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MOLECULES

Recent PDE4 inhibitor clinical candidates

Being located in a variety of cell types and tissues, PDE4 (cyclic nucleotide phosphodiesterase 4) is an attractive target for the treatment of a wide array of disorders such as those affecting the inflammatory, respiratory and CNS systems [1]. For the past two decades, several PDE4 inhibitors have been investigated for the treatment of asthma and chronic obstructive pulmonary disease (COPD) but, none has succeeded in reaching the market mainly because of the presence of dose-limiting emetogenic toxicity [2]. Nonetheless, work in this area continues and two clinical candidates (Fig. 1) have recently been reported.

The first, MK-0873 (**1**) from Merck, is in phase I clinical studies for the treatment of COPD and asthma [3], while the second compound, apremilast (**2**) from Celgene, is in phase II clinical trials for psoriasis [4]. MK-0873 is different from earlier PDE4 inhibitors in its chemotype. Although it is not PDE4-subtype selective (PDE4A IC_{50} of 6.7 nM) it displays favorable anti-inflammatory activity as demonstrated by its ability to inhibit TNF-α (tumor necrosis factor-α) production in the human whole blood assay (IC_{50} = 178 nM). MK-0873 (intraperitoneal) provided potent and dose-dependent inhibition of ovalbumin-induced broncoconstriction in sensitized guinea pigs and protected sheep (intravenous) against late-phase bronchoconstrictor response to antigen challenge. Oral bioavailability in rats and dogs is high (F_{po} = 98% and 100%, respectively), and it has a half-life of two hours in both species. In squirrel monkeys, MK-0873 showed a 200-fold window between the emetic threshold concentration of 5.1 μM and the concentration need for TNF-α suppression (23 nM), suggesting that there is a low potential for emetogenic side effects.

Apremilast is similar in structure to previously reported PDE4 inhibitors. It inhibits PDE4 with an IC_{50} of 74 nM and TNF-α production in the human whole blood assay with an IC_{50} of 110 nM and was found to be efficacious in inhibiting TNF-α production and neutrophilia in rats. Oral bioavailability in female rats was 64% accompanied by a circulating half-life of three hours. In an open-labeled study in patients having severe plaque-type psoriasis, apremilast improved the psoriasis clinical efficacy scores in 74% of the patients treated with 20 mg of the drug orally for 29 days.

Crystal structure of mouse P-glycoprotein

P-glycoprotein (P-gp) was originally discovered as a protein responsible for multidrug resistance to cancer chemotherapy, but since then its function as a general drug transporter has become widely appreciated. It is expressed along the wall of the small intestine and at the blood–brain barrier where it acts as an efflux pump to limit the oral bioavailability and CNS-uptake of drug molecules. Structural information for this protein would be very beneficial in facilitating the design of molecules which circumvent P-gp mediated efflux. Therefore, the crystal structure of mouse P-gp, which shares 87% sequence identity with human P-gp, determined at 3.8 Å by Aller *et al.* is very significant (Fig. 2) [5].

The apo structure shows an inward-facing protein conformation, which presumably

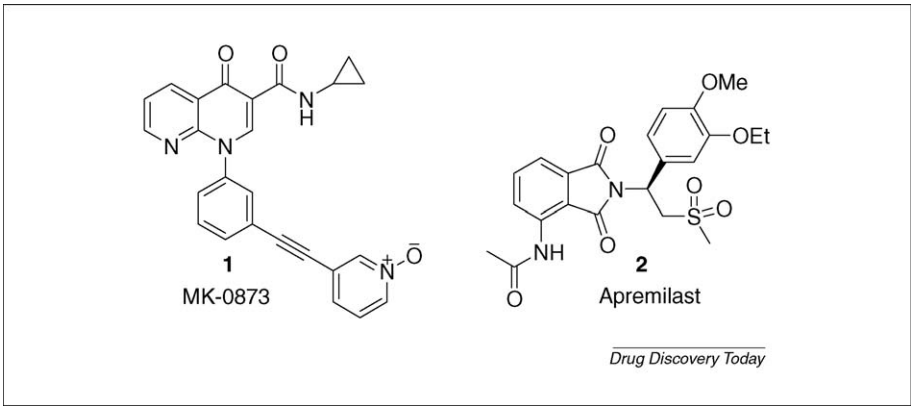

FIGURE 1

Structures of PDE4 inhibitors and MK-0873 (**1**) and apremilast (**2**).

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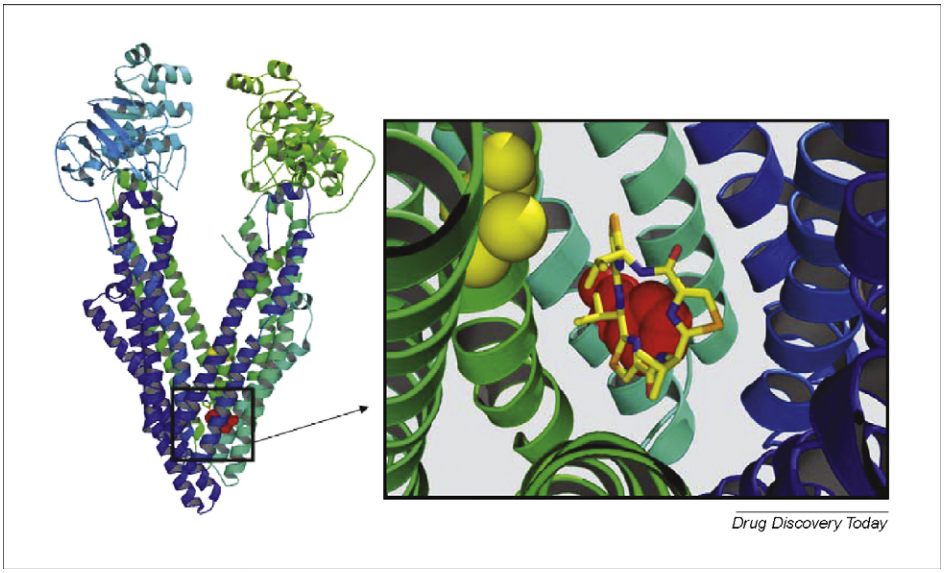

FIGURE 2

X-ray crystal structure of the mouse P-gp (coordinates, PDB 3G61). The bound ligand and key residues are highlighted, Phenylalanine-728 (yellow spheres), Valine-982 (red spheres) and cyclic peptide inhibitor (yellow).

represents an initial state of the transport cycle, with an enormous internal drug binding cavity of about 6000 $Å^3$ within the lipid bilayer (Fig. 2). It also reveals two portals, formed by the transmembrane α-helix domains, that are open to the inner leaflet of the lipid bilayer to capture molecules into the binding pocket. The drug binding pocket is mainly composed of hydrophobic residues with F728 and V982 (human sequence numbering) being two key drug binding elements along with more polar residues in its lower region. Interestingly, co-crystal structures of P-gp bound to a pair of enantiomers of a cyclic-peptide inhibitor revealed two distinct binding modes. While the *R*-isomer binds in a 1:1 manner, two molecules of the *S*-isomer bind simultaneously in the pocket at a slightly different location from that of the *R*-isomer. This provides another example which highlights the promiscuous drug binding capability of P-gp. The finding that drugs may bind to P-gp in a 'multi-valent' fashion may also complicate compound design and computer modeling to eliminate the P-gp efflux liability of a compound.

1 Houslay, M.D. *et al.* (2005) Phosphodiesterase-4 as a therapeutic target. *Drug. Discov. Today* 10, 1503–1519
2 Spina, D. (2008) PDE4 inhibitors: current status. *Br. J. Pharmarcol.* 155, 308–315
3 Guay, D. *et al.* (2008) Optimization and structure–activity-relationship of a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides: identification of MK-0873, a potent and effective PDE4 inhibitor. *Bioog. Med. Chem. Lett.* 18, 5554–5558
4 Man, H.-W. *et al.* (2009) Discovery of (*S*)-*N*-{2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide (Apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-α inhibitor. *J. Med. Chem.* 52, 1522–1524
5 Aller, S.G. *et al.* (2009) Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science* 323, 1718–1722

Kap-Sun Yeung
kapsun.yeung@bms.com