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Preclinical jockeying on the translational track of adenosine A_{2A} receptors

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In a recent issue of *Experimental Neurology*, Hodgson et al. (2010) reported positive results of late preclinical (non-human primate, NHP) studies of an adenosine A_{2A} receptor antagonist developed as a neurotherapeutic by Schering-Plough and now Merck. Preladenant (a.k.a. SCH 420814) recently advanced to phase III clinical trials for antiparkinsonian activity in early- as well as later-stage Parkinson disease (PD). Reflecting the therapeutic promise of A_{2A} antagonists for CNS disorders, preladenant is one of at least six independent drug development programs targeting this G-protein-coupled receptor in clinical trials in pursuit of an indication for PD and possibly other neuropsychiatric conditions. Preladenant at the moment appears to have taken the lead in this pack of A_{2A} therapeutic programs, galloping ahead of others that also reached the phase III stage of clinical development on what may be the home stretch of this exciting but tricky translational track.

Potential to reduce parkinsonism without bringing out dyskinesia?

Building on their similarly supportive preladenant data in rodent models of PD (Hodgson et al., 2009), the authors now describe the effects of preladenant on parkinsonism as well as on L-Dopa-induced dyskinesia (LID), in a model of relatively advanced PD using MPTP-lesioned, L-Dopa-primed NHPs. In addition, preladenant was studied in a model of neuroleptic-induced extrapyramidal symptoms (EPS). Six MPTP-treated monkeys with stable parkinsonian syndromes were treated with either 1 or 3 mg/kg preladenant; 3, 6 or 12 mg/kg L-Dopa subcutaneously; or combination therapy (3 mg/kg L-Dopa plus 1 or 3 mg/kg preladenant). Compared to vehicle, significant improvements in minimum and mean parkinsonian scores were seen in animals treated with preladenant at a dose of 3 mg/kg, L-Dopa at all doses and the combination of preladenant plus 3 mg/kg L-Dopa therapy. (The one exception was that with 3mg/kg L-Dopa, improvements were in minimum parkinsonian scores only, not mean scores.)

More to the point, combining this marginally threshold dose of L-Dopa with preladenant resulted in significant improvement in minimum and mean parkinsonian scores compared to low-dose L-Dopa alone. In a subgroup analysis, the three animals with the lowest baseline parkinsonian score were found to have a greater reduction in parkinsonian score with preladenant compared to the three animals with the highest baseline parkinsonian score.

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Given these findings, the authors suggest that preladenant may have more efficacy as monotherapy in subjects with milder disease rather than those in later stages.

Locomotor activity was also significantly improved in animals treated with the combination compared to vehicle, but this only appeared after post-hoc analysis. Locomotor activity quantified by mobility counts on an automated electronic monitoring system represents a less specific index of antiparkinsonian activity as it also picks up hyperkinetic behaviors.

The study also addresses the anti-dyskinesogenic potential of preladenant. Effective antiparkinsonian doses of the A_{2A} antagonist on its own produced not even a hint of dyskinesias despite the fact that these MPTP-lesioned animals had been primed for them by prior repeated L-Dopa treatment. In addition, it was suggested that preladenant showed no synergistic or potentiating effects on dyskinesia when co-administered with a low dose of L-Dopa. However, the combination produced a trend toward greater dyskinesia than with L-Dopa alone, though no statistically significant increase was shown with the six animals studied. It would be informative to also examine adjunctive preladenant with more effective antiparkinsonian L-Dopa doses, as might be more relevant to adjunctive A_{2A} antagonist use in the relatively advanced PD patients being modeled under this paradigm.

The authors' suggestion that adjunctive antiparkinsonian effects of preladenant might be achieved in advanced PD without exacerbation of pre-existing LID is also tempered by prior translational experience with istradefylline (a.k.a. KW-6002). Like preladenant, it had shown no significant dyskinesogenic or LID-potentiating properties in NHP models of PD (Kanda et al., 1998; Kanda et al., 2000; Grondin et al., 1999). However, when studied in human subjects, istradefylline increased "on" time with dyskinesia compared to placebo (Hauser et al., 2003) even though severity of dyskinesia was not significantly increased. There was also an accompanying decrease in "off" time in patients on the study drug, leading the authors to suggest that the increase in "on" time with dyskinesia may have been preferable to patients than increased "off" time. Subsequent studies differentiated between "troubling" and "nontroubling" dyskinesias. One showed that "on" time with troubling dyskinesias were slightly but significantly increased compared to placebo, whereas there were no significant differences in "on" time with any dyskinesia (troubling and nontroubling combined) between istradefylline and placebo (Mizuno et al., 2010). A study by Stacy et al. (2008) suggested a clinically meaningful reduction in "off" time without increased troublesome dyskinesia, whereas LeWitt et al. (2008) showed an increase in "on" state without troublesome dyskinesia. A study by Hauser et al. (2008) showed no significant increase in "on" time with or without dyskinesia: troublesome, nontroublesome or both. It remains to be established whether antiparkinsonian preladenant doses have an effect on established LID in PD patients.

Potential to reduce extrapyramidal side effects of antipsychotics?

The authors also reported preladenant's effect on development of extrapyramidal symptoms (EPS) in animals treated with haloperidol. Preladenant at doses of 1 mg/kg and 3 mg/kg was effective in significantly delaying the time to onset as well as decreasing the extent of EPS in response to haloperidol. The findings lend support to the prospects of broadening the application to other parkinsonian syndromes and related disorders of the basal ganglia beyond those of PD. The authors thoughtfully point out the logical concern that any benefits of A_{2A} receptor antagonists in treating neuroleptic-induced EPS might be offset by possible pro-psychotic effects, given the long-standing contention that A_{2A} receptor *agonists* might prove effective antipsychotic agents (Ferré, 1997). However, in animal models of the disordered sensorimotor gating of psychosis, A_{2A} antagonists have been found to have little psychosis-inducing capacity (Weiss, et al., 2003). Moreover, in the clinical trials of these

drugs reported to date, no significant increase in psychotomimetic events has been noted even in relatively advanced PD subjects who have a reduced threshold for hallucinations and other psychotic complications of therapy. In any event, the EPS findings support the prospects of broadening the CNS applications of A_{2A} antagonism from antiparkinsonian actions to beneficial effects in other parkinsonian syndromes and related basal ganglia disorders beyond PD.

Potential advantages over other A_{2A} antagonists?

The current paper fills in the gap between published preclinical rodent data and preliminary human trial results with preladenant (Hauser et al., 2009). It showcases its systematic preclinical evaluation in a non-human primate model, which has demonstrated neurochemical, anatomical and behavioral validity for PD. Thus it helps place preladenant in good position for further clinical development in PD and related disorders.

But preladenant is not alone in targeting adenosine receptors to gain an indication as a nondopaminergic antiparkinsonian agent. In addition to preladenant, istradefylline (as above; originally developed by Kyowa), vipadenant (a.k.a. BIIB014; developed by Biogen-Idec after licensing from Vernalis) and SYN115 (developed by Synosia and now UCB after licensing from Roche) are also adenosine receptor antagonists with relative specificity for the A_{2A} subtype that have now advanced to phase II or III clinical trials for PD. Istradefylline was at one point leading the pack but fell back in its prospects when a “not approvable letter” was received from the US FDA (Kyowa Kirin Press Release, 2008). Despite the setback, Kyowa Kirin pressed ahead with further phase III human trials for PD in Japan, and has recently reported continued progress (Mizuno, et al., 2010). It also has out-licensed a different A_{2A} antagonist (KW-6356) for clinical development to Lundbeck, another pharmaceutical company (Lundbeck Press Release, 2010), which had earlier pursued its own A_{2A} antagonist into the clinic (Lu AA47070) (Lundbeck Press Release, 2007). Vipadenant showed promise with positive results in phase II clinical trials based on early reports (Papapetropoulos et al., 2010), but was recently shelved over preclinical toxicology concerns. Biogen-Idec indicated its intent to return to the clinical starting gate with a back-up candidate from Vernalis (Vernalis Press Release, 2010), reflecting the promise of the target as well as their commitment to it. According to preliminary reports, SYN115 was found in phase II trials to improve motor function without significant adverse effects; functional imaging data corroborated its putative mechanism of action (Black et al., 2010a, b). Another A_{2A} antagonist, ST-1535 (developed by Sigma-Tau), has cleared phase I human studies on a clinical development course toward an antiparkinsonian indication (Pinna, 2009).

Moreover, non-selective adenosine antagonists like the long-approved antiasthmatic drug theophylline and the ubiquitous dietary psychostimulant caffeine also have been or are being pursued as antiparkinsonian therapy. The failure of early clinical trials of these adenosine receptor blockers as symptomatic therapy may have reflected substantial limitations of trial design or the pharmacological non-selectivity for the A_{2A} receptor (Morelli et al., 2010). In any event, the established long-term safety of these adenosine antagonists and their ready availability and low cost have supported renewed consideration, with caffeine currently undergoing re-examination in more careful PD trials (McGill University Health Center, 2009; 2010).

So how does preladenant compare to other candidates in this class? The authors suggest that greater adenosine receptor subtype selectivity confers an advantage upon preladenant. They emphasize the potential benefits of preladenant’s high selectivity for A_{2A} over A_1 receptors with a greater than 1000-fold affinity ratio (Neustadt et al., 2007), compared to ~60-fold for

istradefylline and only ~4-fold for caffeine (Fredholm et al., 1999). However, it remains uncertain whether highly selective A_{2A} receptor antagonists necessarily have greater anti-parkinsonian efficacy or even an improved side effect profile with respect to dyskinesias and otherwise. The authors point to a relatively low 3:1 dosage ratio for preladenant's antiparkinsonian effects in monkeys compared to rodents, and contrast this to a 30:1 ratio that they cite for istradefylline, suggesting a greater specificity of action for preladenant. However, this monkey: rodent ratio for istradefylline depends on the species; the authors referenced a study with macaques in noting the 30:1 ratio, whereas one obtains a ratio of just 2:1 if relying on the published marmoset data (Kanda et al., 1998; Kanda et al., 2000).

More importantly, it remains to be established whether avoiding any A_1 antagonism would indeed be advantageous for an antiparkinsonian A_{2A} antagonist. On the one hand, it has been postulated that inhibition of A_1 receptors on striatonigral neurons of the direct pathway may promote motor activity by disinhibiting the stimulant effects of dopamine D1 receptors, whereas blocking A_{2A} receptors on striatopallidal neurons of the indirect pathway may activate the motor stimulant actions of D2 receptors, similarly resulting in motor activation (Ferré et al., 1997). On the other hand, presynaptic A_1 and A_{2A} receptors on corticostriatal neurons acting on these striatal output neurons have opposing actions: A_1 receptors inhibit, and A_{2A} receptors stimulate, glutamate release (Ciruela et al., 2006). Preclinical behavioral pharmacology studies have shown that adenosine A_1 antagonism, like A_{2A} antagonism, can in fact stimulate motor activity under some circumstances (Karcz-Kubicha et al., 2003; Bata-García et al., 2010). However, in most toxicological and pharmacological models of parkinsonian motor dysfunction, A_{2A} antagonists are consistently effective in reversing it, whereas A_1 antagonists are either less effective or ineffective (Kelsey et al., 2009). It stands to reason that if activity at the A_1 receptor in fact were unnecessary for the desired effect of an adenosine antagonist, then greater A_{2A} selectivity over A_1 would be an asset.

The authors also postulate that the high A_{2A} over A_1 selectivity of preladenant favors the anti-dyskinesogenic potential of adenosine antagonists. Consideration of the role of adenosine in dyskinesia is often muddied by a failure to clearly distinguish between the phases of dyskinesia. Adenosine receptors have distinct effects on the induction versus the maintenance and/or the expression of this maladaptive plasticity, which characteristically occurs after repeated treatment with exogenous dopaminergic drugs in the setting of endogenous dopamine depletion. Although it was first hoped that A_{2A} receptor blockade might directly suppress the manifestation of established levodopa-induced dyskinesia, it quickly became clear from the first clinical trials of istradefylline that the only real prospects for reducing established dyskinesia with an A_{2A} antagonist might be through an indirect strategy of achieving adjunctive antiparkinsonian benefits that allow for a reduction in the dosing of levodopa (Bara-Jiminez et al., 2003; Hauser et al., 2003).

More promising is the concept of using A_{2A} antagonism to disrupt the neuroplasticity that leads to the sensitized involuntary choreic responses to levodopa. Both genetic and pharmacological approaches to A_{2A} receptor inactivation, when implemented prior to or with (but not after) the dopaminergic drug treatment have attenuated the development of dyskinesia (Fredduzzi et al., 2002; Bibbiani et al., 2003; Xiao et al., 2006). Interestingly, a recent study found that genetic depletion of the A_1 receptor may be just as effective as A_{2A} receptor depletion in reducing the development of levodopa-induced dyskinesia (Xiao et al., 2010). Given these findings, as well as the above mechanistic uncertainty as to whether A_1 and A_{2A} receptors would have opposing effects (e.g., post-synaptically) in the striatum, or offsetting effects (pre-synaptically), a prediction of anti-dyskinetic advantage from greater A_{2A} to A_1 selectivity is tenuous at best.

Perhaps the strongest case for the theoretical advantage of greater A_{2A} specificity can be made based on evidence for a lower risk of developing tolerance to motor stimulant actions of a purer A_{2A} antagonist compared to a non-specific adenosine antagonist. Such tolerance appears attributable to the A_1 receptor-blocking component of mixed adenosine antagonists (Karcz-Kubicha et al., 2003). By contrast, relatively specific A_{2A} antagonism has not shown tolerance to antiparkinsonian actions (Pinna et al., 2001), further enhancing the potential for benefits of long-term treatment with the more selective of the candidate A_{2A} antagonists in development. Interestingly, preliminary clinical data have suggested that an antiparkinsonian effect of mixed A_1/A_{2A} antagonism with caffeine in advanced PD may be achievable, but only transiently due to such tolerance (Kitagawa et al., 2007).

Nevertheless, it is remarkable that initial clinical trials of specific A_{2A} antagonist therapy did not monitor or report concomitant use of caffeine in PD subjects, whose average intake of ~200 mg per day (Simon et al., 2008) of this adenosine antagonist may substantially disrupt striatal A_{2A} receptor ligand binding and signaling, possibly obscuring actions of the test drug (El Yacoubi et al., 2001; Moresco et al., 2005; Brooks et al., 2010). Controlling or stratifying for baseline caffeine consumption levels thus could be informative or even essential to understanding the potential of A_{2A} antagonist therapy for PD. Ultimately, head-to-head comparisons may be required in PD patients to discern the importance of adenosine receptor subtype selectivity.

Beyond symptomatic benefit for movement: Prospects for non-motor and disease-modifying benefits

The primate data presented by Hodgson et al. nicely bridge the gap between rodent and human studies in support of preladenant's potential to treat both parkinsonian and neuroleptic-induced extrapyramidal motor symptoms. The work highlights the realistic expectation of gaining an initial indication for an adenosine A_{2A} antagonist as a novel nondopaminergic treatment for the motor deficits of PD. In preliminary reports of a recent phase II trial of preladenant, it appeared to significantly decrease "off" time and increase "on" time compared to placebo in patients with moderate-severe PD, without increased overall dyskinesias (Hauser et al., 2009). In post-hoc analysis, preladenant was apparently not associated with increased overall dyskinesia severity or increased proportion of time spent in "on" state with troubling dyskinesias in patients with moderate-severe PD (Huyck et al., 2009). Results were generally consistent with those published for multiple phase II and III trials of istradefylline in relatively advanced PD (Bara-Jimenez et al., 2003; Hauser et al., 2003; LeWitt et al., 2008; Stacy et al., 2008; Hauser et al., 2008; Factor et al., 2010; Mizuno et al., 2010).

But beyond the welcome utility of additional improvement for movement disorders, adenosine A_{2A} antagonism is being considered for complementary symptomatic indications. These are based on evidence that A_{2A} receptor activation may contribute to the pathophysiology of a range of neuropsychiatric disorders and dysfunctions such as depression, excessive daytime sleepiness, restless legs syndrome, attention deficit hyperactivity disorder, and cognitive fatigue (El Yacoubi et al., 2003; Müller et al., 2007; Ferré et al., 2007; Pires et al., 2009). Conversely, the potential for non-motor adverse CNS effects of antagonizing the A_{2A} receptor should be appreciated based on its direct actions or its modulation of dopaminergic neurotransmission (Morelli et al., 2010), warranting monitoring for insomnia, impulse control disorder, dopamine dysregulation syndrome, etc, in addition to psychosis.

Perhaps most exciting amongst the potential actions of A_{2A} antagonists are their prospects for disease-modifying benefits in PD and possibly other neurodegenerative conditions like

Alzheimer's disease (Morelli et al., 2010; Canas et al., 2009; Takahashi et al., 2008; Arendash et al., 2010). A remarkable convergence of epidemiological and laboratory data has advanced the proposal that A_{2A} receptor blockers may help prevent PD or slow its progression (Morelli et al., 2010). The consumption of coffee and other caffeinated beverages (but not decaffeinated coffee) has been consistently linked to reduced risk of developing PD. The biological plausibility of protection by caffeine or more specific antagonists of the adenosine A_{2A} receptor has been demonstrated repeatedly in multiple models of the disease. In addition to the neuroprotective potential of A_{2A} antagonism in PD, a possible prophylactic effect on dyskinesia development has been proposed for early adjunctive therapy (with an A_{2A} antagonist paired to the administration of L-Dopa) based on preclinical studies in rodent and NHP models of PD, as above (Bibbiani et al., 2003; Xiao et al., 2006). Consistent with these aspirations, a recently posted major phase III clinical trial of preladenant by Schering-Plough has adopted a "delayed-start" design (D'Agostino, 2009) and a proposed size (1000 subjects) and duration (one year) that may offer the first real insights into the disease-modifying effects of A_{2A} antagonism in PD.

Thus on the proverbial racetrack of neurotherapeutic development, a pack of adenosine A_{2A} antagonists appear to be jockeying for position as they enter the home stretch toward clinical indications, likely initially for the symptoms of PD. Which, if any, of the current 'A_{2A} thoroughbreds' will cross that finish line first is uncertain as any one might pull up lame or sprint ahead. More important may be the next races for additional indications; these may be tougher, but the purses bigger. Certainly, with the high stakes of neuropsychiatric illness it's not just the owners who'd love a big win with adenosine A_{2A} antagonists; it would be great if people with Parkinson's and other CNS diseases could catch a big break.

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