**Highlighted Papers**

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### Effect of α7 Nicotinic Receptor Agonist on L-Dopa–Induced Dyskinesias

Previous studies in rats and monkeys have shown that β2-selective nicotinic acetylcholine receptor (nAChR) agonists reduce L-Dopa–induced dyskinesias (LIDs). Because rodent studies also suggested an involvement of α7 nAChRs in LIDs, the authors tested the effect of the potent, selective α7 agonist, ABT-107 [5-(6-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]oxo)-1H-indol-3-yl]-N-(1-(1H-indol-3-yl)ethyl)benzamide], MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned monkeys were gavaged with L-Dopa/carbidopa twice daily, which resulted in stable LIDs. Oral administration of ABT-107 then decreased LIDs by 40–60%. The LIDs returned to control levels only after a 6-week ABT-107 washout, suggesting long-term molecular changes were involved. There was no effect of ABT-107 on Parkinsonism or cognitive performance. The authors next tested ABT-107 together with the β2 agonist, ABT-894 [5-(6-dichloro-pyridin-3-yl)-1-(2H-1,2,3-triazol-4-yl)-1H-indole], previously shown to reduce LIDs in Parkinsonian monkeys. The effect of combined treatment on LIDs was similar to that with either drug alone. Thus, α7 and β2 nAChR–selective drugs may function via a final common mechanism to reduce LIDs.

See article at *J Pharmacol Exp Ther* 2014, **351**:25–32.

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### Therapeutic Targeting of Src Kinase in Pulmonary Fibrosis

Myofibroblasts are effector cells in fibrotic disorders that synthesize and remodel the extracellular matrix (ECM). This study investigated the role of the Src kinase pathway in myofibroblast activation in vitro and in fibrogenesis in vivo. The profibrotic cytokine, transforming growth factor β1 (TGF-β1), induced rapid activation of Src kinase that leads to myofibroblast differentiation of human lung fibroblasts. The Src kinase inhibitor AZD0530 (saracatinib) blocked TGF-β1–induced Src kinase activation in a dose-dependent manner. The therapeutic efficiency of Src kinase inhibition in vivo was tested in the bleomycin murine lung fibrosis model. Collagen accumulation, total fibrotic area, and expression of α-smooth muscle actin and ECM proteins were significantly decreased in lungs of AZD0530-treated mice. These results provide evidence for targeting the noncanonical TGF-β signaling pathway involving Src kinase as an effective therapeutic strategy for lung fibrosis.

See article at *J Pharmacol Exp Ther* 2014, **351**:87–95.

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### Pegylation Prevents Phospho-Ibuprofen Hydrolysis

Esterase hydrolysis of drugs can accelerate their elimination, thereby limiting their efficacy. Covalently attaching polyethylene glycol (PEG) on drugs (pegylation) is known to improve the efficiency of many drugs. Using as a test agent the novel phospho-ibuprofen (PI), the authors examined whether pegylation of PI (PI-PEG) could abrogate its hydrolytic degradation by esterases. PI-PEG was stable in the presence of cells over-expressing carboxylesterases, while PI was extensively hydrolyzed. In mice, PI was nearly completely hydrolyzed, but intravenous administration of PI-PEG resulted in significant levels in blood and in colon cancer xenografts. Compared with controls, PI-PEG inhibited the growth of the xenografts by 74.8% and reduced intestinal tumor multiplicity in Apcmin/mice by 73.1%, prolonging their survival (100% versus 55.1% of controls). These results demonstrate that pegylation protects PI from esterase hydrolysis and improves its pharmacokinetics and efficacy in preclinical models of colon cancer.

See article at *J Pharmacol Exp Ther* 2014, **351**:61–66.

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### Pharmacology of GSK-961081, an Inhaled Muscarinic Antagonist/β2 Agonist

The objective of the present studies was to characterize the pharmacologic properties of GSK-961081 [(R)-1-3-(2-chloro-4-(((2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-5-methoxyphenyl)amino)-3-oxopropyl)piperidin-4-yl[1,1’-biphenylyl(2'-ylcarbamate], an inhaled compound possessing both muscarinic antagonist (MA) and β2-adrenoceptor agonist (BA) properties (MABA). In competition radioligand binding studies at human recombinant receptors, GSK-961081 displayed high affinity for hM2 (K_i = 1.4 nM) and hM3 muscarinic receptors (K_i = 1.3 nM) and hβ2-adrenoceptors (K_i = 3.7 nM). GSK-961081 behaved as a potent hβ2-adrenoceptor agonist (EC_{50} = 0.29 nM for stimulation of cAMP levels) with 440- and 320-fold functional selectivity over hβ1- and hβ3-adrenoceptors, respectively. In a guinea pig broncho-protection assay, inhaled GSK-961081 produced potent, dose-dependent inhibition of bronchoconstrictor responses via MABA mechanisms. GSK-961081 demonstrated greater lung selectivity than the MA tiotropium and the BA salmeterol. These preclinical findings suggest that GSK-961081 has the potential to be an inhaled lung-selective bronchodilator.

See article at *J Pharmacol Exp Ther* 2014, **351**:190–199.

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End.