

# ADVANCES IN DRUG DISCOVERY

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## NK1 receptor antagonist by Roche

DailyUpdates 23rd February, 2006: The tachykinins were first identified in 1931 however realization of the therapeutic potential of antagonists that block their action has only taken place over the last decade. Tachykinin receptor antagonists have been implicated in various conditions such as depression/anxiety, pain, airway disease, incontinence, nausea and bowel disorders.

The tachykinins are the products of two genes, preprotachykinin I which produces substance P (SP) and neurokinin (NK)A and preprotachykinin II which produces NKB. In 1986 the research community classified the tachykinin receptors into 3 subtypes, NK1, NK2 and NK3 receptors and one of the earliest examples of advanced development of the tachykinin antagonist class was in the field of depression and anxiety following pioneering work in a number of laboratories and especially those of Merck & Co.

Both the limbic system and the mesencephalic brain stem express high levels of SP-like immunoreactivity supporting their role in anxiety and depression. This is further evidenced by the anxiogenic effect of NK1 or NK2 agonists when administered into the CNS and the observation that SP levels are altered in experimental models of stress, anxiety and depression. On the basis of this data first generation NK1 receptor antagonists such as CP96345 were investigated for anxiolytic activity. Of ground breaking importance, MK-869 became the first NK1 antagonist to demonstrate therapeutic activity in patients with a cohort of depressed patients displaying significant improvement in both the level of depression and anxiety. The magnitude of this effect was similar to paroxetine while accompanied by fewer adverse effects.

As discussed in our recent feature [The World Market for Antidepressants 2006](#), sales of antidepressant will crash over the next few years producing revenues in 2010 of only \$7bn. This loss of almost 50% of total revenues is due to patent expirations. The lackluster pipeline is unlikely to halt this massive revenue loss in the near-term. This situation could have been different had the initial success of MK-869 been reproduced however this was not the case and in a subsequent study required for regulatory approval efficacy was not observed. Further development of

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MK-869 for the treatment of depression was subsequently terminated. Data later emerged to suggest that this failure was due to an elevated placebo effect opening the way for other NK1 receptor antagonists, however by that time MK-869 was on its way to becoming the first approved NK1 antagonist (launched as Emend; Aprepitant) but with the indication being nausea and vomiting.

A Roper Starch survey of chemotherapy patients found that prior to starting treatment, 32% reported surviving cancer as their biggest concern versus 40% who said side effects were their biggest concern. The most serious adverse effects of chemotherapeutic agents include anemia and related fatigue; neutropenia and associated risks of infection; and nausea and vomiting. Consequently the development of supportive care products to combat fatigue and neutropenia has played an important role in oncology research and development (see our feature Cancer Market Top 20 Drugs - Supportive Care Grows the Cancer Market).

According to the National Cancer Institute, over 500,000 Americans received chemotherapy in 2004. Patients receiving chemotherapy for cancer reported a greater degree of treatment-induced nausea and vomiting than generally recognized. An estimated 75% suffer from nausea or vomiting within 24 hours of treatment, and about 90% of all patients suffer from chemotherapy-induced nausea or vomiting 2-5 days after treatment (delayed onset chemotherapy-induced nausea and vomiting). If left untreated, chemotherapy-induced nausea and vomiting can result in a delay or discontinuation of chemotherapy and the majority of patients thus receive an antiemetic. The 5-HT<sub>3</sub> receptor antagonists revolutionized the treatment of chemotherapy-induced nausea and vomiting and Zofran (Ondansetron), the market leader, generating annual US sales worth approximately \$1.0 billion in 2003.

The vomiting reflex involves both central and peripheral components and the emetic response is integrated in the vomiting center a region including the nucleus tractus solitarius. SP and NKA are expressed in this region of the brain. The ferret has been extensively studied to determine the anti-emetic activity of tachykinin antagonists and prototypic antagonists were found to reduce retching in various animal models, including cisplatin-evoked emesis. Of importance the effects of NK1 and 5HT<sub>3</sub> antagonism during the acute phase of emesis were additive. Perhaps even more important was the observation that NK1 receptor antagonism blocked both acute and delayed emesis; this finding was important since the control of delayed nausea and vomiting following cytotoxic administration has traditionally been a challenge.



Following the successful completion of two trials of over 1000 cancer patients receiving **highly** emetic chemotherapy, the FDA announced the approval of Emend (aprepitant) in 2003. In 2006, the FDA extended its approved indications to include the use of Emend in combination with other antiemetics, for the prevention of nausea and vomiting in cancer patients undergoing initial or repeat treatment with **moderately or highly** emetogenic chemotherapy

The trials and tribulations of Emend have been followed by a surge of activity from a number of other companies developing NK1 receptor antagonists including GSK

who have **vestipitant and casopitant in phase II** development for depression, anxiety, and nausea & vomiting. Roche have also been involved in the development of NK1 receptor antagonists.

In their study due to be published in the March edition of *Bioorg Med Chem Lett*, Hoffmann and colleagues from Roche describe the design of two promising NK1 receptor antagonists, netupitant and befetupitant. These two molecules were optimized from a lead NK1 antagonist with nanomolar affinity identified during a random screen of Roche's corporate library. Netupitant and befetupitant both displayed sub-nanomolar affinity at the NK1 receptor. Further *in vivo* study demonstrated that oral pretreatment with either of these compounds blocked NK1-induced foot tapping in gerbils with an efficacy approaching 0.1mg/kg.

The excellent potential of netupitant and befetupitant has resulted in the licensing of netupitant to the Swiss company, Helsinn Healthcare in 2006. Helsinn already has experience in the anti-emetic market having developed the 5HT3 antagonist Aloxi (palonosetron), which was launched in 2004. The improved pharmacokinetic properties of this compound mean that it is useful for the prevention of **delayed** nausea and vomiting, an indication for which it gained approval. Since 5HT3 and NK1 receptor antagonists exert additive effects there is considerable potential for the combined use of Aloxi and netupitant.

Befetupitant remains a licensing opportunity and deserves consideration from companies involved in the development of anti-emetics. Hopefully befetupitant may also strengthen the antidepressant pipeline and companies involved in the field of psychiatry may also be interested in contributing to the advance of befetupitant. Licensing-related inquiries should be directed to [kurt.gathof@roche.com](mailto:kurt.gathof@roche.com) at Roche.

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