

**INCYTE CORPORATION**



**CCR5 ANTAGONIST PROGRAM**

***Orally-Administered Therapeutics for  
HIV Infection***

**As of June 2006**



## Therapeutic Rationale

The chemokine receptor CCR5 is the obligate co-receptor for R5 HIV strain entry into host cells. *In vitro* studies have demonstrated that the natural ligands for CCR5, RANTES, MIP-1a, and MIPb, as well as neutralizing monoclonal antibodies to CCR5 are potent inhibitors of HIV infectivity. Interestingly, approximately 1% of the population is homozygous for a mutation of the CCR5 gene that results in a 32 base pair deletion (CCR5 delta32), rendering these individuals functionally CCR5 null. While there are no known liabilities associated with the inherited deficiency of this receptor, individuals homozygous for CCR5 delta32 are naturally resistant to HIV infection. For these reasons, antagonism of CCR5 is being pursued as an attractive therapeutic approach for the management of HIV infection. Emerging Phase II clinical results show impressive (greater than 1.5 log) reductions in HIV viral loads following 10-14 days of treatment with small molecule CCR5 antagonists suggesting that these compounds have the potential to become an important component of the next generation of anti-HIV regimens.

Incyte's CCR5 antagonist program was designed to identify potent, selective, proprietary compounds with: 1) anti-HIV activity comparable to CCR5 antagonists currently in clinical development, 2) pharmacokinetic properties that are expected to allow a small, single daily dose to yield plasma protein binding-adjusted free trough concentrations exceeding the IC<sub>90</sub> for HIV infectivity, and 3) low potential for drug-drug interactions. These properties should allow INCB9471 to be developed as a single agent and to be readily co-formulated with another anti-HIV medication. At this time, INCB9471 and INCB15050 represent our lead clinical candidates. INCB9471 was discovered first and represents our most advanced clinical candidate in this program.

INCB9471 is a potent (less than 10 nM) inhibitor of CCR5 ligand binding, ligand-induced chemotaxis and R5 HIV infection of human blood mononuclear cells. The compound is highly selective against other chemokine receptors, as well as in the Cerep panel of



more than 50 GPCRs, ion channels, enzymes and transporters, with  $IC_{50}$  in all assays greater than 1  $\mu$ M (the highest concentration tested). Similar to other CCR5 antagonists in clinical development, INCB9471 is a non-competitive, reversible CCR5 antagonist with a slow off-rate. INCB9471 shows no agonist activity as determined by the absence of compound induced calcium mobilization, ERK phosphorylation or CCR5 internalization, tested at a maximal concentration of 5  $\mu$ M.

INCB9471 demonstrates potent *in vitro* anti-HIV activity and inhibited the infection of PBMC's by all of the 9 primary R5 HIV strains tested with  $IC_{50}$  values ranging from 0.5-2.6 nM. The R5 HIV strains tested include representatives of clades B, C, E and G. INCB9471 was also characterized for inhibition of infectivity using a panel of 26 additional R5 HIV isolates representing clades A, B, C, D, E, F, G, and J. These infectivity assays were performed using a recombinant CCR5 assay system. Again, INCB9471 inhibited infection by all R5 HIV strains tested with potencies ( $IC_{50}$ ) ranging from 2-23 nM. The shift in potencies observed between the PBMC and recombinant systems is consistent with that routinely observed with other compounds in this class and likely reflects a technical artifact introduced by the greater than normal levels of CCR5 expression in the recombinant cell line.

INCB9471 effectively inhibits infection of cells by R5 HIV strains that are resistant to the four existing classes of anti-HIV therapeutics: protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the fusion inhibitor T-20, with no significant change in  $IC_{50}$  values compared to that required for inhibition of infectivity of the corresponding wild type HIV strain. As expected, INCB9471 is inactive against X4 HIV strains.

INCB9471 exhibits excellent *in vitro* ADME properties, including high Caco-2 permeability, low intrinsic clearance in human liver microsomes, and a free fraction of 16% in human serum. INCB9471 is metabolized by CYP3A4 and not by the polymorphic P450s, 2D6, 2C9 and 2C19, and does not inhibit the five major human CYP isozymes when tested at concentrations up to 25  $\mu$ M. These data suggest that INCB9471 is likely to exhibit predictable pharmacokinetics in the clinic with a low potential for drug-drug interactions.



The oral pharmacokinetic properties of INCB9471 have been evaluated in multiple preclinical species, including rat, dog and cynomolgus monkey. In all species studied, INCB9471 exhibited low systemic clearance, moderate volume of distribution, long terminal half-life following IV dosing, and excellent bioavailability (greater than 95%) following oral dosing.

Safety studies to date have included IND-enabling GLP 28-day studies in rat and cynomolgus monkey, as well as the ICH safety pharmacology and genotoxicity batteries. Results of these studies fully support proceeding to clinical studies. The IND and first Phase I in healthy volunteers are scheduled for 1H06.

INCB15050 is a structurally distinct back-up molecule with similarly excellent potency, selectivity, and pharmacokinetic profile. This compound is currently being scaled for 28 day IND enabling studies.

As clinical trials of CCR5 antagonists continue, and later as CCR5 antagonists enter the HIV treatment armamentarium, it is anticipated that resistant HIV strains will emerge. It should be noted that even relatively small structural changes can have a profound impact on the efficacy of small molecule CCR5 antagonists against wild-type virus and against resistant strains. In the INCB9471 chemical series, a small structural change can define the presence or absence of anti-HIV activity. Similarly, Pfizer has reported on two series of CCR5 antagonists which bind to the same residues on CCR5, that differ only by the substitution of a ring nitrogen for a carbon, but which show a 6-log difference in potency against an in-vitro-generated CCR5 escape mutant. Thus, the nature and number of CCR5 antagonists that will find a place in clinical practice remains to be defined.