway. As mentioned above, macrophage MR and GR expression profiles induced by LPS or IFN-γ have recently been generated (Barish et al. 2005). LPS stimulation increased GR gene expression fivefold over baseline after just 4 h, whereas MR gene expression was completely suppressed within 4 h. In terms of the GR, this finding supports the well-described, potent anti-inflammatory action of GR signalling. In addition, reduced MR expression in response to LPS is consistent with studies that have described a pro-inflammatory role for MR signalling.
The immunosuppressive effects of GR signalling include inhibition of transcription factors such as nuclear factor κB (NFκB) and activating protein 1 (Clark 2007), suppression of inflammatory prostaglandins (Bailey 1991) and induction of apoptosis in T and B lymphocytes (Tuckermann et al. 2005). In macrophages, glucocorticoid exposure alters the expression of many pro- and anti-inflammatory genes (Ehrchen et al. 2007) and promotes phagocytosis of apoptotic cells (Liu et al. 1999). While the molecular cascade triggered within macrophages following glucocorticoid exposure remains largely unknown, evidence supporting a role for macrophage GR signalling is emerging for a number of inflammatory disease processes.

Atherosclerosis and macrophage GR

Atherosclerosis is a progressive disease characterised by an inflammatory event in which monocyte-derived macrophages play a central role (Libby 2002). Macrophages are involved in all key stages of atherosclerosis development: the early inflammatory event, the development of the fatty streak and finally the plaque rupture. The initial inflammatory response stimulates elevated expression of leukocyte adhesion molecules, such as intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, which in turn increases monocyte attachment (Libby 2002). Once attached, chemokine interactions induce monocyte migration into the tunica intima and differentiation into tissue resident macrophages. Mature macrophages express scavenger receptors that attract oxidised low density lipoproteins (oxLDL) and lipids to produce foam cells and ultimately the ‘fatty streak’ (Libby 2002). Macrophages are thought to destabilise the plaque via production and secretion of matrix metalloproteinases, which solubilise extracellular matrix and initiate rupture of the fibrous cap (Yan & Hansson 2007).

Glucocorticoid treatment has been shown to reduce macrophage accumulation in a model of cholesterol-induced atherosclerosis (Poon et al. 2001) and decrease neointimal proliferation following balloon angioplasty (Villa et al. 1994). A role for macrophage GR signalling in a model of atherosclerosis has recently been identified by transplanting bone marrow derived from macrophage GR-null mice into LDL receptor deficient mice (Preusch et al. 2008). Interestingly, deletion of GR from macrophages had no effect on atherosclerotic lesion size or macrophage number, suggesting that the effects of glucocorticoids on atherosclerosis are only partially mediated through GR. Deletion of GR from macrophages did, however, reduce vascular calcification and vascular expression of receptor activator of NFκB ligand (RANKL), bone morphogenetic protein 2 and msh homobox 2. These findings are consistent with

**Corticosteroids, macrophages and disease**

Corticosteroid hormones and their receptors have numerous physiological functions but also play leading roles in various pathological events. Glucocorticoids are involved in the aetiology and progression of disease states such as atherosclerosis, osteoporosis and metabolic syndrome, whereas mineralocorticoids are thought to be important in promoting inflammation, hypertension and cardiac and renal fibrosis. In the following section, we summarise the current understanding of the pathophysiological consequences of GR and MR signalling specifically in macrophages.

**GRs, macrophages and disease**

Due to their potent anti-inflammatory properties, glucocorticoids have been used to treat inflammatory diseases for over 50 years (Hench et al. 1950).
previous studies that have ascribed a role for these factors in the development of vascular calcification (Kaden et al. 2004).

### Glucocorticoid-induced osteoporosis and osteoclasts

Skeletal mass is maintained by the balance between the bone-forming activity of osteoblast and the bone reabsorption activity of osteoclast. Osteoclasts are bone resident macrophages that specifically differentiate in response to macrophage colony stimulating factor and RANKL (Boyle et al. 2003, Teitelbaum & Ross 2003). Prolonged glucocorticoid treatment is often associated with bone loss, ultimately leading to osteoporosis. Given the importance of osteoclasts in osteoporosis, we will briefly discuss the current understanding of the role of osteoclast GR signalling in osteoporosis.

Glucocorticoids suppress osteoblast activity in vivo (Weinstein et al. 1998, Weinstein 2001) although their effects in vitro are controversial (Aubin 1999, Smith et al. 2000, Purpura et al. 2004). The role of GR specifically in osteoclasts has been recently defined in mice in which GR were conditionally disrupted in the bone marrow monocytes/osteoclast lineage (Kim et al. 2006). These authors showed that glucocorticoid signalling via GR inhibits proliferation of osteoclastogenic cells, apoptosis of mature osteoclasts and osteoclast function in vitro and in vivo, by altering the activity rather than the number of osteoclasts. Furthermore, they suggested that glucocorticoid-induced bone mass reduction is not only mediated by directly inhibiting osteoblasts, but also by inhibiting osteoclast activity, which in turn disrupts the remodelling cycle and suppresses osteoblast activity (Kim et al. 2007).

### Metabolic syndrome and macrophage GR

Metabolic syndrome is defined by a cluster of risk factors including obesity, insulin resistance and hypertension that ultimately lead to chronic metabolic disorders such as type 2 diabetes and cardiovascular disease. These pathologies are associated with a state of chronic, low-grade inflammation in white adipose tissue that is characterised by increased cytokine production and macrophage infiltration (Dandona et al. 2004, Hotamisligil 2006, Shoelson et al. 2006). Increased macrophage recruitment in adipose tissue has been demonstrated in obese animal models and humans, although their functional role in promoting metabolic dysfunction is unclear (Weisberg et al. 2003, Xu et al. 2003).

Glucocorticoids play a role in adipocyte maturation, function and distribution. Differentiating adipocytes produce increasing levels of the enzyme 11βHSD1 to convert inactive cortisone into cortisol, in turn amplifying local glucocorticoid levels (Seckl et al. 2004). Selective over-expression of 11βHSD1 in adipose tissue produces a metabolic syndrome phenotype characterised by visceral obesity, insulin resistance and dyslipidemia (Masuzaki et al. 2001, 2003). In contrast, systemic deletion of the enzyme protects against metabolic dysfunction following high fat feeding (Seckl et al. 2004). In terms of macrophages, local amplification of glucocorticoids by 11βHSD1 has been shown to increase macrophage phagocytic activity (Gilmour et al. 2006). Furthermore, in vitro 11βHSD1 blockade in macrophages reduces mRNA levels and secretion of IL-1β, TNF-α and monocyte chemoattractant protein 1 (MCP-1), suggesting that intracellular amplification of glucocorticoids by 11βHSD1 may contribute to the pro-inflammatory state of activated macrophages (Ishii et al. 2007). Collectively the above findings implicate macrophages, GR and 11βHSD1 in the pro-inflammatory phenotype of metabolic dysfunction, although further studies are required to determine the mechanisms underlying the connection between inflammation and metabolic syndrome.

### Glucocorticoid-induced hypertension and macrophages

Glucocorticoid-induced elevation in blood pressure is well documented in humans and experimental animals (Grunfeld 1990, Whitworth 1994); in particular Cush-}

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MRs, macrophages and disease

The classical effects of MR signalling are in epithelial tissues where activation promotes sodium reabsorption and potassium secretion (Davis 1960). As mentioned above, MR are also present in non-epithelial cells/tissues such as the hippocampus (McEwen & Wallach 1973), macrophages (Armanini et al. 1985a, Lim et al. 2007), VSMC, placenta and heart (Pearce & Funder 1988, Lombes et al. 1992). In the absence of the aldosterone specificity-conferring enzyme 11βHSD2, MR are overwhelmingly occupied by glucocorticoids. Signalling via non-epithelial MR, whether bound by glucocorticoids or aldosterone, appears to play a significant role in extra-renal pathological events.

Administration of MR antagonists, eplerenone or spironolactone, reduces macrophage accumulation in a number of disease models, including peritoneal fibrosis (Nishimura et al. 2008), myocardial infarction (Fraccarollo et al. 2008) and both angiotensin II- (Neves et al. 2005) and aldosterone-induced vascular inflammation and damage (Rocha et al. 2002, Young et al. 2003). In terms of specific macrophage MR activity, aldosterone treatment enhances expression of the inflammatory and oxidative stress markers, p22phox and PAI-1 in isolated human monocytes (Calo et al. 2004). These data suggest a role for specific macrophage MR signalling in mediating the pro-inflammatory and oxidative phenotype characteristic of many pathologies.

Atherosclerosis and macrophage MR

As noted above, macrophages play a critical role in atherosclerosis. In apolipoprotein E-deficient (ApoE-deficient) mice, a model of atherosclerosis, MR blockade decreases oxidative stress and inflammation (Suzuki et al. 2006). More specifically, aldosterone treatment increases oxidative stress in macrophages derived from ApoE-deficient mice (Keidar et al. 2004). This study showed that macrophages isolated from aldosterone treated mice have an enhanced ability to oxidize LDL and increased superoxide anion production; these effects were reduced by MR blockade. Aldosterone activation of MR in endothelial cells specifically modulates ICAM-1 expression and promotes leukocyte adhesion (Caprio et al. 2008), supporting a role for MR signalling in endothelial cells in the initial stages of atherosclerosis. Together, these findings highlight a key role for both macrophage and endothelial MR signalling in atherosclerosis.

MR-mediated inflammation and tissue remodelling

Activation of an MR, in the context of inappropriate sodium status, has major cardiovascular pathophysiological consequences including hypertension and cardiac fibrosis. Recent studies have suggested that inflammation may be a key mechanism translating MR signalling into cardiac and vascular remodelling. Mineralocorticoid/salt-induced pathology is characterised by an early vascular inflammatory response with elevated cardiac expression of inflammatory mediators such as monocytes/macrophages, MCP-1 and adhesion molecules (ICAM-1 and VCAM-1), prior to the onset of collagen deposition (Rocha et al. 2000, 2002, Fujisawa et al. 2001, Young et al. 2003). Furthermore, mineralocorticoid/salt treatment is also associated with increased monocyte/macrophage infiltration and expression of inflammatory markers such as osteopontin, MCP-1, IL-6 and IL-1β in the kidney (Blasi et al. 2003). MR antagonism prevents inflammation-induced peritoneal fibrosis and reduces macrophage infiltration and expression of MCP-1, TGF-β, PAI-1 and Sgk-1 (Nishimura et al. 2008).

In cardiac and renal disease models, reduced monocyte/macrophage infiltration is accompanied by a substantial reduction in fibrosis. While MR signalling and macrophages appear to be important in inflammatory conditions in the kidney and heart, the role of macrophage MR signalling in mediating these responses is unknown. To address this question our laboratory has generated macrophage MR-null mice using the Cre-lox system and compared their responses to administration of mineralocorticoid/salt with those of wild-type mice. Selective deletion of MR from macrophages protected against mineralocorticoid-mediated cardiac fibrosis, despite normal macrophage recruitment (Rickard et al. unpublished data). In contrast, reduced tissue remodelling in osteopontin-null mice and MCP-1-null mice is accompanied by decreased macrophage infiltration (Persy et al. 2003, Dewald et al. 2005). In the macrophage MR-null mice, the reduced cardiac damage appears to be due to altered macrophage function following loss of MR signalling from these cells. In contrast, the sustained macrophage recruitment is thought to be consequence of MR signalling in other cell types in the cardiovascular system following mineralocorticoid/salt treatment.

Mineralocorticoid-induced hypertension and macrophages

Chronic inappropriate activation of an MR is well recognised to promote hypertension. Excess plasma mineralocorticoids promote sodium and water retention and potassium secretion leading to the maintenance of blood pressure at a higher set point (Kuhlmann et al. 1939). MR antagonists have been shown to be effective anti-hypertensive agents in essential hypertension, suggesting a role for MR signalling in hypertension (Connell et al. 2008). A number of experimental models...
of hypertension have demonstrated increased macrophage recruitment in the heart (Rocha et al. 2002, Rickard et al. 2007), brain (Tagami & Yamori 1988) and kidneys (Rodriguez-Iiturbe et al. 2001). Anti-hypertensive agents reduce both macrophage recruitment and blood pressure in these models, although the correlation between inflammation and blood pressure control has not been widely explored. Furthermore, immunosuppressive agents also reduce blood pressure (Norman et al. 1985), suggesting that immune cells including macrophages may be involved in the initiation of hypertension in addition to their role in its progression. Elevated expression of junctional adhesion molecule-1, glycoprotein 39 precursor and MCP-1, and increased leukocyte adhesion, has been shown in the nucleus tractus solitarius in both pre-hypertensive and adult SHR, further supporting a role for inflammation in the initiation of hypertension (Waki et al. 2007, 2008). Finally, our laboratory has recently demonstrated that specific deletion of the MR from macrophages mitigates hypertension in the mineralocorticoid/salt model (Rickard et al. unpublished data). Together, the above findings suggest that the inflammatory component of blood pressure elevation may be more important than previously thought.

Conclusion

Corticosteroid hormones acting via GR and MR have important, well-described roles in normal physiology and pathophysiology. It is now evident that macrophage GR and MR signalling contributes significantly to disease. Whether the GR and MR promote inflammation, remodelling or resolution of inflammation appears to depend upon multiple factors including ligand concentration, cellular context and their relative expression level within monocytes/macrophages. Given the side effects of GR agonists in the treatment of inflammatory disease, and of MR antagonists in the treatment of cardiovascular disease, the development of tissue selective compounds, perhaps specifically targeted at inflammatory cells, would be of significant clinical benefit.

Declaration of interest

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