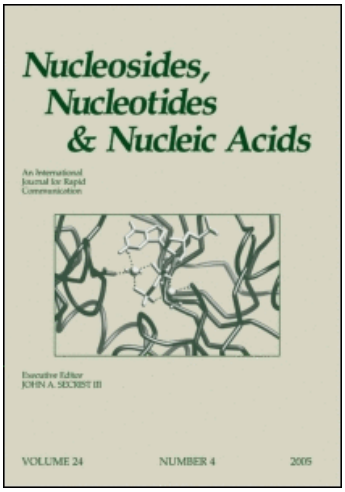

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PURINERGIC PHARMACEUTICALS FOR THE 1990s

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*Abstract.*After more than 60 years of research, the only purinergic compound approved on the basis of its ability to interact with adenosine receptors is adenosine itself in an i.v. formulation for the treatment of cardiac arrythmias. Yet purinergic systems in both the CNS and periphery have been implicated in a wide variety of diseases. The key to exploring the potential of purinergic therapeutics lies in the selection of appropriate therapeutic targets and the development of novel and selective ligands.

Adenosine research has had a long and chequered history in the pharmaceutical industry most of it focussed on the potential use of agonists in the treatment of hypertension [1]. With this singular focus on an area for which a plethora of drugs exist (Table 1), it is not surprising that the currently available adenosine agonists have had limited support and even less success, even at the level of preclinical evaluation, as therapeutic candidates. While agents such as N^6-cyclopentyl adenosine (CPA) and CGS 21680 ((2-*p*-carboxyethyl)phenylamino)-5'- *N*- carboxamido adenosine) are highly selective for A_1 and A_{2a} receptors respectively [2], these agents are still relatively promiscuous in terms of their tissue interactions and consequent physiological effects. And, despite a wealth of literature, it is uncertain whether the CNS actions of adenosine agonists can readily be delineated from their cardiovascular ones and vice versa [1,3]

The consequences of adenosine receptor activation have been studied extensively in the cardiovascular system using physiological paradigms and in the CNS using biochemical ones. The brain has the highest density of adenosine receptors in the mammal, other tissues having one fifth to one tenth the density [4]. From this it may be presumed that adenosine subserves an important role in CNS function, while peripheral tissues are less sensitive to alterations in adenosine availability. The situation with ATP-sensitive tissues is less clear, compounded by the paucity of selective ligands available and little in the way of selective antagonists [2]. The recent

Table 1: Current drug therapies in targeted area for adenosine agonists

a) Antihypertensive agents

1949 -	Hydralazine - vasodilator
1955 -	Mecamylamine - cholinergic antagonist
1957 -	Guanethidine - sympatholytic
1957 -	Chlorothiazide - diuretic
1960 -	Methyldopa - α-adrenergic agonist
1969 -	Prazosin - α-adrenergic antagonist
1978 -	Captopril, enalapril - angiotensin convering enzyme (ACE) inhibitors
1990s -	Renin inhibitors,angiotensin II antagonists,α_2 adrenergic agonists

b) Hypnotic/sedatives - muscle relaxants

1869 -	Chloral hydrate - 'anesthetic-like'
1922 -	Barbital - benzodiazepine receptor modulators/inhibitory effectors
1944-	Antihistamines -
1960-	Benzodiazepines - diazepam - potentiation of GABA actions

c) Antipsychotics

1952 -	Chlorpromazine - dopamine receptor antagonist
1958 -	Haloperidol - dopamine receptor antagonist
1974 -	Clozapine - dopamine receptor antagonist with reduced side effect liability
1989 -	Clozapine - dopamine receptor antagonist with reduced side effect liability
1990s-	Risperidone - dopamine/serotonin-2 receptor antagonist ,SCH 39116 - selective dopamine-1 receptor antagonist, CI 943 - unknown mechanism, BMY 14802-1 - sigma receptor antagonist

d)Anticonvulsants

1868 -	Bromide -
1912 -	Phenobarbitone - GABA receptor modulator.
1936 -	Phenytoin - sodium channel blocker
1953 -	Primidone - phenobarbital prodrug
1958 -	Ethosuximide - inhibitory potentiator - ? dopamine.
1963 -	Carbamazepine - sodium channel blocker
1965-	Clorazepate - potentiation of GABA actions.
1967 -	Valoproic acid - possible GABA potentiator
1990s -	Progabide - GABA agonist, Gabapentin - GABA related but not direct agonist, lamotrigine - inhibition of glutamate release, tiagabine - GABA uptake blocker, vigabatrin - GABA aminotransferase suicide inhibitor and calcium entry blockers

e) Analgesics

1817 -	Morphine - endophin/enkephalin mimic.
	Meperidine - modified opiate
	Oxycodone- modified opiate
	Levorphanol - modified opiate
	Methadone - modified opiate
1964 -	Pentazocine - modified opiate
1968 -	Buprenorphine - modified opiate
1990s -	WIN 48098 - NASID- 'like' analgesic, ketorolac

(continued)

Table 1 Continued

f) Antidepressants

1957 -	Iproniazid - MAO inhibitor
1956 -	Imipramine - monoamine uptake blocker
1960 -	Amitryptiline - monoamine uptake blocker
1988 -	Fluoxetine - 5HT uptake blocker
1990s -	Sertraline - 5HT uptake blocker, paroxetine - 5HT uptake blocker, α-2 receptor antagonists, rolipram - PDE inhibitor corticotropin releasing factor antagonists, S-adenosyl methionine mimics

g) Anxiolytics

1960 -	Diazepam - benzodiazepine receptor ligand
1986 -	Buspirone - $5HT_{1A}$ receptor partial agonist
1990 -	ZK 112.119 , CGS 20625 - non- benzodiazepine benzodiazepines Second generation $5HT_{1A}$ receptor partial agonists (gepirone, tandospirone etc.) and other serotonin receptor ligands (odansetron, fluprazine)

h) Putative anti-ischemics

1990s-	21 aminosteroids (lazaroids) - free radical scavengers, superoxide dismutase (SOD) - free radical scavengers, MK 801 - indirect NMDA antagonist- CGP 39551,direct NMDA antagonist, CNQX- excitatory amino acid K-receptor antagonist, barbiturates

i) Nootropics/Cognition enhancers

1981-	Hydergine - dopamine ergot mixture
1980s -	Piracetam - unknown mechanism
1987 -	HWA 285 - xanthine cerebral blood flow enhancer
1990s -	Muscarinic agonists,tacrine - chlolinesterase inhibitor, nerve growth factor(s)

j) Anti-inflammatory agents

1870s -	Aspirin - cyclooxygenase inhibitor
1948 -	Cortisone
1963 -	Indomethacin -cyclooxygenase(CO) inhibitor
1964 -	Ibuprofen - CO inhibitor
	Naproxen - CO inhibitor
1970 -	Diclofenac - CO/5-lipoxygenase (5-LO) product inhibitor.
1979 -	Diflunisal - CO inhibitor
	Piroxicam - CO inhibitor
1988 -	Tenoxicam - CO inhibitor
1990s -	PAF antagonists, 5- LO inhibitors, C5a antagonists, leukotriene antagonists, phospholipase A_2 inhibitors, interleukin antagonists.

See references 6 - 8 for further information.

delineation of four ATP receptor subtypes, designated x,y, z and t [5] ,with selective agonists [2] may be anticipated to lead to a better understanding of the role of ATP as an extracellular effector agent as efforts in medicinal chemistry are increased.

There is relatively little information in the public domain regarding the evaluation of adenosine in the clinic. Adenosine itself has proven to be very effective as a hypotensive agent in surgery for aneuryism [9] and for the treatment of cardiac arrythmias [10]. As Fujisawa-Lyphomed's Adenocard™, adenosine was approved for use in the U.S.A. in 1989 and received the Food and Drug Adminstration's '1A' category as an important new medication for the treatment of supraventricular tachycardia. In both instances, adenosine's half life of 10s was an advantage in restricting its actions to the targeted use. In the 1970s, Boehringer Mannheim evaluated a number of adenosine agonists as cardiovascular agents while Takeda evaluated CV 1808 (2-phenyl aminoadenosine) as a coronary vasodilator [11]. Clinical evaluation of the agonist, metrifudil (N^6-o-methylbenzyl adenosine) indicated a tendency for agonists to elicit agitation [12] while adenosine *infusion* can cause headaches, flushing, listlessness and angina [13], responses that may reflect bolus effects rather than responses to adenosine *per se*. In the late 1980's Parke Davis, evaluated CI 936 (N^6-(2,2-diphenylethyl) adenosine),a potent, A_2 receptor-selective agonist, as a potential antipsychotic agent. The latter compound experienced some problems in toxicology including emesis but was withdrawn because of cardiovascular liability [14] .

Adenosine as a therapeutic entity

Cardiovascular - As noted, the primary target for adenosine agonists in the cardiovascular system has been as antihypertensive agents. While adenosine itself was considered to be of limited interest because of its nonselective actions at both A_1 and A_2 receptors, reducing blood pressure by an A_2-mediated relaxation of the coronary vasculature and a reduction in cardiac output through A_1-receptor mediated blockade of cardiac conduction, A_2-selective agonists (typified by CGS 21680) were able to effectively decrease blood pressure by the oral route without inducing bradycardia [15]. Yet even receptor selective adenosine agonists do not compare favorably with other drug classes as antihypertensive agents. Table 1 lists key agents in this therapeutic class which, over the years, have resulted in incremental advances in the ability of the clinician to control blood pressure. From what is known of the hypotensive actions of adenosine agonists in preclinical models, they do not appear to offer any advantages over these agents. And, based on their CNS actions and still unknown chronic effects on immune system function, they may in fact be contraindicated. There has been some speculation [1] that adenosine agonists, because of their effects on neutrophil free radical production [16] , platelet aggregation [1,17] and endothelial integrity may have anti-atherosclerotic actions. The limitations of presently available preclinical models of atherosclerosis will probably require that any *bona fide* evidence for a role in limiting atherogenesis will require human data.

Adenosine can effectively block atrioventricular node conduction via activation of A_1 receptors and based on use patents developed by the Charlottesville group [18], has been brought to market for the treatment of supraventricular tachycardia [10]. The xanthine adenosine antagonists are effective cardiotonic agents but are somewhat non-selective in their effects . While other classes onf non-xanthine antagonists have been developed [19] none has yet shown promise in regard to cardiovascular function. And in fact, few of these entities have actually reached clinical trials.

Central Nervous System- in the brain, adenosine systems have been implicated in a wide variety of disease states [4] based on evidence derived from biochemical, electrophysiological and behavioral evaluation of: i) the direct effects of adenosine agonists and antagonists; ii) the effects of adenosine agonists and antagonists on the actions of a wide variety of psychotropic drugs; and iii) the effects of such drugs on adenosine systems and exogenously applied adenosine agonists and antagonists. In view of the very high concentrations of adenosine and adenosine receptors in mammalian brain, the seeming ubiquitous role of the purine nucleoside in CNS (mal)function may be considered to underlie its role as a paracrine effector mediating organ homeostasis [20]. It is important however, to note that adenosine, acting via presynaptic A_1 receptors is an effective inhibitor of the release of a wide variety of neurotransmitters including: acetylcholine, dopamine, serotonin, norepinephrine, GABA, glutamate, histamine and certain peptides and hormones. While the role of adenosine within the context of the selective feedback inhibitory processes associated with the individual transmitters has yet to be defined, it is probable that this effect is manifest under normal conditions as a purinergic inhibitory tone. Under conditions of reduced oxygen availability however, adenosine levels are increased in order to regulate the oxygen supply/demand ratio and restore normal tissue function [21]. The purine may then subserve a predominant role in the modulation of cellular communication.

Adenosine systems have been implicated in the actions of the following drug classes: analgesics, antipsychotics, anxiolytics, antidepressants, nootropics/cognition enhancers, muscle relaxants/hypnotics, anti-ischemic agents and anticonvulsants. Because of interactions with phencyclidine, opiates, amphetamines and alcohol, it is also possible that purinergic systems may be involved in the molecular processes related to substance abuse although the common denominator may be the effect of adenosine on dopamine release and subsequent alterations in the responsiveness of the dopamine reward systems.

Analgesics: The role of adenosine in the transmission of pain is a confusing one with contradictatory results with both agonists and antagonists. The purine does however appear to mediate certain aspects of pain transmission [22] . In the analgesic area however (Table 1) interest in newer agents is confined to those that would be as efficacious as the opiates that have a reduced incidence of respiratory depression, addiction liabiliy and gastrointestinal stasis.

Antipsychotics: There is an extensive literature on the effect of adenosine on dopaminergic systems in the brain [4] and, as noted [14] , CI 936 was identified preclinically as a novel antipsychotic agent. The effects of this novel A_2-selective agonist were apparently compromised by its effects on cardiac function. Comparison of its activity with classical neuroleptics (chlorpromazine) and atypical (clozapine) agents (Table 1) is not feasible, given that the side effects (e.g. tardive dyskinesia) of the majority of antipsychotics are only robustly manifest after chronic administration in the clinic. While there is a real unmet medical need in this area, nearly 40 years of research have failed to identify the cause(s) of the tardive dyskinesia, blood dyscrasias and hepatotoxicity that have been seen in successive generations of antipsychotic agent.

Anxiolytics: The benzodiazepine (BZ) , diazepam and a wealth of related structures represent the major source of drugs to treat anxiety [23].These entities agents are however, addictive, sedating, are potent muscle relaxants and potentiate the actions of alcohol. Newer anxiolytics are represented by non-BZs that interact with the BZ receptor including CGS 20625 and the β-carboline, ZK 112,119, and a number of serotonin receptor ligands including the $5HT_{1A}$ partial agonists, buspirone, gepirone and related structures as well as fluprazine and CGS 18102, the $5HT_2$ antagonist, risperidone and the $5HT_3$ antagonist, odansetron. These latter agents are effective and safe in individuals who are naive to BZs but have efficacy problems during BZ withdrawal. There is a large body of data supporting an interaction between adenosine and the BZs [24] at the molecular level. In addition caffeine, the prototypic xanthine antagonist, is anxiogenic [4] . However, given the large number of products already on the market and in development and the fact that despite its side effects, diazepam is a very safe drug, it is unlikely that presently available adenosine receptor ligands will represent novel agents for use in generalized affective disorders.

Antidepressants: These drugs are primarily represented by agents that increase the availability of monoamines in the synaptic cleft. Limited studies have indicated that adenosine may interact with tricyclic antidepressants and a novel adenosine receptor antagonist, CP 66, 713, entered clinical trials as an antidepressant based on activity in a preclinical behavioral despair paradigm [25]. While fluoxetine (Prozac™), a selective 5HT-uptake blocker (Table 1) has been heralded as a major advance in the effective treatment of depression, it is still probable that newer agents with a more rapid time of onset will be useful especially as population demographics delineate an increase in the elderly depressed.

Nootropics/cognition enhancers : Agents effective in enhancing memory are few and far between. Caffeine , the 1-substituted xanthine, HWA 285 [4] and the 8-cyclopentyl xanthine KFM 19 [26] have proven effective as cognition enhancers. A variety of other agents exist (Table 1) that have been variously reported to improve memory in inhibitory avoidance paardigms in rodents. These agents have also been proposed as potential therapies for the senile dementias, most notably of the Alzheimer's type. The reported efficacy of such agents is highly variable although

several have been approved for human use [27]. The cholinesterase inhibitor, tacrine, is in extensive clinical trials as a means to enhance cholinergic function in Alzheimer's. There is a major unmet medical need in this area and if brain selective adenosine antagonists can be developed as cognition enhancers, these will represent a significant contribution to the pharmacopea.

Muscle relaxants/hypnotics.: The sedating actions of adenosine are well known, with caffeine administered in beverage form acting as a central stimulant (and diuretic) by blocking the actions of endogenous adenosine [4]. In animals, adenosine reduces locomotor activity. Despite the limitations of presently available compounds (overdose, addiction, after effects) used as hypnotics and/or muscle relaxants, the cardiovascular liability of direct agonists has precluded any real effort in assessing their clinical potential as drugs for these indications.

Anti-ischemic agents : Stroke is a major cause of death and brain damage and has received considerable attention in the research community as the mechanisms underlying the cause of cell death become better understood [23]. The ischemia occurring in stroke results in an increase in the excitatory neurotransmitter, glutamate. This amino acid, through its interaction with the N-methyl-D-asparate (NMDA) receptor, causes a rapid influx of calcium into neurons, primarily in the hippocampus. Under normal conditions, the mitochondria are able to achive calcium homeostatis by pumping out the excess cation. However, during stroke, energy stores are depleted and the calcium accumulates, leading to cell death. This situation may then be exacerbated during reperfusion due to an increased recruitment of neutrophils and further damage via free radical formation.

Adenosine levels are also increased during stroke-related ischemia and it can be hypothesized that adenosine, via its activation of presynaptic A_1 receptors, has the potential to inhibit glutamate release and thus prevent the subsequent events related to cell death. The major focus of research efforts in this area has been on the NMDA receptor with direct (CGP 39551) and indirect (MK 801) antagonists being effective in gerbil models of stroke. Adenosine agonists are also effective in this model [28] as are a large number of other centrally active agents. The apparent anti-ischemic action of these entities is confused by the sensitivity of the gerbil model to body temperature and the ability of many of these compounds to alter core temperature independent of any anti-ischemic effect has apparently led to 'false positives'. Under controlled conditions however, adenosine agonists are effective anti-ischemic agents. As the consequences of stroke are life threatening and often associated with high blood pressure, the side effects of non-selective adenosine agonists may be tolerable on the acute basis necessary to prevent brain damage. The hypotensive and anti-platelet/neutrophil actions may also be synergistic in reducing the further cell loss potentially associated with reperfusion injury.

Ischemia-related cell death, both central and cardiac, can also be reduced by free radical scavengers. Agents currently under evaluation for this use are the 21-aminosteroid (lazaroid) free radical scavengers as well as the free radical scavenger, superoxide dismutase (SOD) coupled to polyethyelene glycol (PEG-SOD) to prolong its plasma half life.

Anticonvulsants: Adenosine has been proposed as an endogenous anticonvulsant [29].The potential of the purine as an anti-epileptic agent parallels in many respects its role as an anti-ischemic agent. However, unlike stroke, anticonvulsants are usually prophylatically and thus ligand selectivity is of primary importance. Several classes of anticonvulsant exist (Table 1) many working through their ability to potentiate or mimic the actions of the inhibitory transmitter, GABA. Carbamazepine, one of the major entities in this drug class has weak interactions (μM) with adenosine A_1 and A_2 receptors [4] but no clear relationship has emerged for a purinergic mechanism of action. The major limitations in current anticonvulsant agents are their varying efficacy, tetratogenicity, photosensitivity and, to varying degress, their ability to impair memory.

Renal Adenosine has a complex physiological role in the kidney involving indirect effects on the renin-angiotensin system, renal blood flow and glomerular filtration rate [30]. Adenosine appears to be a physiological regulator , acting as a homeostatic effector in maintaining kidney function independent of blood pressure changes. The purine has antidiuretic and antinatriuretic actions and plays a key role in the hemodynamic changes accompanying acute renal failure (ARF) acting in a synergistic manner with the ischemic episode. Based on the protective actions of theophylline in ARF , Jacobson and colleagues [31] have made a xanthine prodrug, N-acyl-γ-glutamyl xanthine amine congener (XAC), XAC being a potent and selective adenosine antagonist. The prodrug is cleaved by the kidney specific enzyme, γ-glutamyl transpeptidase to yield localized XAC thus avoiding the actions of the xanthine on other tissues. The pyrazolopyridine, FR 113,453 [32] is an A_1-selective renal vasodilator.

Immune Function New receptors and ligands for systems involved in the immune response are being discovered on an almost weekly basis. Immunological diseases represent a major unmet medical need and the primary approach to therapy at the present time is to search for antagonists of the lymphokine/cytokine mediators of the inflammatory response (Table 1). The role of purinergic systems in the immune response has not been extensively studied but it is known that adenosine can inhibit lymphocyte proliferation and T cell mediated lysis as well as modulate monocyte differentiation [33] and the expression of T-cell 'subset specific' surface antigens [34]. The latter effect diminishes helper T cell function and can impair B- cell differentiation [20,34]. More recently it has been reported [35] that adenosine formed from ATP following B cell activation , part of a 'purinergic cascade' [2], can act to affect T cell activity.

Inflammation. There are a variety of mediators of the inflammatory response that affect nearly all organ systems. In addition to the more obvious manifestations of inflammation such as headache, arthritis, infection and tissue trauma, the possibility that heart disease and Alzheimer's disease may be prophylatically treatable by the use of aspirin has attracted considerable interest.

In addition to the classical cyclooxygenase inhibitors, the non-steroidal antiinflammatory agents (NSAIDs), other classes of agent that have the potential to combat the inflammatory response include various antagonists of the arachidonic acid response and inhibitors of the enzymes in the pathways (5-lipoxygenase) as well as DMARDs (disease modifying antirheumatic drugs) such as cortisone and methotrexate. Complement C5a and platelet activating factor (PAF) antagonists represent newer approaches to therapy. Interestingly however, adenosine ligands have comparable, if not superior efficacy to NSAIDs, in animal models of inflammation [36], effects that may be related to their ability to attenuate neutrophil - associated damage. One unanswered question however, based on the known activities of currently available adenosine agonists and the use of nucleosides in the treatment of immunodeficiency diseases, is whether agonists given chronically may compromise the function of the immune system.

Indirect agonists

The problem with the side effects associated with the promiscuous activation of adenosine receptors by agonists has led to an increased focus on agents that can indirectly alter the effects of endogenous adenosine. These have a theoretical advantage in that they would principally target organs where adenosine production is altered, presumably those subject to disease - associated trauma.Such agents can be divided into nucleoside transport inhibitors, adenosine potentiators and allosteric modulators.

The prototypic transport inhibitor is dipyridamole but more selective and potent agents typified by mioflazine are in clinical trials as hypnotics [37] and are rumoured to be undergoing evaluation as anticonvulsants.The possible existence of multiple nucleoside transporter proteins may provide the mechanism by which to selectively target tissues. A second class of compound that potentiates the actions of adenosine is Gensia Pharmaceutical's AICA (5-amino- 4- imidazole carboxamide) riboside [38]. This adenosine analog through some unknown and somewhat controversial [1] mechanism can enhance adenosine levels in regions where trauma-induced (ischemia etc.) ATP breakdown is occurring. AICA-riboside is in Phase II clinical trials for potential use in reperfusion injury. The third type of adenosine potentiator is represented by a new class of allosteric enhancer of adenosine actions, the aminobenzoyl- thiophene, PD 81,723 [39].

ATP receptors as therapeutic targets

For many years, the hypothesis that ATP was a intercellular mediator was treated as an academic curiosity. Without selective agonists and antagonists, the ability to test the hypothesis was limited to a few ATP analogs available in limited quantities with experimentation accordingly limited to a very few tissues. Evidence for ATP receptor subtypes [6] has prompted renewed efforts in defining both the pharmacology and role of ATP in tissue function with β,γ-dichloromethylene-ATP being identified as a reasonably potent P_{2x} receptor antagonist [40]. Activity in the area of ATP receptor ligands has increased exponentially in the past year and will play a key role in determining the inter-relationships betwen ATP, ADP, AMP and adenosine in the regulation of cellular homeostasis [2].

Receptor heterogeneity

Drug discovery has traditionally depended on the sequence:

a) Identification of molecular target (enzyme, receptor, transporter, ligand responsive element etc.) and first generation agonists/antagonists.

b) Structure activity relationship development with identification of potential subtypes of target.

c) Identification of target subtype selective ligands.

d) The use of these agents to define disease pathology and design selective and efficacious therapeutic agents.

This approach, often termed rational drug design [41,42], in concert with targeted screening has led to the discovery of significant entities that have been invaluable as drugs or research tools. In the therapeutic arena, the Nobel laureate, Black's efforts [43] have led to two major therapeutic agents, the β-blocker, propranolol and the histamine H_2 blocker, cimetidine. At the research level, rational drug design has resulted in agents like the non-peptide cholecystokinin-A receptor antagonist, MK 329 [44]. The advent of molecular biology has enhanced this approach to drug discovery with the identification of receptor superfamilies resulting in novel targets for molecular design approaches [41,44].

Purinergic drugs?

Is the continued optimism in regard to the potential of adenosine and/or ATP ligands, agonists or antagonists, a result of a myopic view of the therapeutic world based on the narrow research interests of its proponents? Or is it a tenable drug discovery strategy that will yield important new therapeutic entities in the 21st century?

When one considers that it was only a decade ago that ATP- related research was considered largely an academic pursuit and that selective ligands and the concept of indirect modulators were not even proposed, it may be anticipated that with the choice of appropriate therapeutic targets and a better understanding of the role(s) of adenosine and ATP in disease etiology, the next decade will allow the choice between the two options noted above based on data rather than armchair skepticism. This author has noted [20] that the field of peptide- related drug targeting has many similarities in terms of ubiquity of effect and unknown pathophysiology to the purines. Yet because peptide-related research is 'in vogue', its popularity rejects the application of the objectivity that has rightfully accompanied adenosine-related research, an area which is only now able to be addressed in this context as knowledge of the systems and receptors has accumulated. Of the areas in which adenosine (and to a lesser extent, ATP) has been implicated as a drug target, the two that appear most promising are those in which knowledge of the disease states is primitive (but developing) and for which there are few (if any) safe and effective medications. A decrease in the effort related to the potential antihypertensive use of

adenosine ligands with, instead a more focussed effort in designing (and discovering) entities that modulate CNS and inflammatory/immune responses represents a more optimal approach to developing purinergic drugs.

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