

**INCYTE CORPORATION**



**CCR2 ANTAGONIST PROGRAM**

***Orally-Administered Therapeutics for  
Inflammation-Driven Diseases***

**As of June 2006**



## Therapeutic Rationale

Inflammation has long been recognized as the primary pathogenic mechanism in classic autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. Increasingly, however, inflammation is being implicated as a major component in highly prevalent, chronic diseases that were not traditionally regarded as inflammatory, such as atherosclerosis and insulin resistance. A safe, non-immunosuppressive treatment that abrogates the chronic inflammatory process thus has the potential to deliver significant therapeutic benefit across a broad range of major disorders.

The chemokine receptor CCR2 plays a central role in the establishment and maintenance of chronic inflammatory processes. CCR2 and its ligands (the macrophage chemoattractant proteins, primarily MCP-1) represent a critical signaling pathway responsible for the recruitment of peripheral blood monocytes to sites of immune-mediated inflammation, where they become inflammatory macrophages. Inflammatory macrophages are believed to orchestrate the establishment and maintenance of numerous chronic inflammatory states by producing (1) pro-inflammatory mediators (and clinically validated therapeutic targets) such as  $\text{TNF}\alpha$  and  $\text{IL-1}\beta$  that perpetuate and exacerbate the disease process, (2) matrix metalloproteases that degrade extracellular matrix and thus are responsible for the local tissue and joint destruction that ensues, and (3) chemoattractant proteins, most notably MCP-1, which perpetuates the influx of inflammatory blood monocytes, leading to chronic local inflammation.

Several lines of evidence, derived in large measure from studies of knockout mice deficient in either CCR2 or MCP-1, support the view that this receptor/ligand pair represent the primary chemokine signaling pathway for macrophage recruitment in chronic inflammation. CCR2 ligands are potent chemoattractants for peripheral blood monocytes. In addition, these ligands are produced locally at sites of inflammation in both experimental models of disease and clinical samples. CCR2 knockout mice show a marked impairment of macrophage influx into sites of inflammation in a range of animal models. Strikingly, CCR2 knockout mice are less susceptible to the development of inflammatory diseases, including experimental autoimmune encephalomyelitis (a model of multiple sclerosis), atherosclerosis, insulin resistance, and inflammatory bowel disease. Equally important, the CCR2 knockout mice develop normally, have a normal distribution of resident tissue macrophages (lung macrophages and hepatic Kupffer cells), and intact humoral and cellular immune responses. This unique profile suggests that CCR2 antagonism will allow the selective reduction of excessive, chronic inflammation without concomitant immune suppression.

Early in our CCR2 program, we explored this hypothesis in greater detail by examining the effect of administering Incyte proprietary CCR2 antagonists in a variety of preclinical models. As described below, we found that blockade of the CCR2/MCP-1 axis in normal (wild type) animals through administration of a selective, rodent-active, small molecule CCR2 antagonist, INCB3344, resulted in significant attenuation of the signs



and symptoms of disease in preclinical animal models of rheumatoid arthritis, multiple sclerosis, diabetes, and atherosclerosis. It is worth pointing out that INCB3344 represents a critical tool in the discovery process because selective antagonists of human CCR2 are often not potent antagonists of the rodent receptor. Finally, it is important to note that while CCR2 antagonism by INCB3344 inhibited immune-mediated inflammation in these disease models, the capacity to generate humoral and T cell-mediated immune responses to new antigens was not impacted, supporting the view that CCR2 antagonists represent potent anti-inflammatory agents that do not result in immunosuppression.

### ***Potential Therapeutic Indications***

In the following discussion, we will summarize the evidence supporting the role of macrophages in general, and of CCR2 signaling in particular, in the following disease processes, as well as provide some of the results we have obtained with Incyte's rodent-active CCR2 antagonist INCB3344 in preclinical models of these diseases:

- Rheumatoid Arthritis
- Multiple Sclerosis
- Diabetes
- Atherosclerosis

### **Rheumatoid Arthritis**

Macrophages and macrophage-like cells constitute up to 80% of the inflamed rheumatoid synovial lining, and are responsible for 85% of the production of the proinflammatory cytokines  $TNF\alpha$  and  $IL-1\beta$ . These inflammatory macrophages are also a major source of CXCL13, the primary B-cell attractant chemokine.

A number of clinical studies have generated evidence relating the level of macrophage burden to clinical outcome:

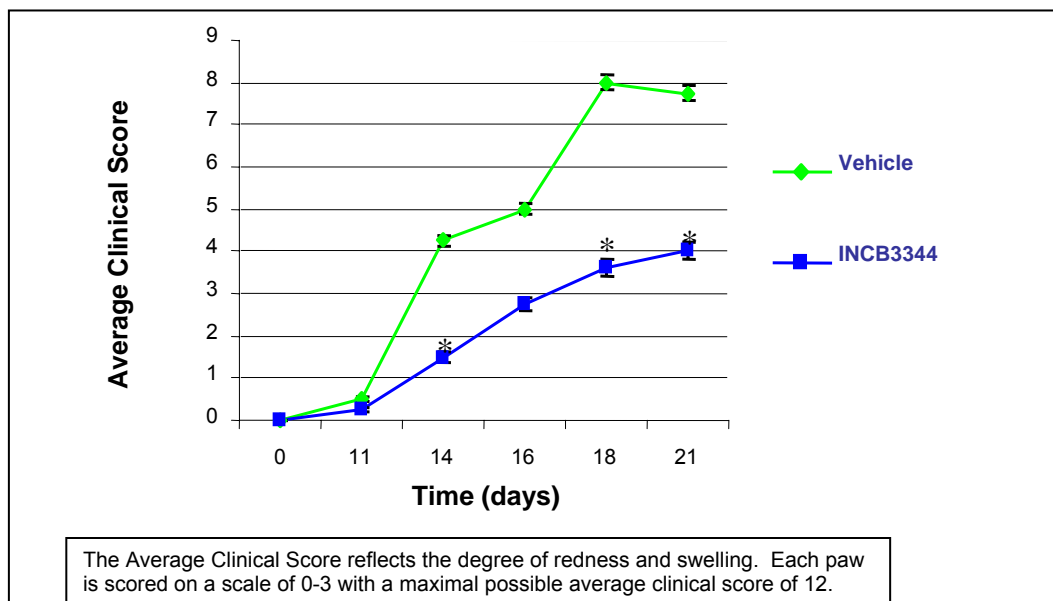
- (1) A correlation has been demonstrated between radiologic outcome and synovial sublining macrophage counts, while the level of other cell types was not similarly correlated<sup>1</sup>.
- (2) Reduction of synovial macrophage density has been correlated to the level of clinical improvement, both in the course of DMARD treatment<sup>2</sup> and after anti-TNF therapy<sup>3</sup>.

Preclinical disease model evidence supporting the potential therapeutic role of CCR2 antagonism in rheumatoid arthritis includes the following:



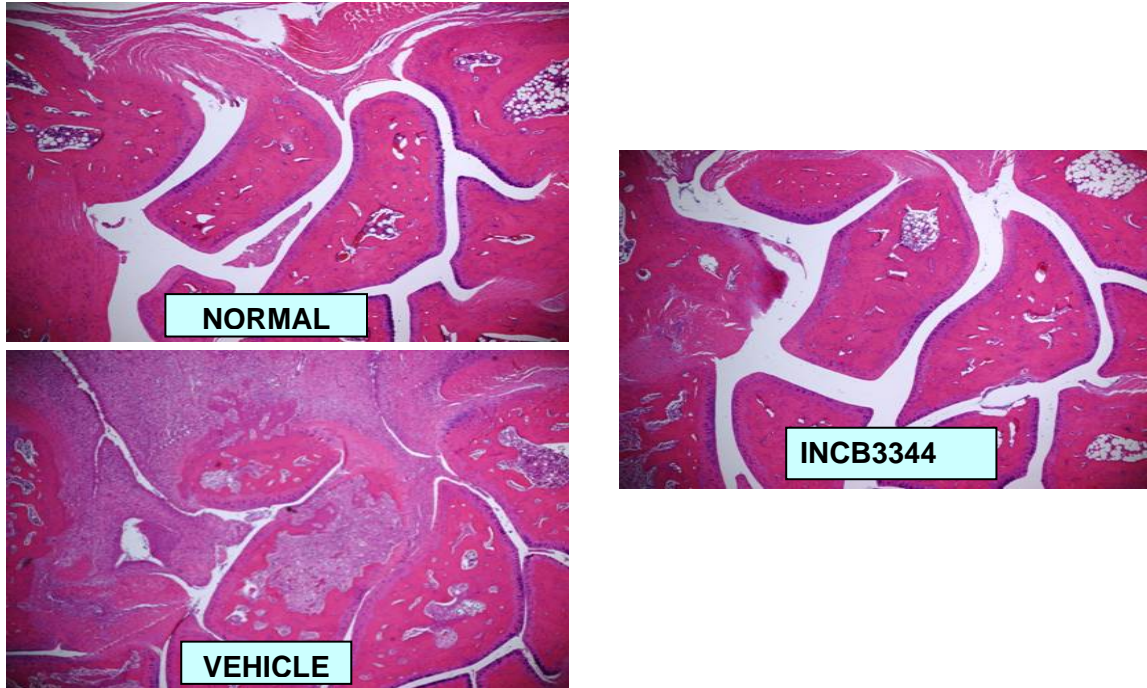
- (1) In the rodent adjuvant-induced arthritis model, inhibition of CCR2 signaling, achieved either through use of a protein antagonist (a truncated MCP-1 peptide) in mouse<sup>4</sup>, or through generation of anti-MCP-1 antibodies by DNA vaccination in rat<sup>5</sup>, results in a reduction in the incidence and severity of arthritis.
- (2) Incyte experiments have demonstrated that oral dosing of INCB3344 in both preventative and therapeutic modes in the rat adjuvant arthritis model significantly reduces the incidence and severity of the disease. As illustrated below, INCB3344 dosed orally significantly decreased the clinical score and histological signs of arthritis, including inflammation, synovial proliferation, and bone resorption. The magnitude of protection from joint inflammation and destruction provided by INCB3344 administration is quite comparable to that obtained by neutralizing MCP-1 antibody.

**Figure 1: INCB3344 efficacy in rat adjuvant-induced arthritis model**





**Figure 2: Impact of INCB3344 treatment on histological signs of arthritis in rat adjuvant-induced arthritis model**



The histological analyses of animals given only vehicle show marked joint destruction, synovial proliferation and bone erosions, all of which are significantly attenuated in the animals given the CCR2 antagonist, INCB3344. Normal paw histology is shown for comparison.

## Multiple Sclerosis

Accumulation of inflammatory macrophages in the human central nervous system is a key step in the pathological cascade of multiple sclerosis, leading to exacerbations of the disease. In active MS lesions, monocytes are found in perivascular cell cuffs and at the demyelinating edges of evolving lesions. The destruction of axons, demyelination, and oligodendrocyte cell death is directly related to the number of activated macrophages migrating into the lesions<sup>6</sup>.

Preclinical disease model evidence for the potential therapeutic role of CCR2 antagonism in multiple sclerosis includes the following:

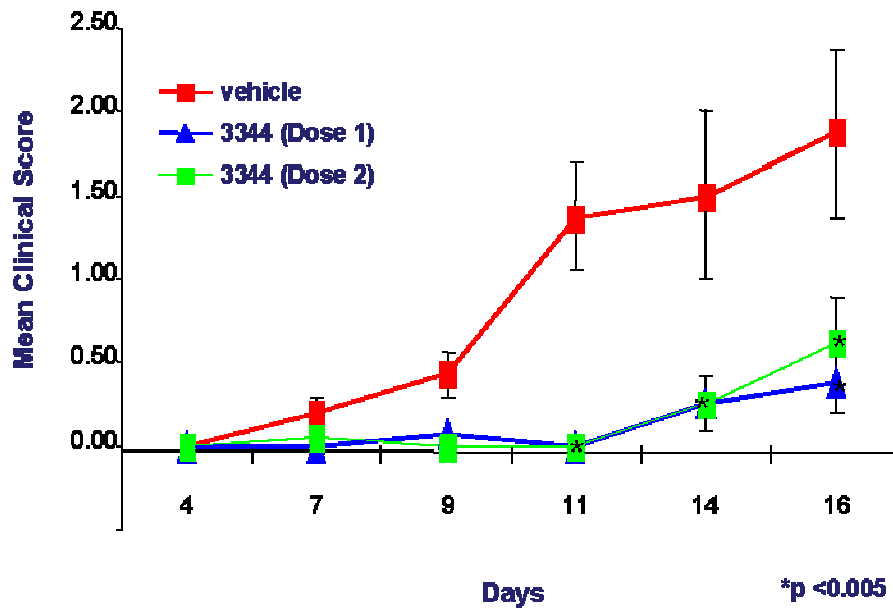
- (1) In CCR2-deficient mice, macrophage recruitment to sites of neuronal damage is reduced, and a decrease in demyelination is observed<sup>7</sup>. Furthermore, CCR2 knockout mice are resistant to disease in the experimental autoimmune encephalomyelitis (MOG-EAE) model of multiple sclerosis<sup>8</sup>, and the relapse



phase of the relapsing-remitting EAE model is significantly attenuated in MCP-1 knockout mice<sup>9</sup>.

- (2) Additionally, INCB3344 significantly reduces the development of EAE in the MOG-EAE model, as shown below.

**Figure 3: Impact of INCB3344 treatment on clinical score in MOG-EAE model**



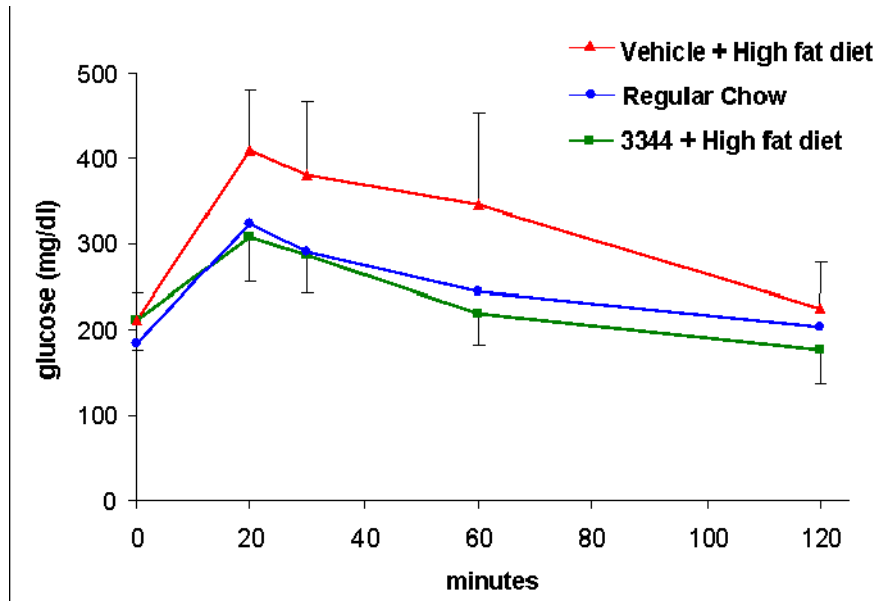
## Diabetes

A growing body of evidence suggests that chronic inflammation may play a key role in the pathogenesis of diabetes. There is a significant increase in circulating, as well as adipose tissue, MCP-1 levels in obese humans and in animal models of diabetes/obesity. Two recent studies<sup>10,11</sup> show correlations between the degree of adiposity, adipose tissue macrophage burden, and insulin resistance in humans. Furthermore, obese CCR2  $-/-$  mice exhibit significantly decreased adipose tissue macrophage burden and improved insulin sensitivity<sup>12</sup>.

CCR2 may mediate the migration of peripheral blood monocytes into adipose tissue, as is the case with other inflammatory diseases, and hence CCR2 antagonists may have a favorable impact on glucose tolerance. Results using our rodent-active CCR2



antagonist, INCB3344, in the diet-induced obesity model in mice demonstrate significantly improved glucose tolerance following a 4-week treatment, as shown below:



## Atherosclerosis

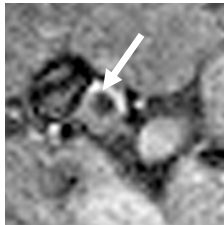
Inflammation plays a key role in the development of complex atherosclerotic plaque, and foam cells, which are derived from peripheral blood monocytes, are a major cell type in these plaques. Pro-inflammatory factors and enzymes produced by macrophages/foam cells perpetuate the inflammatory process and lead to plaque instability and subsequent clot formation.

- (1) CCR2 gene deletion has been shown to reduce macrophage accumulation in the blood vessels and to ameliorate the generation of atherosclerotic plaque in the ApoE knockout mouse model<sup>13</sup>. Administration of the truncated MCP-1 protein antagonist of CCR2 had a similar effect<sup>14</sup>.
- (2) The figure below shows suppression of plaque formation in the abdominal aorta with INCB3344 administered orally in the ApoE knockout model (the illustration is of one particular pair of mice, but is typical of the results observed throughout the experiment). The white lining of the aorta in the control mouse represents calcified plaque, which is not seen in the INCB3344 treated mouse, as highlighted by the arrow in the figure below.

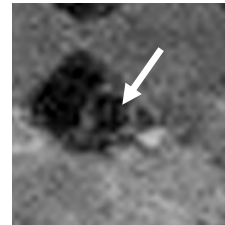
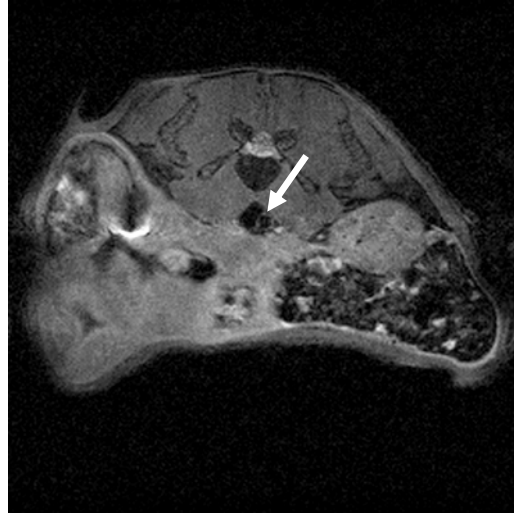


**Figure 4: INCB3344 Atherosclerosis Intervention Study in Apo E Knockout Mice**

**Control Mouse**



**INCB3344 Treated Mouse**



The results of the experiments described above, together with additional data from both Incyte and the scientific literature, support the potential for therapeutic intervention with CCR2 antagonists in multiple disease indications.

## **Properties of Incyte CCR2 Antagonists**

While CCR2 has been a target of interest in the pharmaceutical industry for some time, it has proven difficult to generate compounds that are sufficiently potent and selective against other chemokine receptors, have acceptable PK properties, and lack the liabilities of hERG channel and cytochrome p450 induction. Incyte has discovered novel, potent, orally-available small molecule antagonists of the CCR2 receptor. These compounds are highly selective and display excellent preclinical and clinical pharmacokinetic properties. Incyte has also developed multiple distinct chemical series of antagonists, increasing the overall likelihood of success of the program and offering multiple assets for pursuit across numerous potential indications.



The recent alliance Incyte formed with Pfizer attests to the broad scope of the program (see attached press release: Pfizer and Incyte Enter Collaborative Research and License Agreement for the Development and Commercialization of CCR2 Antagonists -- Nov. 21, 2005).

Incyte's most advanced oral CCR2 antagonist, INCB3284, has shown the following properties:

- single digit nanomolar potency in *in vitro* binding and functional assays
- greater than 400-fold selectivity against CCR5 in binding assays
- greater than 1,000-fold selectivity against CCR1 in binding assays
- high selectivity against a panel of relevant GPCRs, enzymes, and ion channels
- high selectivity against hERG in patch clamp assays
- no significant inhibition of cytochrome p450 enzymes
- excellent preclinical and clinical pharmacokinetic profile

INCB3284 completed a Phase I single and multiple dose (10 day) study in healthy volunteers and was very well tolerated in this trial, exhibiting a safety profile equivalent to placebo. During the multiple dose portion of the study, delayed type hypersensitivity (DTH) testing was performed as a potential surrogate test of pharmacological activity, with results consistent with the inhibition of DTH response we have observed with related Incyte CCR2 antagonists in preclinical rodent and primate models.

In addition to INCB3284 and related compounds, Incyte has identified three additional chemical series of CCR2 antagonists, each of which is significantly distinct from the INCB3284 series. Development candidates have been selected from each series. As noted above, we believe that the availability of multiple chemically-distinct series increases the probability of success of the overall program and offers the opportunity to progress different compounds in different indications, creating a broad franchise that encompasses multiple therapeutic areas.

As previously mentioned, the program has recently been partnered with Pfizer, with Pfizer gaining worldwide rights to all indications other than multiple sclerosis and an additional undisclosed indication, for which Incyte will have rights to pursue certain compounds on its own. We anticipate that the IND for the first MS compound will be filed in 2H06.



## References

- <sup>1</sup> Mulherin, et. al. Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. *Arthritis and Rheumatology* 1996; **39**: 115-124.
- <sup>2</sup> Smith, et al. Treatment-induced remission in rheumatoid arthritis patients is characterized by a reduction in macrophage content of synovial biopsies. *Rheumatology* 2001; **40**: 367-374.
- <sup>3</sup> Smeets, et al. Tumor necrosis factor  $\alpha$  blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. *Arthritis & Rheumatism* 2003; **48** (8): 2155-2162
- <sup>4</sup> Gong, et al. An antagonist of monocytes chemoattractant protein 1 (MCP-1) inhibits arthritis in the MRL-*1pr* mouse model. *Journal of Experimental Medicine* 1997; **186** (1): 131-137
- <sup>5</sup> Youssef, et al. C-C chemokine-encoding DNA vaccines enhance breakdown of tolerance to their gene products and treat ongoing adjuvant arthritis. *Journal of Clinical Investigation* 2000; **106** (3): 361-371
- <sup>6</sup> Van Der Voorn, et al. Expression of MCP-1 by reactive astrocytes in demyelinating multiple sclerosis lesions. *American Journal of Pathology* 1999; **154** (1): 45-51
- <sup>7</sup> Siebert, et al. The chemokine receptor CCR2 is involved in macrophage recruitment to the injured peripheral nervous system. *Journal of Neuroimmunology* 2000; **110** (1-2): 177-185
- <sup>8</sup> Izikson, et al. Resistance to experimental autoimmune encephalomyelitis in mice lacking the CC chemokine receptor (CCR2). *Journal of Experimental Medicine* 2000; **192** (7): 1075-1080
- <sup>9</sup> Huang, et al. Absence of monocytes chemoattractant protein 1 in mice leads to decreased local macrophage recruitment and antigen-specific T helper cell type 1 immune response in experimental autoimmune encephalomyelitis. *Journal of Experimental Medicine* 2001; **193** (6): 713-726
- <sup>10</sup> Xu et. al. Chronic inflammation in fat plays a crucial role in the development of obesity related insulin resistance. *Journal of Clinical Investigation* 2003; **112** (12): 1821-1830
- <sup>11</sup> Weisberg et. al. Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation* 2003; **112** (12): 1796-1808
- <sup>12</sup> Charo, Israel. Chemokine Gordon Research Conference 2004
- <sup>13</sup> Boring et. al. Decreased lesion formation in CCR2<sup>-/-</sup> mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* 1998; **394** (6696): 894-897
- <sup>14</sup> Inoue et. al. Anti-monocyte chemoattractant protein-1 gene therapy limits progression and destabilization of established atherosclerosis in apolipoprotein E-knockout mice. *Circulation* 2002; **106**: 2700-2706



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FOR IMMEDIATE RELEASE

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**PFIZER AND INCYTE ENTER COLLABORATIVE RESEARCH AND LICENSE  
AGREEMENT FOR THE DEVELOPMENT  
AND COMMERCIALIZATION OF CCR2 ANTAGONISTS**

***Pfizer Gains Worldwide Development And Commercialization Rights  
Across A Broad Range Of Indications***

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***Incyte May Receive Up To \$803 Million In Payments And Retains Rights In Multiple  
Sclerosis And An Additional Undisclosed Indication***

**NEW YORK, NY, and WILMINGTON, DE** – November 21 -- Pfizer Inc, (NYSE: PFE) and Incyte Corporation (NASDAQ: INCY) announced today that the two companies have entered into a global collaborative research and license agreement for the development, manufacture and marketing of novel oral CCR2 antagonists.

Under the agreement:

- Pfizer gains exclusive worldwide development and commercialization rights to Incyte's portfolio of CCR2 antagonist compounds, the most advanced of which is currently in Phase IIa studies in rheumatoid arthritis and insulin-resistant obese patients. Pfizer's rights extend to the full scope of potential indications, with the exception of multiple sclerosis and one other undisclosed indication, where Incyte retains exclusive worldwide rights, along with certain compounds. Incyte will not have obligations to Pfizer on pre-clinical development candidates it selects for pursuit in these indications.
- Incyte will receive an upfront payment of \$40 million and will be eligible to receive additional milestone payments of up to \$743 million for the successful development and commercialization of CCR2 antagonists in multiple indications, as well as royalties on worldwide sales.
- Pfizer will purchase \$20 million in convertible subordinated notes, with \$10 million to be issued within 20 days after the effective date of the agreement and another \$10 million to be issued after Incyte files an Investigational New Drug Application in a



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retained Incyte indication. The notes will bear no interest and will be convertible into Incyte common stock at a premium.

- Pfizer will also provide research funding to Incyte to support the continued expansion of the CCR2 compound portfolio.

The agreement is subject to antitrust review and approval, and other standard closing conditions.

“This transaction is a further step in our strategy to augment Pfizer’s internal research and development efforts with high-potential, externally sourced product candidates and technologies,” said Martin Mackay, Pfizer Senior Vice President Worldwide Research and Technology. “We are excited about Incyte’s CCR2 antagonist program and its potential use in treating a range of chronic diseases with significant unmet medical need.”

Paul A. Friedman, M.D., President and CEO of Incyte, stated: “Our CCR2 antagonist program has the potential to generate multiple products in a variety of major indications, and Pfizer, with its unique breadth of capabilities, is ideally positioned to maximize the value of the program to patients. The deal structure, which provides for us to retain certain compounds for our independent pursuit in two potentially high-value specialty indications, supports our efforts to build a leading drug discovery and development company. We look forward to working with Pfizer to realize the full potential of our first internally-developed program.”

### **About CCR2 Antagonism**

The chemokine receptor CCR2 has a central role in the establishment and maintenance of chronic inflammatory processes. CCR2 and its primary ligand, MCP-1, represent a critical signaling pathway for the recruitment of peripheral blood monocytes to sites of immune-mediated inflammation, where they become inflammatory macrophages. Macrophages are among the predominant cell types found at sites of chronic inflammation, and clinical observations show a close correlation between lower macrophage burden, reduced severity of disease, and improved outcomes in rheumatoid arthritis. There is a growing body of evidence that the presence of inflammatory macrophages contributes to the pathogenesis of numerous other disorders, and positive effects of blockade of the CCR2/MCP-1 axis have been shown in animal models of rheumatoid arthritis, multiple sclerosis, diabetes, atherosclerosis, neuropathic pain and inflammatory bowel disease.

### **About Pfizer**

Pfizer Inc discovers, develops, manufactures and markets leading prescription medicines, for humans and animals, and many of the world's best-known consumer brands.

### **About Incyte**

Incyte Corporation is a Wilmington, Delaware-based drug discovery and development company with a growing pipeline of oral compounds to treat HIV, inflammation, cancer and diabetes. The company's most advanced product candidate, dextelvucitabine, DFC (formerly Reverset) is an oral, once-a-day therapy in Phase IIb clinical development to treat patients with HIV infections. The company's lead internal compounds include INCB3284, a proprietary oral CCR2 antagonist



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that is in Phase II development for a number of inflammation-driven diseases, and INCB7839, a proprietary oral sheddase inhibitor that is in Phase I development as a potential treatment for cancer. Incyte has several other early drug discovery programs underway in the areas of cancer, inflammation, diabetes and HIV.

### **Forward Looking Statements**

**PFIZER DISCLOSURE NOTICE:** The information contained in this release is as of November 21, 2005. Pfizer assumes no obligation to update any forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about an agreement between Pfizer Inc and Incyte Corporation and about possible product candidates that may be developed from Incyte's portfolio of compounds and the potential benefits of such product candidates. This information involves substantial risks and uncertainties including, among other things, the satisfaction of conditions to closing the agreement; the uncertainties inherent in research and development activities; decisions by regulatory authorities regarding whether and when to approve any drug applications for product candidates that may be developed from Incyte's portfolio of compounds as well as their decisions regarding labeling and other matters that could affect the commercial potential of any such product candidates; and competitive developments.

A further list and description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2004 and in its reports on Form 10-Q and Form 8-K.

**INCYTE DISCLOSURE NOTICE:** Except for the historical information contained herein, the matters set forth in this press release, including statements with respect to the purchase of convertible subordinated notes, the potential indications and benefits of CCR2 antagonist compounds, and the potential benefits from and payments under the agreement, are all forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially, including the satisfaction of conditions to closing the agreement and the sale of the convertible subordinated notes, the high degree of risk associated with drug development and clinical trials, results of further research and development, the impact of competition and of technological advances, and other risks detailed from time to time in Incyte's filings with the Securities Exchange Commission, including its Quarterly Report on Form 10-Q for the quarter ended September 30, 2005. Incyte disclaims any intent or obligation to update these forward-looking statements.

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