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Selective p38α Inhibitors Clinically Evaluated for the Treatment of Chronic Inflammatory Disorders

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Introduction

p38α is a member of the well characterized mitogen activated protein (MAP[a]) kinase family of serine/threonine protein kinases. p38α is widely expressed in endothelial, immune, and inflammatory cells and plays a central role in the regulation of proinflammatory cytokine production including TNF-α, IL-1β, and IL-6.[1,2] Selective blockade of any one of these cytokines with biologic agents has proven efficacious for inflammatory diseases including rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease.[3,4]

The p38 subfamily of MAP kinases includes four isoforms (p38α, p38β, p38γ, and p38δ) that are encoded by separate genes. Analysis of differential tissue expression and activation of these isoforms in synovial tissue extracted from RA patients has suggested that the p38α isoform is overactivated within inflamed tissue and may be a preferred target for intervention in the disease.[5−7] This expectation has prompted a huge investment by the pharmaceutical industry in the development of p38α inhibitors as potential oral disease modifying anti-rheumatic drugs (DMARDs).[8,9]

This Perspective will summarize key learnings from over 15 years of industrial experience with p38α as a drug target, with a focus on the rational design of highly selective small molecule inhibitors, followed by a discussion of data for examples **1**−**11** that have entered into or are recruiting for phase 2 clinical studies (summarized in Table 1). To date, these results have been disappointing. We conclude that p38α inhibition alone is unlikely to be a successful strategy toward treating chronic inflammatory disorders. Others have also concluded that "the era of optimism surrounding the use of p38 MAPK inhibition for the treatment of RA is over".[10]

Kinome Selectivity

It is generally believed that, for the treatment of chronic diseases like rheumatoid arthritis, small molecule kinase inhibitors have to be highly selective in order to avoid unwanted effects caused by off-target kinase inhibition. Highly selective inhibitors are also required for unambiguous pharmacological evaluation of drug targets. This requirement for high kinase selectivity is a high hurdle, considering the fact that the human genome contains over 500 protein kinases sharing a high degree of sequence homology.[11] Nevertheless, selective kinase inhibition is possible and has been demonstrated for several targets, with exceptional examples including the CSF1R inhibitor 5-[[3-methoxy-4-[(4-methoxyphenyl) methoxy]phenyl]methyl]-2,4-pyrimidinediamine (GW2580)[12,13] and the dual EGFR/ERBB2 inhibitor 4-[[3-chloro-4-(3-fluorobenzyloxy)-phenyl]amino]-6-[5-[[(2-methanesulfonylethyl)amino]methyl]-furan-2-yl]quinazoline (lapatinib).[13,14]

First and second generation p38α inhibitors like 4-[5-(4-fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-1*H*-imidazol-4-yl]-pyridine (SB203580)[15] and **4**[16] were not highly selective against other human kinases, complicating the interpretation of their disclosed results.[13] Multiple reviews summarizing earlier work on p38 inhibitors have been published.[17] However, more recent "third generation" inhibitors are much improved and clearly demonstrate that selective p38 inhibition is possible. In this section, we summarize the kinome selectivity profiles of three third generation compounds for which the chemical structures and phase 2 clinical trial data are publicly available: **2**,[18] **5**,[19] and **1**.[20] The selectivity profiles of these p38α inhibitors are then discussed in the context of their binding modes and protein−ligand interactions observed by protein crystallography. We also include recently disclosed data on the p38α inhibitor **9**,[21] which appears to be highly selective although it has not been tested against as many off-target kinases as the other three examples.

All of these third generation inhibitors are highly kinase selective, with the Scios inhibitor **2** being an outstanding example (Table 2). In a panel of 321 human protein kinases, **2** binds strongly to only p38α (K_D = 0.48 nM) and its closely related isoform p38β (K_D = 15 nM). The Vertex inhibitor **5** binds to p38α (K_D = 3.7 nM) and p38β (K_D = 17 nM); in addition, **5** shows moderate binding to five other kinases. The Roche inhibitor **1** binds to p38α (K_D = 1.3 nM) and more weakly to JNK2/3 and p38β (K_D of 16/19 and 120 nM, respectively). Compound **1** additionally binds weakly to five other protein kinases. The Pfizer inhibitor **9** has been reported to inhibit p38α (K_i = 5.8 nM) and p38β (K_i = 40 nM) but no other targets out of two panels covering 58 kinases.[21]

The high degree of p38α selectivity that has been achieved with these hinge-binding, ATP-competitive inhibitors is remarkable. Notably, all four compounds share one common off-target kinase, p38β. Compound **1** has the largest window between the two p38 isoforms. Because of the high similarity between p38α and p38β (75% sequence identity), in particular

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[a]Abbreviations: ACR, American College of Rheumatology improvement criteria; COPD, chronic obstructive pulmonary disease ; CNS, central nervous system; CRP, c-reactive protein; DAS, disease activity score in joints; DMARD, disease modifying anti-rheumatic drug; GI, gastrointestinal; MAP, mitogen activated protein; MM, multiple myeloma; RA, rheumatoid arthritis.

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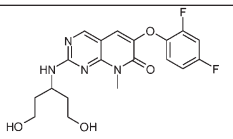
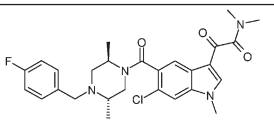
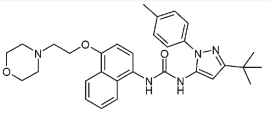
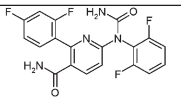
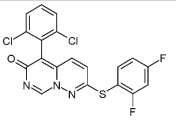
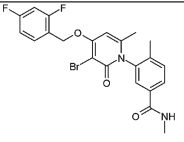
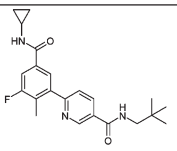
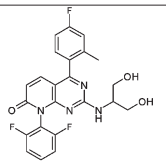
Table 1. Structures and Reported Status of the Reviewed p38α Inhibitors

p38α inhibitor	Structure	Status
Pamapimod **1**		Discontinued
Scio 469 (Talmapimod) **2**		Discontinued
BMS-582949 **3**	Not disclosed	Phase 2 for RA
BIRB-796 (Doramapimod) **4**		Discontinued
VX702 **5**		Discontinued
VX745 **6**		Discontinued
ARRY-797 **7**	Not disclosed	Phase 2 for acute inflammatory pain
ARRY-614 **8**	Not disclosed	Phase 1; enters trials for myelodysplastic syndromes June 2009
PH 797804 **9**		Phase 2 for RA, neuropathic pain Recruiting for COPD
GW-856553 (Losmapimod) **10**		Phase 2 for COPD, cardiovascular disease and depression
SB-681323 (Dilmapimod) **11**		Phase 2 for neuropathic pain

at the ATP binding site, some degree of p38β off-target activity appears unavoidable.

The p38α inhibitors **1**, **2**, **5**, and **9** achieve their high kinase selectivity by positioning ligand side chains in multiple

Table 2. Selectivity Profiles of p38α Inhibitors in Phase 2 Clinical Trials

2 (SCIO-469)	**5** (VX-702)	**1** (Pamapimod)
	p38α K_D[a] in μM	
0.00048	0.0037	0.0013
	Off-Target Kinases (K_D in μM)[a]	
P38β (0.015)	P38β (0.017)	JNK2 (0.016)
	ACVR2β (0.092)	JNK3 (0.019)
	NLK (0.16)	P38β (0.12)
	JNK3 (0.78)	RSK4β (0.15)
	JNK2 (2.6)	NLK (0.17)
	PIK4Cβ (3.3)	JNK1 (0.19)
		CSNK1ε (0.26)
		RSK3β (0.32)

[a] Compounds with > 50% inhibition at 10 μM in a 321 human kinase assay panel where followed up with K_D determination.[63] Off-target kinases with K_D < 1000-fold the p38α K_D are listed in the order of their K_D values. Selectivity profiles for **6** and **4** have previously been published.[13]

"selectivity hotspots". These hotspots are regions in or in proximity to the ATP binding site where the amino acid sequence of p38α is distinct from the majority of other human kinases. Therefore, engaging this region of the protein with the appropriate ligand interaction results in significant selectivity gain. Here, we will describe four p38α selectivity hotspots and discuss how they are addressed by the above-mentioned inhibitors. X-ray crystal structures of p38α complexed with **1** (manuscript in preparation) and **9**[21] are available. Structures of **2** and **5** bound to p38α are not available, and structures of close analogues[22,64] will be used instead to analyze their binding modes (Figure 1).

Back Pocket (T106). The back pocket is a lipophilic region that is separated from the ATP binding site by the side chain of the "gate keeper" residue. In p38α, this gate keeper is T106, which because of its small size and rotatability allows inhibitors to enter the back pocket directly from the ATP binding site.[23] About 20% of all human protein kinases share threonine as the gate keeper residue (Table 3). Interestingly, all four inhibitors described in this section fill the p38α back pocket with similar fluorinated phenyl side chains, and in all structures the gate keeper T106 side chain adopts the same conformation, which allows back pocket access (Figure 1). Presumably, occupying this hotspot is contributing to the high selectivity profiles observed for **1**, **2**, **5**, and **9**.

Hinge (G110). The N- and C-terminal lobes of protein kinases are connected by the "hinge" sequence (T106−D112 in p38α). Typically, the backbone carbonyl of hinge residue X (H107 in p38α) and the backbone NH and carbonyl of residue X + 2 (M109) are directed toward the ATP binding site and therefore available for H-bonding interactions with inhibitors. P38α, however, is able to flip the peptide bond between M109 and G110, resulting in a structural replacement of the exposed M109 backbone carbonyl by the G110 backbone NH. This peptide flip is considered energetically feasible in p38α because of the small size of the G110 side chain.[24] About 8% of all human protein kinases have glycine at the equivalent sequence position (Table 3). The inhibitor **9** binds to the p38α hinge in its peptide-flipped conformation (Figure 1d). On the basis of the crystal structures of analogues of **2** and **5** bound to p38α (Figure 1a,b), we can assume that these inhibitors also bind to the peptide-flipped hinge conformation, which is not accessible to the majority of human kinases. Consequently, addressing this selectivity hotspot improves kinome selectivity.

Front Hinge (M109−D112, Deletion). Sequence and structure alignments reveal that in about 14% of all human kinases, including p38α, one amino acid, in most cases a glycine, is deleted from the front hinge region (M109−D112 in p38α, Table 3). This results in additional space available for ligand binding in the deletion region of these kinases.[8] Analysis of the **1**, **2**, **5**, and **9** binding modes shows that all four ligands fill, at least partially, this front hinge selectivity hotspot (Figure 1).

Hydrophobic Pocket (A157). Of all amino acids that present their side chain to the ATP binding site, the one most unique to p38α is A157 (Table 3). Alanine is found at that position in only five other human protein kinases: p38β, p38γ, p38δ, and τ tubulin kinases 1 and 2. This fact has recently been discussed as a selectivity driver for a series of highly potent phthalazinine p38α inhibitors.[25] A157 forms the bottom of a hydrophobic subpocket at the C-terminal side of the ATP binding site. **1**, **2**, and **5** are all within 4 Å of the A157 methyl side chain, suggesting that kinases with larger residues at this position are likely to bind these ligands with lower affinity. Enzymatic experiments using site-directed mutant variants as performed with first generation p38α inhibitors[26] will be required to assess the contribution of the A157 selectivity hotspot toward the kinome profiles of **1**, **2**, and **5**.

It is remarkable that three independently discovered p38α inhibitor classes as distinct as **1**, **2**, and **5** all achieve kinome selectivity by interacting with the same three selectivity hotspots: back pocket, front hinge, and hydrophobic pocket. Compounds **2** and **5** have in common that they additionally trigger the Gly110 hinge flip and therefore address all four p38α selectivity hotspots described in this manuscript. The recently described **9** fills the back pocket, occupies the front hinge region, and binds to the peptide-flipped hinge conformation, but it does not take full advantage of the unique hydrophobic pocket. It is also noteworthy that the four inhibitors described in this paragraph are all DFG-in binders, and yet their kinome selectivity profiles are superior to the profile of the DFG-out binding p38α inhibitor **4**.[13] This observation does not support the perception that higher selectivity can be more easily achieved with kinase inhibitors that bind to the DFG-out conformation. Finally, **1**, **2**, **5**, and **9** demonstrate that the design of highly kinase selective, druglike p38α inhibitors is possible.

Reported Phase 2 Clinical Trials

Multiple p38α inhibitors have advanced into clinical trials. In this section, we summarize the results from p38α inhibitors for which phase 2 data have been disclosed along with phase 1 data for more recent examples reported to be clinically active in phase 2 studies (Table 1).

1 (Pamapimod).[20] Compound **1** is a potent and highly selective inhibitor of phosphorylated p38α (IC_{50} = 14 nM). The preclinical pharmacology of **1** has recently been published in detail and is briefly summarized below.[20] Compound **1** inhibited the production of TNFα by human monocytic cells (THP-1, IC_{50} = 25 nM) and inhibited production of IL-1β and TNFα in human whole blood (IC_{50} = 100 nM IL-1β). In a variety of in vivo preclinical models, **1** inhibited TNFα, IL-1β, and IL-6 production. In acute PK/PD models in rodents, **1** inhibited LPS induced TNFα production in rodents (ED_{50} = 0.3 mg/kg rats; ED_{50} = 1.0 mg/kg mice) as well as TNFα-induced IL-6

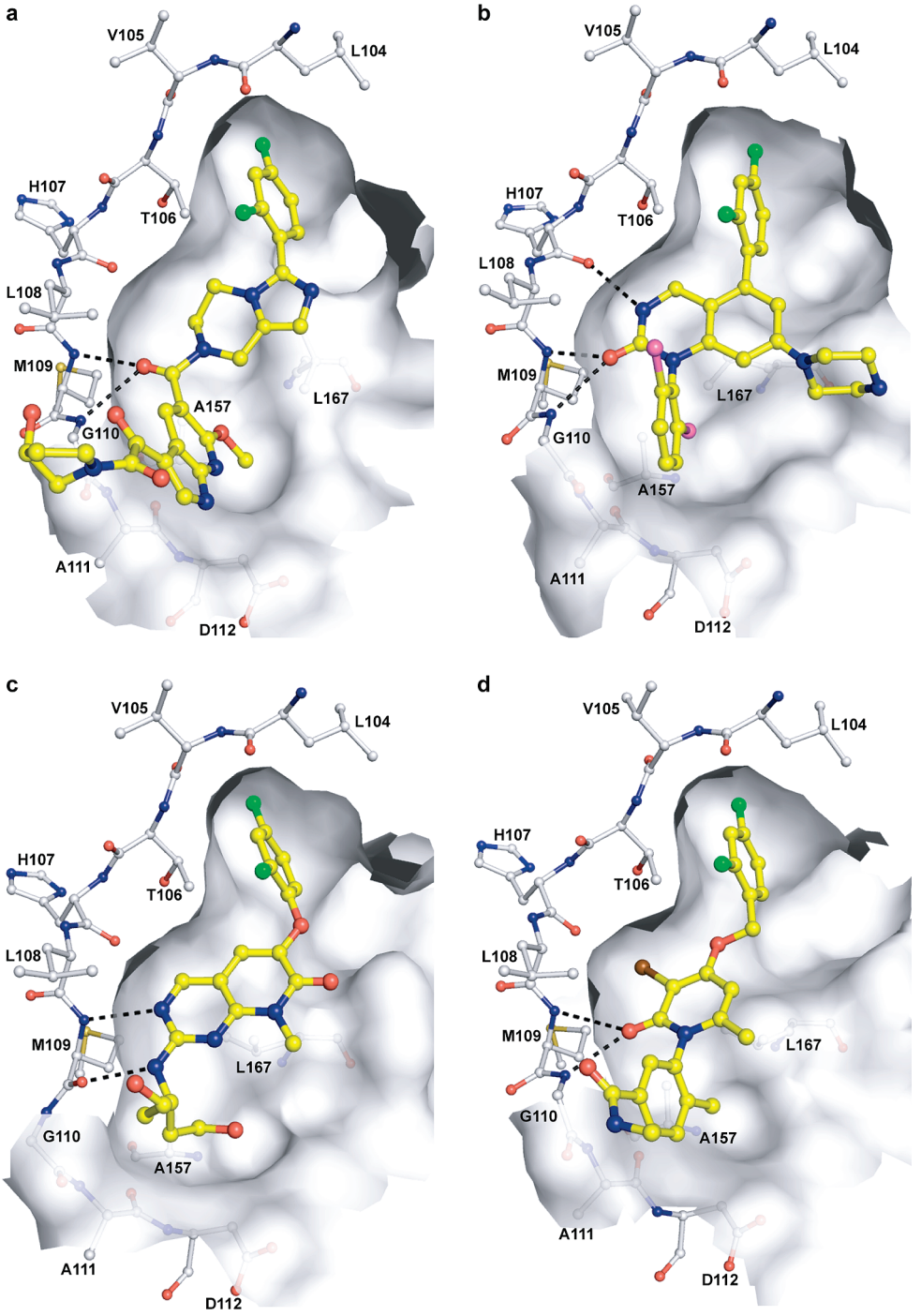


Figure 1. X-ray crystal structures: ball-and-stick representations of p38α (gray) complexed with inhibitors (yellow). Hydrogen bonds are indicated by black dashes. Water molecules are not displayed. (a) Heterobicyclic analogue of **2** (PDB accession number 2QD9, 1.7 Å resolution).[22] (b) Heterobicyclic analogue of **5** (PDB code 1M7Q, 2.4 Å).[64] (c) **1** (PDB code 3FLW, 2.1 Å, manuscript in preparation). (d) **9** (PDB code 3HLL, 1.95 Å).[21]

Table 3. Human Kinome Frequency of Amino Acids That Determine Selectivity Hotspots

	T106	G110	M109−D112, del	A157
no. kinases	97	41	72	6

production (ED_{50} = 1.1 mg/kg) and LPS-induced IL-6 production (ED_{50} = 0.5 mg/kg). In a chronic in vivo model of inflammation in rodents, **1** was efficacious at blocking murine collagen induced arthritis (ED_{50} = 100 mg/kg), and in a rat model of hyperalgesia, **1** increased tolerance to pressure in a dose-dependent manner (ED_{50} = 20 mg/kg), suggesting that p38α inhibition may also reduce the pain associated with inflammation.

In the first of two phase 2 trials, **1** was evaluated for safety and efficacy in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis (204 patients). The primary efficacy end point was the proportion of patients reaching the American College of Rheumatology 20% improvement criteria (ACR20) at 12 weeks. Secondary end points of the trial included ACR50 and ACR70 response rates and changes from baseline in the Disease Activity Score in 28 joints (DAS28). After 12 weeks of dosing, fewer patients

taking **1** had an ACR20 response (23%, 18%, and 31% in the 50, 150, and 300 mg q.d. groups, respectively) compared with patients taking methotrexate (45%). For each of the eight ACR core component criteria, the methotrexate group showed greater improvement from baseline compared with the three dose groups on compound **1**. Similar results were observed with the secondary end points of the trial with the conclusion that **1** was not as effective as methotrexate in the treatment of active RA. In the 300 mg dose group, a drop in C-reactive protein (CRP) levels from baseline was observed but was not sustained after 2 weeks of dosing, suggesting that compensatory inflammatory pathways may have been up-regulated in response to prolonged p38α inhibition.

Compound **1** was generally well tolerated across the dose groups with the most common adverse events, characterized as mild, included infections, skin disorders, and dizziness. The incidence of these adverse events increased with dosage levels, and they occurred with greater frequency in **1**-treated patients than in methotrexate-treated patients.[27]

The efficacy and safety of **1** was also evaluated in a phase 2 trial in patients with active rheumatoid arthritis receiving stable methotrexate therapy (328 patients). The primary efficacy end point was the proportion of patients reaching ACR20 at 12 weeks. Secondary end points of the trial included ACR50 and ACR70 response rates and changes from baseline in DAS28. After 12 weeks of dosing, the percentage of patients taking **1** with ACR20 response (40%, 40%, 42%, 31%, and 43% in the 25 and 75 mg b.i.d. and the 50, 150, and 300 mg q.d. groups, respectively) was similar or slightly higher compared with placebo (34%); the differences were not statistically significant. Secondary efficacy end points showed similar results. CRP levels showed modest decreases after 1 week in all **1** dose groups, which were not sustained through the fourth week of the study. Compound **1** was generally well tolerated; the most common adverse events were characterized as mild and included infections, gastrointestinal (GI) disorders, dizziness, and skin disorders. More adverse events were observed at higher doses of **1** compared to placebo.

On the basis of the results of these phase 2 trials, Roche has discontinued development of **1** for RA.[28]

6 (VX-745).[29] Vertex reported the first clinical "proof-of-principle" of p38α-targeting with **6**, a potent, selective inhibitor based on a pyridazinopyridone scaffold. Compound **6** is potent against p38α (IC_{50} = 10 nM) and blocks TNFα production in LPS-stimulated HWB in vitro (IC_{50} = 177 nM).[29]

In a phase 2 clinical trial involving 59 patients, administration of **6** at 250 mg b.i.d. resulted in ACR20 scores at 12 weeks for 43% of subjects, compared to only 8% of patients in a placebo control arm. The drug was generally well-tolerated, with the most significant adverse event being elevation in liver transaminases, which was reversible upon discontinuation of the drug. Other adverse events were GI-related.[30]

These initially disclosed results were encouraging and still appear to be the best reported for a p38α inhibitor with respect to efficacy; however, less information has been disclosed on **6** than for other late-stage p38α inhibitors, such as **1** and **5**. In September 2001, Vertex announced the discontinuation of **6** because of adverse effects noted in the central nervous system (CNS) for one of two animal species receiving high doses.[31] The blood levels associated with the neurological effects were approximately 10 times higher than those seen in their human clinical trials up to that point. Subsequent meeting reports detailed that CNS toxicity had been observed in dogs after 6 months of dosing.[32] The company further noted that **6** crosses the blood−brain barrier but that follow-up compounds such as **5** do not.

5 (VX-702).[19] Compound **5** is a ring-opened analogue of **6** that does not cross the blood−brain barrier and presumably has a decreased probability of causing CNS-related adverse events. Preclinical in vitro potencies for this compound have not been reported, but Vertex reported potency in ex vivo assays from phase 1 tolerability studies; **5** inhibited IL-6, IL-1β, and TNFα production in LPS-primed blood with IC_{50} values of 59, 122, and 99 ng/mL, respectively.[33]

Vertex recently reported detailed results from two 12-week randomized, double-blind, placebo-controlled phase 2 RA studies. The first study, labeled VeRA, investigated 5 and 10 mg b.i.d. dosing for patients with previous inadequate responses to DMARDs (313 patients total). The drug was generally well-tolerated, and the number of adverse events was similar to placebo, the most serious being infections, which were overall more frequent for the arms treated with **5** than for those treated with placebo (three serious infections in the 10 mg group and two in the 5 mg group, compared to zero in the placebo group). However, the efficacy seen in this study was unimpressive, with few patients achieving ACR50 (11−13% vs 9% placebo) and ACR70 responses (2% for both doses vs 3% for placebo). DAS28 improvements were also modest.[34]

The second study, labeled Study 304, investigated 10 mg q.d. and 10 mg twice-weekly dosing for subjects also on methotrexate (117 patients total). The 10 mg q.d. arm showed similar drug levels to the 10 mg b.i.d. arm of the VeRA study, while the twice-weekly arm showed much lower trough levels of drug. The results for Study 304 were similar to those for VeRA, although with an overall lower level of adverse advents. There were two serious infections (one from each dosed arm) but also two serious infections in the placebo arm. There was one additional serious adverse event, a gastric ulcer perforation in the 10 mg q.d. group. There were very few ACR50 and 70 responses with no dose-response trends.[34]

Across both studies, there were no clinically significant elevations of liver enzymes and no dropouts due to elevations in liver enzymes. There were also no reported CNS effects. There were dose-dependent, reversible increases in QtcF intervals but no significant cardiac-related adverse events. For both studies, the authors observed a significant decrease in CRP and other biomarkers within the first week of dosing, but this decrease reversed during week 2 and levels were back to baseline by week 12. The study authors' conclusion is unfortunately very similar to others presented in this review: "... opportunities to achieve meaningful, sustained suppression of the chronic inflammation seen in RA through inhibition of p38 MAPK may be limited."[34]

2 (SCIO-469).[18] Scios has developed a series of small-molecule, orally available, p38α inhibitors, with **2** (SCIO-469) going furthest in clinical evaluation. Compound **2** is highly potent against p38α with a reported IC_{50} of 9 nM. The compound inhibited LPS-induced TNFα release from human whole blood ($IC_{50} \approx 0.3$ μM) and inhibited LPS-induced IL-1β release from human PBMCs in a dose-dependent manner.[35]

A phase 1 study investigated the safety, pharmacodynamics, and pharmacokinetics of **2** in healthy volunteers.[36,37] A phase II study to determine the analgesic efficacy of **2** in acute postsurgical dental pain has also been completed (263 subjects). Inflammatory mediators and cytokines such as

TNFα and IL-1 are known to contribute to peripheral and central sensitization and to modulate acute, chronic, and neuropathic pain; therefore, inhibition of p38 could be beneficial in managing pain.[38,39] All patients treated with **2** showed a significantly longer time to rescue medication compared with placebo.[40] This study represents the first clinical demonstration of acute analgesic effects by inhibition of p38α.

Scios is also the first company to disclose clinical exploration of p38α inhibitors in multiple myeloma (MM). The rationale to study p38 inhibitors in this disease is that blockade of p38 kinase will inhibit the production of tumor-promoting factors such as IL-6 and VEGF in the multiple myeloma bone marrow microenvironment and enhance the ability of proteasome inhibitors such as bortezomib to induce the apoptosis of MM cells.[41] In 2006, Scios released the results of a phase II trial of **2** as monotherapy (60 mg po t.i.d.) or in combination with bortezomib, which showed stable disease in 24% of the 28 patients receiving the drug in monotherapy for patients with replased refractory MM.[42] To our knowledge, no follow-on studies have since been reported.

In October 2008, Scios reported the results for a randomized, double-blinded, placebo-controlled phase 2 study of **2** at different oral dosing regimens (100 mg extended release (ER) q.d., 30 mg immediate release (IR) t.i.d., or 60 mg immediate release t.i.d.). The study, performed in patients with active RA not receiving methotrexate, was for 12 weeks followed by a 12-week extension phase (302 subjects). ACR20 and ACR50 response rates between active groups vs placebo group at week 12 did not reach statistical significance: ACR20 and ACR50 rates were 24% and 9% for placebo, 23% and 8% for 100 mg ER, 26% and 8% for 30 mg IR, 33% and 16% for 60 mg IR. There was a trend of improvement in ACR20 and decrease in CRP levels observed at week 2 that did not persist at week 12. Reported notable adverse events included rash and ALT elevations. Scios made the following conclusions from the study: there were no significant differences in ACR20 responses at week 12 (primary end point) between **2** and placebo; declines in CRP during early treatment did not persist to week 12 and did not correlate with stable **2** plasma levels; the transient effect of **2** on CRP suggests a complex role of p38α MAPK in inflammation; the 60 mg immediate release t.i.d. regimen showed a dose-limiting toxicity of ALT elevations with 24-week dosing.[43]

4 (BIRB 796).[44] Compound **4** was one of the first p38α molecules that progressed into late stage clinical trials. It has IC_{50} values of 21 and 960 nM for the inhibition of TNFα from LPS stimulated human PBMC and human whole blood, respectively.

Details of phase 1 trials for compound **4** have already been summarized.[8] Results for phase 2 trials of compound **4** at different doses (5, 10, 20, and 30 mg b.i.d.) in RA have not been disclosed to our knowledge.

In 2006, Boehringer Ingelheim reported the results for a randomized, double-blinded, placebo-controlled phase 2 study of **4** at different oral dosing regimens (10, 20, 30, and 60 mg b.i.d.) in 354 patients with active Crohn's disease.[45] The primary end point of the study was clinical remission defined as CDAI (Crohn's disease activity index) of <150 after 8 weeks. There was no statistically significant difference in remission rates between all treatment groups for non-Russian patients including placebo, ranging from 20.0% to 23.9%. There appeared to be inverse dose response for Russian patients for remission rates: 64.3% for placebo, 41.2% for 30 mg dose group, and 41.9% for 60 mg dose group. The difference in trial results between the Russian and non-Russian groups was described as a dramatic region effect with placebo remission rates in Russia being almost 3-fold higher than in non-Russian centers (64% vs 23%). During the study, CRP levels in Russian patients were monitored. Interestingly, similar to the observations in other trials with different p38α inhibitors, it was reported that there was a clear dose-related drop of CRP levels at week 1 (−9.0% for placebo, −25.8% for 10 mg, −36.3% for 20 mg, −37.5% for 30 mg, and −48.0% for 60 mg) but that the effect quickly disappeared at week 2. In general, **4** was well tolerated. The majority of adverse events were related to the gastrointestinal tract and most likely were related to the disease. Other potentially drug-related side effects included infections (mainly upper-respiratory tract infection), symptoms related to the musculoskeletal system, dizziness and headache, rash, and increases in liver function test.[45]

3 (BMS-582949, Structure Not Disclosed).[46] In collaboration with Pharmacopeia Drug Discovery Inc. (now Ligand Pharmaceuticals Inc.), BMS is investigating **3**, a p38α inhibitor for RA, in clinical trials. The in vitro activity of this agent has not been disclosed. A phase 1 study investigated the safety, pharmacodynamics, and pharmacokinetics of single ascending oral doses from 10 to 600 mg of **3** in healthy volunteers.[47] Compound **3** was well tolerated with only mild side effects, such as dizziness and rash. The study demonstrated dose-dependent inhibition of ex vivo LPS-induced TNFα in the two parallel studies. The 600 mg q.d. dose consistently suppressed TNFα inhibition close to 100% on both day 7 and day 28. BMS reported a second phase 1 study in subjects with stable RA receiving concomitant methotrexate, with oral doses of **3** of 30, 100, and 300 mg q.d. The most common adverse events were mild to moderate dizziness, mild upper respiratory infection, and moderate skin rash. Although no details were given, it was hinted that trends toward improving DAS28 scores were noted for the 300 mg dose group compared to lower doses and placebo.[48]

In March 2008, BMS progressed into phase 2 studies in RA with **3** given orally at 300 mg q.d. with concurrent methotrexate treatment for 12 weeks to subjects with RA having an inadequate response to methotrexate.[49] The study is ongoing, according to pipeline information from Ligand and BMS.[50,51] BMS has reportedly completed a phase II trial for **3** in patients with moderate to severe plaque psoriasis[52] and initiated a phase II trial to treat patients with atherosclerosis.[53]

7 (ARRY-797, Structure Not Disclosed).[54] Array Biopharma has entered the clinic with **7**, a highly potent and selective p38α inhibitor (enzyme $IC_{50} = 4.5$ nM) claimed to have low potential to cross the blood−brain barrier. The compound was reported to have been selective versus a panel of 220 kinases. In a phase 1 14-day safety study, the compound was generally well-tolerated, with no serious adverse events at the doses studied. The most frequently reported adverse events were dizziness, headache, and nausea. Ex vivo assays at day 14 measuring PGE-2, IL-1β, and TNFα showed dose dependent reductions in all three inflammation biomarkers.[54]

Array was until very recently recruiting patients for a phase 2 active ankylosing spondylitis study and have completed a phase 1 study assessing PK of this compound in RA patients. In a July 8, 2009, press release, Array announced

that in a phase 1b 28-day RA study, they observed only a transient inhibition of CRP production, similar to other p38 inhibitors. Array has now discontinued testing of **7** in chronic inflammatory diseases.[55] Compound **7** appears headed for pain indications, with two phase 2 studies completed on analgesic efficacy in dental patients undergoing third molar extraction. The results of the first study have been reported and showed significant improvements in pain relief scores for a 400 mg postoperative dose vs placebo, especially in the first 6 h. A second leg of the study, in which patients received a 200 mg presurgery dose and a 200 mg postsurgery dose, also showed reduced pain in the hours following surgery. The amount of pain relief roughly correlated to the plasma concentrations of drug present. No serious adverse events were reported for any leg of the study (103 patients distributed roughly evenly among the two legs and placebo), and the majority of adverse events were mild, the most common again being dizziness, headache, and nausea. The nausea and headache reports were similar to placebo; the dizziness reports were clearly drug-related.[54,56] The second study, results yet to be reported, includes a comparison to celecoxib.

8 (ARRY-614, Structure Not Disclosed).[57] Compound **8** belongs to the N1-substituted 5-aryloxyindazole class.[57] It is a potent inhibitor of p38α (enzyme $IC_{50} < 2$ nM) with limited activity against a panel of 201 kinases, including TIE-2 ($IC_{50} = 30$ nM against TIE2 activity in HUVEC cells). Thus far, the focus for this program appears to be on hematological malignancies, and patients with myelodysplastic disorders are currently recruited for a phase 1 clinical trial. In a phase 1 14 day MAD study, the compound was well tolerated, with no MTD reached after 14 d at 400 mg q.d. Ex vivo assays at day 14 measuring PGE-2, IL-1β, TNFα, and IL6 showed dose dependent reductions in all biomarkers.[58]

9 (PH-797804).[21] Some preclinical data on **9**, including its structure, have recently been released. The compound is a sterically congested pyridone that can potentially exist as one of two separable atropisomers, of which the (aS) atropisomer is responsible for potency (p38α $K_i = 5.8$ nM). The atropisomer is reported to have suitable stability for formulation work.[21]

Compound **9** showed good cellular potency (IC_{50} between 1 and 10 nM for inhibition of Hsp-27 phosphorylation in an LPS-stimulated human cell line) and cellular selectivity with respect to pathways involving JNK and ERK kinases[21] and demonstrated activity in in vivo animal models of acute and chronic inflammation.[59] Pfizer has completed various phase 2 studies on **9**, investigating efficacy and safety in neuropathic pain and in RA, but have not yet released results.

10 (Losmapimod, GW 856553).[60] Compound **10**[60] is an orally active p38 inhibitor in phase 2 development as a treatment for chronic obstructive pulmonary disease (COPD), cardiovascular disease, and depression. The compound belongs to the nicotinamide class of p38 inhibitors and has a p38α $pK_i = 8.1$ and a p38β $pK_i = 7.6$. The compound has a $pIC_{50} = 7.6$ in blocking LPS-induced TNFα production in human whole blood. The molecule is reported to be 100-fold selective against a modest panel of 67 human kinases. To our knowledge, no clinical data have been published to date with this inhibitor.

11 (Dilmapimod, SB 681323).[61] Compound **11**[61] belongs to the pyridopyrimidinone class of p38 inhibitors. Minimal data have been released to date, and the compound is reported to be in development only for neuropathic pain.[62]

Conclusions and Future Directions

The potential of p38α inhibitors to block the synthesis and release of proinflammatory cytokines formed the basis of a tremendous investment by the pharmaceutical industry into their development as therapeutics for rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosis, and other indications characterized by chronic inflammation. As a result, an impressive variety of structurally diverse inhibitors have been developed with excellent druglike properties. Most impressive is the high degree of selectivity that has been achieved despite the fact that most are ATP competitive inhibitors. What this chemically diverse set of competitive inhibitors of p38α have in common is their positioning into distinct regions in or in proximity to the ATP binding site where the amino acid sequence of p38α is distinct from the majority of other human kinases. Identification of such selectivity hotspots is an essential process to enable the successful development of highly selective ATP competitive kinase inhibitors.

Recently, it has become possible to begin a comparative analysis of results from published clinical trials with a small set of chemically distinct yet highly selective p38α inhibitors. Some clear trends have begun to emerge, and preliminary conclusions can be drawn regarding both their efficacy and safety. Unfortunately, the primary efficacy end points for four phase 2 clinical trials with p38α inhibitors in rheumatoid arthritis and for one phase 2 clinical trial in Crohn's disease were not achieved. Similarly disappointing results were reported for secondary end points from these same trials. All five trials reported a significant decrease in inflammatory biomarkers including CRP within the first weeks of dosing, but the effect was not sustained through the duration of the 12-week studies. These results suggest that a compensatory inflammatory pathway may be up-regulated in response to prolonged p38α inhibition in both RA and Crohn's patients.

While p38α inhibitors have been reported to be well tolerated with adverse events described as mild, a number of side effects are commonly reported. The dominant side effects include increase in infections, skin lesions, GI related adverse events, transaminase elevations, and dizziness (although the last was not reported with **5**, which apparently does not penetrate the CNS) and may be mechanism related.

While the combined results reported to date are disappointing, a number of studies are ongoing in RA as well as in other indications including respiratory, oncologic, and neuropathic pain. Results from these trials may yet identify therapeutic utility for p38α inhibitors. An open question remains whether selective inhibition of p38α is preferable versus agents that combine inhibition of p38α with other targets in parallel inflammatory signaling pathways to achieve the desired efficacy in chronic inflammatory diseases.

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Biographies

David M. Goldstein received his Ph.D. in Organic Chemistry from the Department of Chemistry at the University of Virginia in 1992. From 1992 to 1994, he completed postdoctoral studies in Organic Chemistry at the University of Pittsburgh, PA, under the direction of Prof. Peter Wipf. In 1994, he joined Syntex in Palo Alto, CA, and continued on with Roche in 1995. Currently, he is a Senior Director and the Head of Inflammation Chemistry at Roche. David's research is focused on the discovery of small

molecule inhibitors in the areas of inflammatory, respiratory, and autoimmune diseases.

Andreas Kuglstatter received his M.S. degree from the University of Frankfurt, Germany, in 1999 for the characterization of photosynthetic reaction centers under the supervision of Prof. Hartmut Michel, and a Ph.D. from the University of Cambridge, U.K., in 2003 for structural analysis of RNA−protein complexes under the supervision of Dr. Kiyoshi Nagai. After 2 years as a Postdoctoral Fellow at F. Hoffmann-La Roche in Basel, Switzerland, he joined Roche Palo Alto, CA, where he has been head of protein crystallography since 2007.

Yan Lou graduated from the University of Science and Technology of China in 1998. After receiving his Ph.D. in 2002 from Dartmouth College, NH, under the supervision of Prof. David M. Lemal, he joined Prof. E. J. Corey's group at Harvard University, MA, and studied a novel class of chiral Rh(II) catalysts for enantioselective reactions of diazo compounds. In 2005, he joined Roche Palo Alto as a medicinal chemist and worked on different projects in the inflammation therapeutic area, including p38α projects. He is currently the lead chemist of an anti-inflammation project in the lead optimization stage at Roche Palo Alto.

Michael J. Soth received his Ph.D. in Organic Chemistry in 1999 from University of California—Irvine under the direction of Prof. James Nowick and completed postdoctoral studies with Prof. Peter Wipf at the University of Pittsburgh, PA, in 2001. Since 2001, he has worked as a medicinal chemist at Roche Palo Alto and is currently a chemistry team leader.

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