PKs transfer a phosphate from ATP to the side-chain hydroxyl group of a serine, threonine or tyrosine residue of a substrate protein. This in turn can alter that protein’s function; modulating fundamental cellular processes including, metabolism, transcription, growth, division, differentiation, motility and survival. PKs are subdivided into families based on homology. One such group are the stress-activated kinases, which as the name suggests, are activated in response to cellular stresses such as toxins, cytokines, mechanical deformation and osmotic stress. Members include the p38 MAPK family, which is composed of α, β, γ and δ, isoforms which are encoded by separate genes. These kinases transduce extracellular signals and coordinate the cellular responses needed for adaptation and survival. However, in cardiovascular and other disease states, these same systems can trigger maladaptive responses that aggravate, rather than alleviate, the disease. This situation is analogous to adrenergic, angiotensin and aldosterone signalling in heart failure, where inhibition is beneficial despite the importance of these hormones to homeostasis. The question is whether similar benefits could accrue from p38 inhibition? In this review, we will discuss the structure and function of p38, the history of p38 inhibitors and their use in preclinical studies. Finally, we will summarize the results of recent cardiovascular clinical trials with p38 inhibitors.

LINKED ARTICLES
This article is part of a themed section on Conditioning the Heart – Pathways to Translation. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-8

Abbreviations
hsCRP, high-sensitivity CRP; PCI, percutaneous coronary intervention; TAB1, TGF-β-activated binding protein 1; TAK1, TGF-β-activated kinase 1
Tables of Links

| TARGETS | Enzymes* |
|---------|----------|
| Cytokines | Glycogen synthase kinase |
| TNF-α | MKK3 |
| GPCRsb | MKK6 |
| A2A receptors | MAPKAP2 |
| Ion channelsc | p38 MAPK |
| Cx43 | PKA |
| Transportserc | TAK1 |

| LIGANDS |
|---------|
| ACh | NADPH |
| AEA | Nitric oxide (NO) |
| Angiotesin II | SB202190 |
| ATP | SB203580 |
| CD40 ligand | SCH58261 |
| HU210 | TxA2 |
| LPS | U46619 |

*These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson et al., 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (Alexander et al., 2013a,b,c,d,e).

p38 isoforms

The four isoforms of p38 are structurally homologous. The α and β isoforms share 74% sequence identity while the γ and δ isoforms are ~70% similar to each other and ~60% homologous to the α isoform. Significantly, the isoforms have different sensitivities to p38 inhibitors such as SB203580 (Eyers et al., 1998). These inhibitors compete with ATP and tend to inhibit p38α and p38β, over the p38γ and p38δ isoforms, because of small differences in side-chain length of their gatekeeper residues (Eyers et al., 1998). This feature can be used to create inhibitor resistant p38α and p38β knock-in mouse lines (O’Keefe et al., 2007). This strategy implicated p38α in both lethal myocardial ischaemic injury and cardioprotection following preconditioning (Kumphune et al., 2010; Sicard et al., 2010). Similarly, the p38α knockout mouse dies at embryonal day 10.5–11.5 (Adams et al., 2000; Allen et al., 2000) while ablation of the other isoforms, individually or p38α and p38δ in combination, results in live mice without major abnormalities (Beardmore et al., 2005; Sabio et al., 2005). In addition, the loss of one isoform does not alter the expression or activity of the other isoforms. While p38α and p38β are ubiquitously expressed, the other isoforms possess a tissue-specific expression pattern, perhaps indicative of their different roles. p38γ has been implicated in myoblast differentiation and is enriched in skeletal muscle (Lechner et al., 1996). p38δ is predominantly expressed in lungs, kidney, testis, spleen, pancreas and small intestine (Kumar et al., 1997). The subcellular distribution of the isoforms may also indicate divergent roles, as p38α and p38β can be found in the cytosol and the nucleus while p38γ isoform is nuclear located in response to chronic pressure overload (Dingar et al., 2010). This theme can be further elaborated on by the substrates identified to be phosphorylated by the different isoforms. While most substrates such as myelin basic protein and activating transcription factor 2 are phosphorylated by multiple isoforms, some substrates appear to be uniquely phosphorylated by a particular isoform. The MAPK activated PK 2 (MAPKAPK2) has been shown in vitro to be phosphor-

Activation and structure of p38α MAPK

The structure of p38α is similar to that of other kinases with a smaller N-terminal lobe mainly composed of β-pleated sheets and a C-terminal lobe of α helices. The ATP-binding pocket/catalytic cleft is located at the juncture of these two lobes. In addition, an activation loop, with a number of conserved motifs, lies adjacent to the ATP-binding pocket. The activity of p38 is indicated by the dual phosphorylation of the TGY motif in the activation loop of the kinase (Taylor and Kornev, 2011). Upstream kinases, termed MAPK kinases (MKK), such as MKK3, MKK6, phosphorylate these residues (Figure 1) (Derijard et al., 1995; Raingeaud et al., 1996). The specific activator of the p38 isoform depends on the stimulus and the cell type (Remy et al., 2010). In turn, the MKKs are phosphorylated by upstream MAPK kinase kinases such as the TGF-β activated PK (TAK1). This hierarchical three-tiered level of activation is termed the canonical activation
pathway. These components mediate the transduction of an environmental stress signal to elicit a response by the cell.

The conformation of the non-active kinase differs from that of the active kinase. In the inactive kinase, the activation loop occupies and sterically blocks the peptide-binding channel. The two lobes of the kinase are misaligned and therefore two residues, Lys53 of the N-terminal lobe and Asp168 of the C-terminal lobe, are not in close proximity. An active kinase requires cooperation between these key residues to bind the α phosphate group and ribose group of ATP and the companion Mg$^{2+}$ ions (Wilson et al., 1996; Gum et al., 1998).

Activation of the kinase via phosphorylation occurs in a highly ordered mechanism and results in the movement of the activation loop away from the peptide-binding channel (Humphreys et al., 2013). It is thought this movement exerts a ‘crank-handle effect’ on the tertiary structure of the kinase inducing the movement of the two lobes resulting in the alignment of Lys53 and Asp168 facilitating ATP binding. Overall these conformational changes result in the formation of the catalytic ‘hydrophobic spine’ of the kinase (Taylor and Kornev, 2011). In summary, the transphosphorylation of the TGY motif of the activation loop of the kinase, by upstream kinases, results in significant alterations in the conformation of the kinase to facilitate active intramolecular phosphotransfer (De Nicola et al., 2013). This has been observed with the α isoform only (De Nicola et al., 2013). Interestingly, this scaffold-induced mode of activation was shown to be the mechanism through which p38 is activated during myocardial ischaemia (Kumphune et al., 2010). This indicates a significantly different mechanism than the more usual transactivation by MKK3/6 upstream kinases and may only occur under a limited number of circumstances.

**Importance of p38 in biology**

There are numerous lines of evidence indicating the importance of p38 in biology.

The *Saccharomyces cerevisiae* homologue of p38α is the pheromone and stress-sensing *Hog1* gene (Bell et al., 2001). The high-osmolarity glycerol pathway has numerous functions in yeast including modulation of cell cycle progression at several stages and regulation of the biogenesis and export of mRNAs of stress-responsive genes (Duch et al., 2012; Regot et al., 2013). Similar to the mammalian system, *Hog1* is a component in a hierarchical activation cascade and is activated by phosphorylation of its activation loop motif by the upstream kinases, Pbs2 (Brewster et al., 1993). Another conserved feature is the mode of activation through autophosphorylation, in this case by binding to the scaffold protein, TAK1 binding protein 1 (TAB1) (Figure 1) (Ge et al., 2002; Tanno et al., 2003; Li et al., 2005). This binding results in activation of the kinase independent of upstream kinases through autophosphorylation. The binding of TAB1 to p38 resulted in significant alterations in the conformation of the kinase to facilitate active intramolecular phosphotransfer (De Nicola et al., 2013). This has been observed with the α isoform only (De Nicola et al., 2013). Interestingly, this scaffold-induced mode of activation was shown to be the mechanism through which p38 is activated during myocardial ischaemia (Kumphune et al., 2010). This indicates a significantly different mechanism than the more usual transactivation by MKK3/6 upstream kinases and may only occur under a limited number of circumstances.

![Figure 1](image_url)

**Figure 1**

The major pathways of p38 activation. In the canonical activation pathway, TAK1 undergoes autophosphorylation (grey arrow) upon binding to TAB1 (left portion of figure). This activated kinase in turn activates MKK3 or MKK6 by a transphosphorylation reaction (black arrow). Subsequently, the activated MKK phosphorylates p38α. p38α can also be activated by a more direct TAB1-mediated mechanism (right portion of figure). Binding of TAB1 to p38α induces autophosphorylation of p38α and activation of the kinase. TAB1 is also a substrate of p38α and phosphorylated TAB1 is a negative regulator of TAK1 autophosphorylation.
Inhibitor design

Designing a specific p38 kinase inhibitor has proven to be challenging for a number of reasons. The 500 known mammalian PKs share a highly homologous ATP-binding site. Therefore, finding unique target areas for enabling the design of selective inhibitors has been difficult. For this reason, many kinase inhibitors have been shown to inhibit multiple kinase in addition to the original target (Bain et al., 2003). Nevertheless, the prominent role of p38α in cytokine production resulted in early success with inhibitors for use in arthritis, inflammatory bowel disease and chronic obstructive pulmonary disease (Lee et al., 1994). A number of crystal structures of p38α and p38β in the presence or absence of a bound inhibitor are available in the protein databases and they provide a resource for future inhibitor design (Wilson et al., 1996; Wang et al., 1997; Bellon et al., 1999; Chang et al., 2002). The type I inhibitors binds in an ATP competitive manner. As discussed previously, the gatekeeper residue is a key determinant in the binding of the inhibitor and therefore the different isoforms have varied sensitivities to these types of inhibitors (Wilson et al., 1996; Gum et al., 1998). Members of this class also include SB 203580 and losmapimod. A challenge for efficient inhibition with type I inhibitors is that they must compete with physiological concentrations of ATP. To overcome these challenges, second types of inhibitors, which bind to the ATP-binding site and an adjacent region have been designed. Members of these type II inhibitors include BIRB 796 and VX747. BIRB 796 has been shown to inhibit all isoforms of the kinase (Kuma et al., 2005). These inhibitors make use of a pocket vacated by the DFG motif, which lies in the N-terminal portion of the activation loop. When the side chains of Asp and Phe are in the ‘out’ position, the kinase is inactive. BIRB796 binds to the ‘DFG out’ stabilizing it and preventing the kinase changing to an active conformation (Pargellis et al., 2002; Kuma et al., 2005). BIRB796 displays a slow onset of action as the DFG out conformer is rare. Despite the improved characteristics of type II inhibitors over type I inhibitors, translation to clinical studies has not achieved vastly superior results. Therefore, additional scaffolds and modes of inhibition have been sought. One such method has been termed type III inhibitors or allosteric kinase inhibitors. Exploiting less-conserved areas of the kinase distinct from the ATP-binding site offers the opportunity to develop unique inhibitors for a particular kinase with high selectivity because of the divergence of sequence in these less-conserved regions of the kinase.

Alternative sites for inhibitor binding distal to the ATP-binding site have been used by Murga and colleagues (Willemen et al., 2014). As discussed previously, they have shown that phosphorylation of the docking groove of p38 affects partner binding with reduced activation and of the kinase. A candidate inhibitor was designed to target this docking groove with some success. Targeting substrates that depend on this docking groove interaction would enable some modulation of p38 activity without global inhibition. While this approach of targeting p38 is attractive, the benefit would be increased if circumstance-specific inhibition could be achieved. Wang and colleagues have also adopted an alternative design strategy in targeting the TAB1-mediated autophosphorylation (Wang et al., 2013). A cell-permeable peptide was designed to inhibit p38 activity via the non-canonical autophosphorylation activation mechanism. We also had success with this strategy of disrupting p38α and TAB1 interaction, although the sequence targets were different (De Nicola et al., 2013). A detailed structural description of the binding of TAB1 to p38α was used to disrupt the interaction at key contact residues with a cell-permeable peptide preventing binding and therefore p38α autophosphorylation in vitro and in vivo. This strategy indicates that an inhibitor that could also disrupt this interaction would be advantageous in preventing p38α activation during myocardial ischaemia while maintaining its other cellular roles.

Cardioprotection and p38

As summarized earlier, p38 is expressed ubiquitously and implicated in numerous and diverse pathologies. Therefore, perhaps not surprisingly, it plays an important role in many components of the cascade that leads from a healthy vasculature to myocardial infarction and heart failure. Rather than attempt to summarize these studies in the text, we have created a table (see Table 1) that highlights relevant publications addressing the role of p38 in this cascade from endothelial dysfunction → atherosclerosis → platelet activation/ thrombosis → myocardial infarction → post-infarction remodelling, contractile dysfunction, arrhythmia and heart failure. As can be seen from the table, generally, p38 is activated by, and aggravates, cardiovascular pathologies. From an evolutionary standpoint, this seems counterintuitive as selection pressure has preserved p38 in yeast and man. However, the benefits of this kinase are apparent under the ‘ischaemic preconditioning’ heading within Table 1. Ischaemic preconditioning describes the paradoxical increase in resistance to lethal ischaemic injury that follows a brief, sublethal, period of ischaemia. Despite the fact that p38 is activated by, and contributes to, lethal ischaemic injury; it also is involved in triggering the protection of ischaemic preconditioning. Some authors have linked these effects; with transient p38 activation during short preconditioning cycles of ischaemia being responsible for diminished p38 activation during subsequent lethal more prolonged ischaemia (Nagarkatti and Sha’afi, 1998; Marais et al., 2001; Sanada et al., 2001) These opposing roles for p38 make it difficult to predict what may happen in a clinical trial of p38 inhibition.

The findings that p38 activation aggravates many components of atherothrombosis and myocardial infarction, have laid the foundation for recent and relevant clinical trial activity. The companies with agents under investigation
Table 1
Summary of studies examining the role of p38 in the biological processes associated with cardiovascular disease and the effects of the use of p38 inhibitors on these processes

| Biological process | Study | p38 manipulation | Observed effect |
|--------------------|-------|------------------|-----------------|
| Endothelial dysfunction | Choi et al., 2014 | Mouse mesenteric arteries and isolated endothelial cells, subjected to TNF-α in the presence of SB203580. | TNF-α-activated p38 and impaired endothelium-dependent relaxation to ACh; effect inhibited by SB203580. |
|                     | Kassan et al., 2014 | Isolated coronary arterioles, mesenteric and femoral arteries from type 2 diabetic mice subjected to PEG-SOD and NADPH oxidase p22 (phox) siRNA. | Impaired endothelium-dependent relaxation and elevated p38 phosphorylation was reduced after treatment with ROS scavenger or by p22 (phox) down-regulation. |
|                     | Thakur et al., 2010 | Mouse thoracic aortic ring preparation and cultured endothelial cells subjected to AngII, SCH58261 A2A R antagonist and A2AR siRNA. | A2AR is involved in the regulation of endothelial ROS production by Nox2 and requires p38 MAPK signalling. Blockade or knockdown of A2AR inhibited p38 activation, inhibiting AngII effects on EC ROS production. |
|                     | Rajesh et al., 2010 | Cultured primary HCAEC subjected to cannabinoid receptor agonists (AEA and HU210) in the presence of SB203580. | Inhibition of p38 by SB203580 attenuated AEA and HU210-induced cell death. |
|                     | Bao et al., 2007 | Rat aortic ring preparations and MAPKAPK2 (−/−) mouse hearts subjected to treatment with AngII in the presence of SB239063. | AngII-induced hypertension and p38 phosphorylation was attenuated in MAPKAPK2 null mice. AngII-induced vascular dysfunction, superoxide anion production and cardiac remodelling were attenuated in aortic rings by SB239063. |
|                     | Riad et al., 2007 | In vivo rat model of diabetes by administration of streptozotocin in the presence of SB239063. | SB239063 attenuated diabetes-induced p38 phosphorylation and improved impairments in LV and endothelial function. |
|                     | Widder et al., 2004 | Rat aortic ring preparation of hearts subjected to ischaemia by LAD ligation in the presence of SB239063. | SB239063 preserved endothelium-dependent vasodilation, reduced vascular superoxide anion production and p38 and MAPKAPK2 phosphorylation. |
|                     | Ju et al., 2003 | Spontaneously hypertensive rat and cultured HUVECs exposed to TNF-α and LPS in the presence of SB239063. | TNF-α and LPS-induced p38 activation and ICAM expression in HUVECs and in aortas from hypertensive rats. All inhibited by SB239063 and endothelial dysfunction restored in aortic rings. |
| Atherosclerosis | Cheriyan et al., 2011 | Randomized controlled trial of losmapimod (p38α/β MAPK inhibitor) on untreated hypercholesterolaemic patients. Endothelial function assessed by venous occlusion plethysmography. | Losmapimod attenuated inflammation by inhibiting p38 activity and improved NO-mediated vasodilation. |
|                     | Seeger et al., 2010 | MicroCT and planimetry of mouse ApoE−/− aortas and isolated bone marrow-derived mononuclear cells. | Proangiogenic activation of p38 inhibited by SB and resulted in reduction of atherosclerotic lesion size, inflammation and increased vasculogenic cells. |
|                     | Sun et al., 2009 | Isolated cultured macrophages from ApoE−/−, Npc1−/− mice exposed to free cholesterol. | Lipid accumulation in atherosclerotic plaques activates p38 and its targets Ctsk, S100a8, MMP8 and MMP14 via TLR signalling. |
|                     | Proctor et al., 2008 | Transgenic mice expressing inducible SMC-specific DN-p38α subjected to carotid injury and ectopic expression of DN-p38α in cultured rat SMC, in presence of SB202190 or siRNA. | Mice expressing DN-p38α resistant to carotid injury and reduced p38 activity. SB202190 or siRNA blocked PDGF-induced p38 activation and cell proliferation, in A10 SMC. |
|                     | Morris et al., 2008 | In vivo MRI assessment of ApoE−/− mouse aortas with AngII and SB239063. | SB239063 inhibited p38 activity, inflammation in atherosclerotic plaques and phagocytic activity of macrophages and diminished aortic root lesion size. |
| Biological process | Study | p38 manipulation | Observed effect |
|--------------------|-------|------------------|----------------|
| Platelet activation | Alrehani et al., 2013 | HEK293 cells overexpressing αᵦβ₃, and protein phosphate 1 knockdown by siRNA. | p38 negatively regulated PP1α-mediated adhesion to immobilized fibrinogen and fibrin clot retraction, which were abrogated in the presence of p38 inhibitor, SB203580. |
|                    | Yacoub et al., 2010 | Isolated human and CD40−/+ mouse platelets treated with soluble CD40 ligand (sCD40L). | Pro-thrombotic inflammatory CD40L enhanced platelet activation and aggregation via Rac1 and p38. SB203580, prevented p38 phosphorylation and impaired the effects of sCD40L on platelet P-selectin expression and aggregation. |
|                    | Rauch et al., 2007 | Mice subjected to pressure and endothelial cells exposed to human αPL. | Fibrinogen-induced migration and mediated the activation of p38 in an ICAM-1-dependent manner. SB203580 inhibited p38 activity and cell migration. |
|                    | Shen et al., 2007 | Isolated human platelets activated by exposure to collagen in the presence of resveratrol. | Resveratrol inhibited collagen-induced platelet aggregation, p38 MAPK phosphorylation and thromboxane A₂ formation. |
|                    | Vega-Ostertag et al., 2007 | Pressure-perfused CD1 mouse aorta, isolated platelets and cultured endothelial cells exposed to human αPL. | aPL-induced thrombosis and EC activation in vivo and aPL-induced monocyte adherence to HUVEC in vitro, were all attenuated by SB203580. |
|                    | Brooks et al., 2007 | Isolated adult horse platelets and leukocytes following exposure to LPS in vivo and in vitro respectively. | LPS infusion enhanced p38 phosphorylation and TxA₂ production in platelets and leukocytes. SB203580 attenuated LPS-induced TxA₂ release in platelets. |
|                    | Sakurai et al., 2004 | p38α+/− mice subjected to FeCl₃-induced carotid injury model of thrombus formation. | Time to thrombotic occlusion was prolonged in p38α+/− mice and U46619-induced aggregatory response in platelets was impaired with poor binding to fibrinogen. |
| MI                 | Gray et al., 2011 | Administration of GlcNAc-coated SB239063 in rat hearts subjected to regional ischaemia-reperfusion. | GlcNAc-decorated particles loaded with the p38 inhibitor SB239063 reduced apoptotic events and infarct size and improved acute cardiac function. |
|                    | Kumphune et al., 2010 | Drug-resistant-p38α mouse hearts subjected to global ischaemia in the presence of SB203580. | p38α is the dominant active isoform during myocardial ischaemia that contributes to infarction |
|                    | Sy et al., 2008 | PCADK-mediated delivery of SB239063 in rat hearts subjected to regional ischaemia. | Inhibition of p38 by SB239063 improved cardiac function following MI. |
|                    | Kaiser et al., 2004 | Transgenic mice expressing DN-p38 and DN-MKK6, subjected to regional ischaemia by LAD ligation and ectopic expression in cultured rat neonatal cardiac myocytes and transgenic mice. | p38 functions as a pro-death signalling effector in both cultured myocytes as well as the intact heart. |
|                    | Tanno et al., 2003 | MKK3-knockout mouse hearts and H9c2 expressing drug-resistant-p38α subjected to global ischaemia-reperfusion or SI, respectively, in the presence of SB203580. | Absence of MKK3 had no significant effect on post-ischaemic infarction or p38 activation. p38 activation is SB203580-sensitive and TAB1-associated and contributes to myocardial injury. |
|                    | Otsu et al., 2003 | Regional ischaemia-reperfusion by coronary occlusion in p38α−/+ mouse hearts. | Ischaemia-reperfusion induces activation of p38 leading to injury. Reduction of p38α expression results in protection. |
|                    | Martin et al., 2001 | Ectopic expression of drug-resistant-p38α in cultured rat adult cardiac myocytes and H9c2 myoblasts, subjected to simulated ischaemia. | Cardioprotective effect of SB203580 is through specific inhibition of p38α. |
Table 1
Continued

| Biological process | Study | p38 manipulation | Observed effect |
|--------------------|-------|------------------|-----------------|
| Myocardial remodelling | Koivisto et al., 2011 | Ectopic co-expression of p38α or p38β with CA-MKK3 or MKK6 in cultured rat neonatal cardiac myocytes. | p38β increased mRNA levels of pro-hypertrophic genes, BNP and ANF, whereas p38α augmented the expression of the pro-fibrotic genes, CTGF, bFGF and MMP9. |
| LV remodelling | Lau et al., 2007 | 14-3-3(+/-) mouse coronary artery occlusion in the presence of SB202190 and cultured adult mouse cardiac myocytes. | SB202190 increased p38 activation and increased survival in 14-3-3(+/-)-mice, which developed pathological ventricular remodelling with increased cardiomyocyte apoptosis post MI. |
| | Engel et al., 2006 | Rat hearts subjected to regional ischaemia by LAD Ligation in the presence of FGF-2 and SB203580. | Administration of SB203580 and FGF-2, post infarction resulted in cardiomyocyte mitosis, reduction of scarring and rescued heart function. |
| | Tenhunen et al., 2006 | Rat hearts subjected to LAD ligation and adenosine co-transfection of p38α and MKK3b. | p38 activation reduced infarct size, improved ejection fraction, fractional shortening, decreased LV diameter and increased capillary density and reduced apoptosis and fibrosis. |
| | Ren et al., 2005 | Transgenic mice expressing cardiac-specific DN-p38α, subjected to regional ischaemia by LAD ligation. | DN-p38α mice had increased ventricular systolic function 7 days post MI and reduced infarct size, cardiomyocyte apoptosis and Bcl-Xl deamination. |
| | Nishida et al., 2004 | Cardiac-specific p38α conditional KO mice subjected to TAC and cultured isolated neonatal cardiac myocytes. | p38α plays a critical role in cardiomyocyte survival in response to pressure with no effect on hypertrophic growth, despite down-regulation of p38α. |
| | See et al., 2004 | Rat hearts subjected to regional ischaemia by LAD ligation in the presence of RWJ-67657. | RWJ-67657 treatment following myocardial ischaemia had beneficial effects on LV remodelling and dysfunction. |
| | Andrews et al., 2003 | Ectopic expression of CA-MKK6 in cultured rat neonatal cardiac myocytes. | MKK6-mediated activation of p38 prolonged contractile calcium transient, reduced SERCA2 expression, resulting in increased diastolic [Ca2+] and enhanced NFAT activity. |
| | Braz et al., 2003 | Transgenic mice expressing cardiac-specific DN mutants of p38α, MKK3 or MKK6, subjected to abdominal aortic banding or AngII, ISO or PE. | p38 signalling antagonizes the hypertrophic growth response of the adult heart through a dominant mechanism involving crosstalk with the calcineurin–NFAT signalling pathway. |
| Myocardial contractile dysfunction | Wang et al., 2012 | Langendorff-perfused HHcy–/+ mouse hearts subjected to global ischaemia-reperfusion and cultured rat adult cardiac myocytes subjected to Hcy in the presence of SB203580. | Ischaemia-reperfusion resulted in activation of p38 and in impaired cardiac relaxation, contractile function and increased apoptosis that was markedly exaggerated in HHcy mice and cardiomyocytes. SB203580 prevented the Hcy-induced changes. |
| | Yin et al., 2008 | Rat hearts subjected to ischaemia by LAD ligation in the presence of SB203580. | SB203580 suppressed myocardial fibrosis and LV remodelling, attenuated p38 activation and expression of TNF-α, α-SMA and collagen I. |
| Biological process | Study | p38 manipulation | Observed effect |
|--------------------|-------|------------------|----------------|
|                    | Vahebi et al., 2007 | Isolated skinned cardiac muscle fibre bundles from transgenic mice expressing DN-p38α and CA-MKK6. | Activation of p38α directly depresses sarcomeric function by decreased phosphorylation of α-tropomyosin, which is reversed by overexpression of DN-p38α. |
|                    | Bellahcene et al., 2006 | Langendorff-perfused MKK3-knockout mouse hearts and isolated cardiac myocytes subjected to TNF-α. | TNF-α induces contractile depression by activating p38 in the intact heart and in isolated cardiac myocytes in an MKK3-dependent and SB203580-sensitive manner. |
| Arrhythmia          | Lu et al., 2013 | Whole cell patch-clamp analysis on isolated rabbit PV cardiomyocytes, treated with collagen. | Collagen modulated PV electrical activity with changes in AP morphology, increased triggered and spontaneous activity. SB203580 ameliorated collagen-induced p38 phosphorylation and arrhythmogenesis. |
|                    | De Jong et al., 2013 | Cultured isolated rat neonatal cardiac myocytes, subjected to mechanical stretch. | Stretch induced p38 phosphorylation and hypertrophy-related changes including increased cell diameter, reinduction of the foetal gene programme and cell death. |
|                    | Surinkaew et al., 2013 | Rat hearts subjected to LAD ligation in the presence of SB203580. | SB203580 decreased ischaemia-induced ventricular tachycardia/ventricular fibrillation incidence and heat shock protein 27 phosphorylation, and increased connexin 43 phosphorylation. |
| Ischaemic preconditioning | Tang et al., 2011 | Rat hearts subjected to LAD ligation, Langendorff perfusion and cultured, isolated adult ventricular myocytes in the presence of SB203580 or auranofin. | Expression of ventricular K(+) channels is redox regulated and impairment of the Trx system post-MI heart contributes to I(to) remodelling through sustained activation of apoptosis signal-regulating kinase-1-JNK-p38 signalling. |
|                    | Sicard et al., 2010 | Drug-resistant-p38α or p38β mouse hearts subjected to ischaemic preconditioning in the presence of SB203580. | SB203580 attenuated activity of p38 and its substrates and abolished infarct size reduction by IP in WT and drug-resistant-p38β hearts but not in drug-resistant-p38α hearts. p38α is necessary for ischaemic preconditioning. |
|                    | Schulz et al., 2003 | In vivo pig model of ischaemic preconditioning by LAD ligation (regional ischaemia). | IP increases co-localization of p38 with Cx43 and preserves phosphorylation of Cx43 during ischaemia. Inhibition of p38MAPK by SB203580 attenuated IP-induced IS-reduction and led to dephosphorylation of Cx43 that correlates with the propagation of I/R injury. |
|                    | Sanada et al., 2001 | In vivo canine model of ischaemic preconditioning by coronary occlusion (regional ischaemia). | p38 MAPK activation during IP mainly mediates the cardioprotection followed by HSP27 phosphorylation/translocation. SB203580 treatment during IP blunted the infarct size limitation by IP and attenuated phosphorylation/translocation of HSP27. |
|                    | Marais et al., 2001 | Langendorff-perfused rat hearts subjected to global ischaemia-reperfusion and cultured rat neonatal cardiac myocytes | p38 was activated during preconditioning and attenuated during subsequent ischaemia. Non-preconditioned hearts had elevated p38 activation in comparison. p38 inhibition by SB203580 during ischaemia and reperfusion is cardioprotective. |
|                    | Saurin et al., 2000 | Ectopic expression p38α or p38β isoforms in cultured rat neonatal cardiac myocytes subjected to simulated ischaemia in the presence of SB203580. | Inhibition of p38 during prolonged ischaemia reduced injury and contributed to preconditioning-induced cardioprotection. p38α and p38β differentially activated or deactivated respectively, during ischaemia. |
In terms of safety, there was no statistically significant increase in liver enzymes, but alanine transaminase elevations three times above the upper limit of normal were very common in the losmapimod groups. In addition, there was a statistically significant, but very small (−2 μmol·L\(^{-1}\)), increase in serum creatinine at 12 weeks in the losmapimod groups. Study drug discontinuation was twice as frequent among patients receiving losmapimod than among those receiving placebo. This observation was of borderline significance and the cause was unknown. Serious adverse events were very similar across groups.

In terms of efficacy, the principal end point, hsCRP concentration at 12 weeks, did not differ between groups. However, by 12 weeks, CRP had returned to baseline, so a discernable difference was unlikely. However, at earlier time-points, both hsCRP and IL-6 concentrations were significantly lower in the losmapimod groups. Biomarkers of necrosis (creatine kinase and troponin I) did not differ by treatment group. However, in an MRI substudy (92 patients with paired MRI scans) losmapimod was associated with significant improvements in ejection fraction and left ventricular end-diastolic and end-systolic volumes, and also a significant reduction in discharge brain natriuretic peptide in the main cohort. Collectively, these signals hint of a benefit with losmapimod and p38 inhibition in the setting of myocardial infarction despite the fact that SOLSTICE failed to meet its primary efficacy end points. Moreover, this suggestion of benefit was observed despite a losmapimod oral dosing regime that probably only achieved a maximum of 50% inhibition of p38 at the time of peak effect which occurred 4 h after oral dosing (Barbour et al., 2013). This time–concentration profile matched the timing of PCI in SOLSTICE, where approximately 60% of patients in losmapimod and placebo groups underwent PCI at a median of about 5 h after randomization.

The potential efficacy signal in SOLSTICE has encouraged a much larger phase 3 trial with clinical end points. LATITUDE-TIMI 60 (Losmapimod to inhibit p38 MAPK as a therapeutic target and modify outcomes after an acute coronary syndrome–thrombolysis in myocardial infarction 60; NCT02145468) will involve approximately 26 000

### Table 1

| Biological process | Study | p38 manipulation | Observed effect |
|--------------------|-------|------------------|-----------------|
| Nagarkatti et al., 1998 | Simulated ischaemia in rat myoblast cell line H9c2 | Inhibition of p38 before the onset of SI blocks preconditioning, but is protective during prolonged ischaemia. |
| Weinbrenner et al., 1997 | Langendorff-perfused rabbit hearts subjected to global ischaemia-reperfusion in presence of SB203580 | Inhibition of p38 activation abolished protection in preconditioned hearts and cardiomyocytes. |
| Tong et al., 2000 | Langendorff-perfused rat hearts, preconditioned with or without SB202190 | Preconditioning induced uptake of glucose was abrogated by the presence of SB202190. |

**Table 1 Continued**

| Biological process | Study | p38 manipulation | Observed effect |
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include GlaxoSmithKline (losmapimod, various trials), Array-BioPharma (ARRY-371797, NCT02057341) and Bristol-Myers Squibb (BMS-582949, NCT00570752), although the latter programme seems inactive. GlaxoSmithKline has the most active programme with a number of phase 1 trials suggesting a potential benefit in patients with early (Cheriyan et al., 2011) and late (Sarov-Blat et al., 2010; Elkhawad et al., 2012) atherosclerosis. We have summarized these trials previously (Martin et al., 2012), and here will concentrate on the recently published SOLSTICE trial (Newby et al., 2014). SOLSTICE was a GlaxoSmithKline-sponsored phase 2 study performed by the Duke Clinical Research Institute (NCT00910962) (Newby et al., 2014). This study enrolled 535 patients with non-ST elevation myocardial infarction who were randomized in a 3:3:2 ratio to oral losmapimod (two active programme seems inactive. GlaxoSmithKline has the most

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patients worldwide with myocardial infarction and have a study design similar to SOLSTICE, but without the 15 mg loading group (i.e. losmapimod 7.5 mg twice per day vs. placebo). The primary efficacy end point is a composite of major adverse cardiovascular events comprising cardiovascular death, reinfarction or recurrent myocardial ischaemia requiring urgent revascularization at 12 weeks. The main inclusion criterion is type 1 myocardial infarction (an atherosclerotic plaque rupture event) and will include presentation electrocardiograms with both ST and no ST elevation. Study medication will be continued for 12 weeks and follow-up for 24 weeks. It is anticipated that the study will be completed in December 2018.

**Interaction with other signalling pathways**

The p38 MAPK pathway is integrated with multiple other signalling pathways at different levels. For example, p38α has been shown to phosphorylate glycogen synthase kinase 3 and the Wnt signalling pathways (Bikkavilli et al., 2008; Thornton et al., 2008). p38α is part of numerous feedback mechanisms. A recent paper has also indicated p38α may participate in multiprotein complex hypertrophy mediated by a PKA anchoring protein, in combination with M KK3. In addition, p38α is located within a number of feedback loops. These studies reflect p38α as a signalling nexus of multiple signalling pathways the specifics of which are continuing to be elucidated. The multiple pathways also illustrate the complexity in targeting a single PK. It is clear that multiple related pathways may be affected if a single protein is inhibited. Therefore, the ideal inhibition of a kinase requires selective, temporally discrete and circumstance-specific inhibition.

Global inhibition of p38α can lead to detrimental effects to the homeostasis of the organism. Pharmacological inhibition of p38α has been achieved, but the results of the preclinical trials, although encouraging, have not translated to clinical trials with a similar level of success. Therefore, a more selective targeted inhibition of the kinase that could ameliorate the detrimental consequence of activation of the kinase while maintaining the essential functions of the kinase would be highly desirable. The recent studies indicating the TAB1-induced activation of the kinase that mediates myocardial damage would be an eligible target for inhibition and that would allow the circumstance-specific mode of activation to be exploited.

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