

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Pharmaceutical Science to Improve the Human Condition: Prix Galien 2010***Development of Aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting**

Richard Hargreaves, Juan Camilo Arjona Ferreira, David Hughes, Jos Brands, Jeff Hale, Britta Mattson, and Sandy Mills

Merck & Co., Inc., Sumneytown Pike, Pennsylvania

Address for correspondence: Richard Hargreaves, Worldwide Franchise Discovery Head Neuroscience, Merck and Co., WP42-212, P.O. Box 4, 770, Sumneytown Pike, PA 19486. richard_hargreaves@merck.com

Chemotherapy can be a life-prolonging treatment for many cancer patients, but it is often associated with profound nausea and vomiting that is so distressing that patients may delay or decline treatment to avoid these side effects. EMEND™ (aprepitant) is the first and only neurokinin-1 (NK-1) receptor antagonist available on the market for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Aprepitant acts centrally at NK-1 receptors in vomiting centers within the central nervous system to block their activation by substance P released as an unwanted consequence of chemotherapy. By controlling nausea and vomiting, EMEND helps improve patients' daily living and their ability to complete multiple cycles of chemotherapy. The development of aprepitant included a novel nanoparticle formulation to optimize oral absorption and innovative chemistry to discover a prodrug form suitable for intravenous administration to improve compliance and convenience for healthcare professionals and cancer patients.

Keywords: EMEND; aprepitant; neurokinin-1 receptor antagonist; chemotherapy-induced nausea and vomiting; cancer

Introduction

Cancer is one of the leading causes of death worldwide, and its incidence is increasing rapidly as the worldwide population continues to grow and age. Despite truly meaningful progress in the field of targeted chemotherapy, many cancer treatment regimens still use cytotoxic chemotherapeutic agents that produce profound emesis and nausea that occur acutely on the day of chemotherapy and then reappear some days later—often at home away from the gaze and care of the oncologist's office. These debilitating and feared side effects are well documented in open-access sites, such that informed patients who research their cancer treatment options often delay or postpone their therapy and sometimes completely refuse or withdraw from the very therapy that has been prescribed to prolong or save their lives. Control of chemotherapy-induced nau-

sea and vomiting (CINV) is therefore a significant factor in ensuring that oncology patients maintain quality of life during their treatment regimens to get the full benefit of chemotherapy.

Drug therapies have been previously developed for the prevention of nausea and vomiting associated with anticancer chemotherapy (Fig. 1A). In the 1960s, phenothiazine dopamine D₂ receptor antagonists such as prochlorperazine (Compazine®), Stemetil®) that are potent antipsychotic compounds were used to control emesis, but these have several potential mechanistic side-effect liabilities including causing dyskinesias. In the 1980s, it was found that high doses of the dopamine D₂ receptor-5-HT₃ receptor antagonist metoclopramide combined with the steroid dexamethasone had improved efficacy particularly in the control of acute CINV 0–24 h postchemotherapy. In the 1980s, research showed that it was the 5-HT₃ receptor

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Pharmaceutical Science to Improve the Human Condition: Prix Galien 2010*

Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting

Richard Hargreaves, Juan Camilo Arjona Ferreira, David Hughes, Jos Brands, Jeff Hale, Britta Mattson, and Sandy Mills

Merck & Co., Inc., Sumneytown Pike, Pennsylvania

Address for correspondence: Richard Hargreaves, Worldwide Franchise Discovery Head Neuroscience, Merck and Co., WP42-212, P.O. Box 4, 770, Sumneytown Pike, PA 19486. richard_hargreaves@merck.com

Chemotherapy can be a life-prolonging treatment for many cancer patients, but it is often associated with profound nausea and vomiting that is so distressing that patients may delay or decline treatment to avoid these side effects. EMEND™ (aprepitant) is the first and only neurokinin-1 (NK-1) receptor antagonist available on the market for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Aprepitant acts centrally at NK-1 receptors in vomiting centers within the central nervous system to block their activation by substance P released as an unwanted consequence of chemotherapy. By controlling nausea and vomiting, EMEND helps improve patients' daily living and their ability to complete multiple cycles of chemotherapy. The development of aprepitant included a novel nanoparticle formulation to optimize oral absorption and innovative chemistry to discover a prodrug form suitable for intravenous administration to improve compliance and convenience for healthcare professionals and cancer patients.

Keywords: EMEND; aprepitant; neurokinin-1 receptor antagonist; chemotherapy-induced nausea and vomiting; cancer

Introduction

Cancer is one of the leading causes of death worldwide, and its incidence is increasing rapidly as the worldwide population continues to grow and age. Despite truly meaningful progress in the field of targeted chemotherapy, many cancer treatment regimens still use cytotoxic chemotherapeutic agents that produce profound emesis and nausea that occur acutely on the day of chemotherapy and then reappear some days later—often at home away from the gaze and care of the oncologist's office. These debilitating and feared side effects are well documented in open-access sites, such that informed patients who research their cancer treatment options often delay or postpone their therapy and sometimes completely refuse or withdraw from the very therapy that has been prescribed to prolong or save their lives. Control of chemotherapy-induced nau-

sea and vomiting (CINV) is therefore a significant factor in ensuring that oncology patients maintain quality of life during their treatment regimens to get the full benefit of chemotherapy.

Drug therapies have been previously developed for the prevention of nausea and vomiting associated with anticancer chemotherapy (Fig. 1A). In the 1960s, phenothiazine dopamine D₂ receptor antagonists such as prochlorperazine (Compazine®), Stemetil®) that are potent antipsychotic compounds were used to control emesis, but these have several potential mechanistic side-effect liabilities including causing dyskinesias. In the 1980s, it was found that high doses of the dopamine D₂ receptor-5-HT₃ receptor antagonist metoclopramide combined with the steroid dexamethasone had improved efficacy particularly in the control of acute CINV 0–24 h postchemotherapy. In the 1980s, research showed that it was the 5-HT₃ receptor

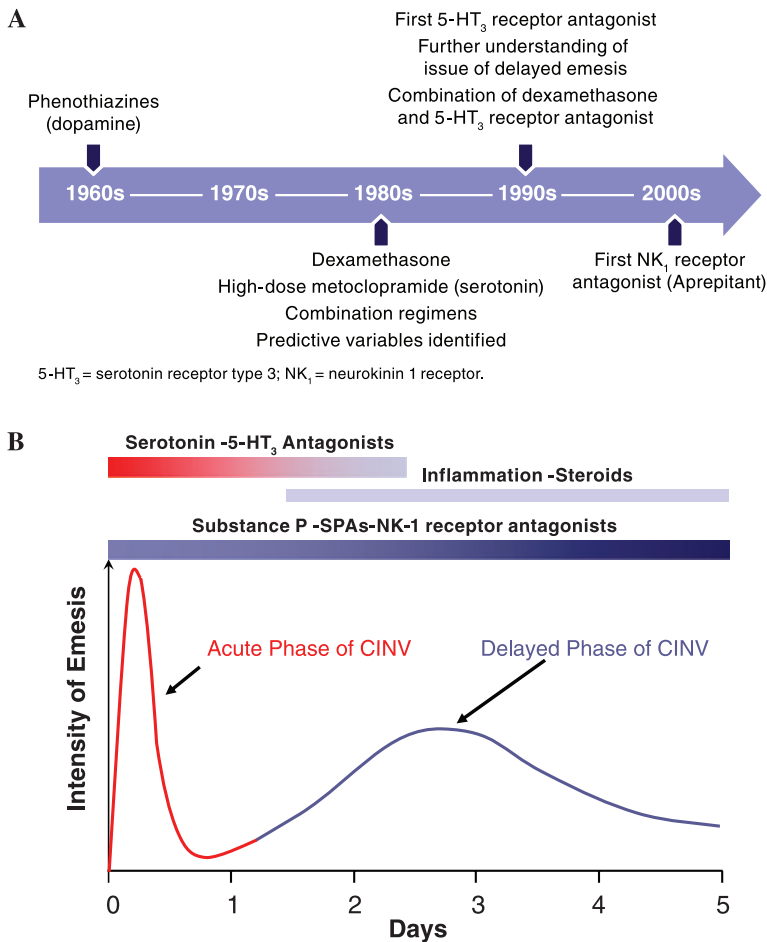


Figure 1. (A) Timeline of agents discovered to prevent emesis. (B) Time course of emesis and drug-sensitive phases.

component of metoclopramide that underpinned its efficacy in CINV, spurring the development of selective 5-HT₃ receptor antagonist drugs with improved tolerability by removing the liability of D₂ receptor antagonism. The first of these to be registered in the 1990s was ondansetron (ZOFRAN[®]), which was effective in the control of acute CINV with some additional benefit in the delayed phase of CINV (>24–120 h after chemotherapy) when combined with a corticosteroid such as dexamethasone. However, although combined therapy with these two agents provided control of CINV symptoms in the acute phase, their protective actions were poor during the delayed phase of CINV, which often occurs at home away from the oncology clinic some days later. Therefore, there remained an important unmet medical need for novel treatment

agents to further improve control of CINV, especially in the delayed phase. Throughout the 1990s, research focused on the role of substance P and neurokinin-1 (NK-1) receptors in emesis and, in particular, the protective effects of NK-1 receptor antagonists against the acute and delayed emetic responses to chemotherapeutic agents (Fig. 1B). In 2003, EMEND^a (aprepitant) became the first and is still the only NK-1 receptor antagonist available on the market for the prevention of CINV in cancer patients. EMEND provides a significant improvement in the number of patients who can tolerate their cancer chemotherapy without episodes of vomiting, particularly during the delayed phase, thereby

^a Registered trademark of Merck & Co., Inc.

improving their quality of life and allowing them to complete and benefit from the full course of their chemotherapeutic treatment regimens.

History of the development of aprepitant

The substance P story has been nearly 80 years in the telling—from the isolation of the peptide, to its sequencing, to the cloning of its receptor and the synthesis of the first small molecule antagonists. The journey began in 1931 when a pharmacologically active substance was isolated from the brain and intestine and named substance P—“P” for powder—by the pioneering pharmacologist John Gaddum working with Ulf von Euler.¹ In 1954, Gaddum continued his research into this extract and showed that substance P was concentrated in the emetic centers of the brain, commenting in his manuscript in the *Journal of Physiology* that “it is tempting to speculate why this is so.”² It was not until 40 years later, in 1971, that the active substance, an 11-amino acid peptide, was isolated, sequenced, and synthesized *de novo* by Susan Lehman and her group.^{3,4} Yet another 20 years went by, to 1991, before the receptor for substance P, the NK-1 receptor, was identified and cloned,⁵ and small-molecule blockers or antagonists of substance P that could access these NK-1 receptors in the emetic centers in the brain were developed. Amazingly, in line with Gaddum’s speculation, these substance P antagonists (SPAs) were shown to be the broadest spectrum antiemetics ever described.

Research at Merck began during the 1980s to discover SPAs with which to understand the role of substance P in health and disease. For many years this proved a difficult task, and only peptide antagonists that were unsuitable as oral drug candidates and that did not cross the blood–brain barrier were synthesized. In the early 1990s, the first small molecule brain-penetrant SPAs became available,⁶ enabling the investigation of the therapeutic potential of the NK-1 antagonist mechanism. Despite strong anatomical evidence supporting a potential role for substance P in pain and affective disorders, the SPAs were inactive as analgesics and as antidepressants. The hypothesis that substance P was involved in emesis was initially supported by three preclinical observations: substance P was localized in the emetic centers of the brain, substance P could cause emesis, and depletion of substance P using a toxin (resiniferatoxin) could prevent eme-

sis in preclinical species with a vomiting reflex. The critical proof that the substance P/NK-1 receptor axis played a crucial role in mediating the vomiting response to a number of stimuli came with demonstration that highly selective SPAs had profound activity against emesis induced by broad range of central and peripherally acting emetogens.^{7,8} Moreover, these SPAs were active in multiple species with a vomiting reflex against a broad range of emetogens,⁹ giving high confidence that the mechanism would translate to clinically meaningful activity.¹⁰ In particular, SPAs were active against emesis induced by chemotherapeutic agents such as cisplatin and uniquely against the delayed phase of emesis that can recur days after treatment with such cytotoxic agents.¹¹ Continued research into the antiemetic mechanism of action of the SPAs showed that SPA molecules had to penetrate the brain to access central NK-1 receptors in the brain-stem emetic centers in order to be effective in preclinical models. Potent SPAs that did not cross into the brain were ineffective as antiemetics.¹² Aprepitant¹³ was chosen for development on the basis of its notable efficacy and long duration of action in the preclinical emesis assays.

PET imaging NK-1 receptors in the brain

Confirmation that drugs reach their targets using markers of engagement is key to successful proof-of-concept testing, especially for drugs acting in the brain. Knowing how hard and how long a drug must hit its target to produce the desired pharmacologic effect is important for dose selection and clinical trial design and interpretation. During the aprepitant program, a novel PET tracer that imaged NK-1 receptors in living human brain was developed to visualize the central sites of action of aprepitant and to assess their occupancy by therapeutic doses of the drug (Fig. 2). Understanding the relationships between dose, plasma concentration, and receptor occupancy for aprepitant helped establish the link between target engagement and changes in the CINV clinical endpoint. This knowledge was important in the selection of the dosing regime for the regulatory filing of aprepitant and ensured that the lowest drug exposure that achieved target engagement consistent with >90% blockade of NK-1 receptors was chosen, thereby maximizing the potential therapeutic safety window of aprepitant.^{14,15} The PET tracer was also used to predict the

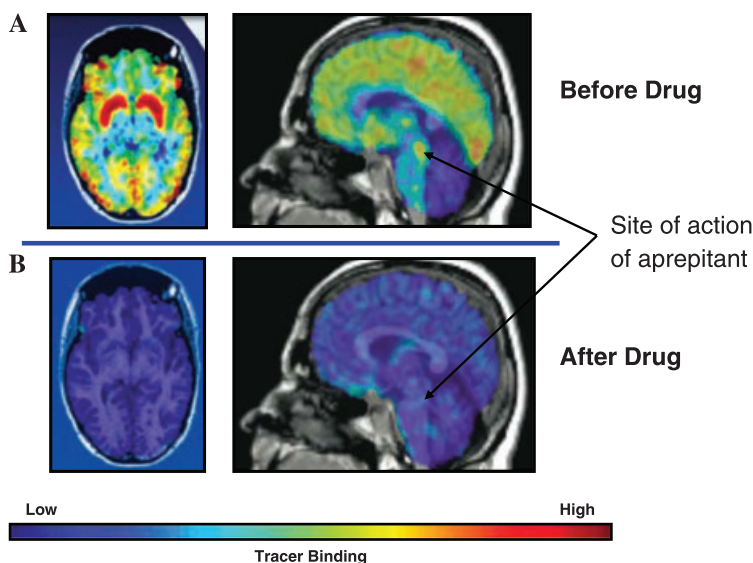


Figure 2. Occupancy of central NK-1 receptors by aprepitant visualized using PET imaging.

bioequivalence of different oral formulations of the drug by linking plasma concentration rather than dose to brain receptor occupancy and clinical efficacy. This was important information because the oral formulation of aprepitant required considerable optimization (see below).

Synthesis of aprepitant: a chemistry challenge

Synthesizing the aprepitant molecule is a synthetic chemistry challenge as it comprises two heterocyclic rings and three stereogenic centers in close proximity. A first-generation route was used for the production of 100 kg of aprepitant, but was deemed not sufficiently economical or environmentally benign for commercial manufacturing. The first-generation synthesis required several hazardous chemicals, such as sodium cyanide, dimethyltitanocene, and gaseous ammonia, and used extremely low temperatures in some steps. In addition, the route was poorly efficient, generating a large quantity of waste. As aprepitant moved through clinical trials and closer to regulatory filing, it became clear that a completely new route was required to address these liabilities. A team of process chemists went back to the drawing board, examined a number of alternate routes, and ultimately designed and developed a novel and efficient manufacturing route.

The streamlined synthesis used a “crystallization-induced asymmetric transformation.”¹⁶ In this process, the desired isomer of aprepitant crystallizes, and, simultaneously, the unwanted isomer is converted to the desired isomer, ultimately providing aprepitant in high yield and purity. This chemistry innovation halved the number of process steps while doubling the overall yield of aprepitant. The synthesis eliminated several hazardous chemicals; used 80% fewer raw materials, reagents, solvents, and less water; and was more energy efficient. The overall waste production was reduced by 85% as compared to the first-generation synthesis. This significant minimization of environmental impact was recognized by the U.S. Environmental Protection Agency in awarding their prestigious 2005 Presidential Green Chemistry Challenge Award to Merck & Co., Inc. for the redesign of the synthesis of aprepitant. Since the manufacturing process innovation occurred during the first year of aprepitant production, these benefits will be realized over the entire life cycle of EMEND.

Biopharmaceutical sciences: oral formulation of aprepitant

Early clinical tablet formulations of aprepitant showed highly variable, large food effects on absorption. Given the targeted patient population, development of a more bioavailable formulation was

crucial for the program. A number of alternate formulations such as liquid-filled capsules, alternative excipients, and amorphous drug substances were tested, but all met with limited success. Ultimately, a nanoparticle formulation that enhanced bioavailability and attenuated the food effect was developed using NanoCrystal[®] technology, licensed to Merck from Elan/Nanosystems. This process involved media milling of drug particles to <200 nanometers, coating onto beads, and encapsulation to provide a convenient formulation for the patient.¹⁷ EMEND was approved by the U.S. Food and Drug Administration (FDA) in 2003. EMEND is dosed orally as a 125 mg tablet on the first day of chemotherapy treatment and as an 80 mg tablet on days two and three after chemotherapy.

Fosaprepitant: a prodrug of aprepitant for intravenous use

The sparing water solubility of aprepitant precluded its formulation in a vehicle acceptable for intravenous administration in humans. Since the availability of both an oral and an intravenous formulation of aprepitant would increase the delivery options available to oncologists and patients and provide maximum clinical dosing flexibility, we sought ways to overcome the solubility issues associated with aprepitant. An unprecedented prodrug strategy was undertaken in the chemistry program to discover a chemical form of aprepitant that had good water solubility, with the potential to be rapidly metabolically converted *in vivo* to the parent aprepitant while releasing innocuous residues, yet exhibited sufficient chemical stability to allow for routine handling and storage. The *N*-phosphoryl derivative of aprepitant (fosaprepitant) was synthesized,¹⁸ and it was shown in a series of preclinical experiments to be metabolically converted to aprepitant both *in vitro* and *in vivo*, as well as to be functionally equivalent to aprepitant *in vivo*. Clinical studies then showed that fosaprepitant has a favorable tolerability in humans and excellent efficacy in the treatment of chemotherapy-induced emesis, thereby demonstrating the viability of the prodrug strategy for the intravenous delivery of aprepitant.¹⁹ Fosaprepitant was approved in 2008. EMEND (fosaprepitant dimeglumine) for Injection (also known as IIVEMEND[®] in Europe) 115 mg can be substituted for the 125 mg oral capsule of aprepitant on the first day of chemotherapy treatment.

Clinical development of aprepitant

During the clinical phase of development, aprepitant was studied in more than 6,500 patients in randomized controlled trials, and showed statistically significant and clinically meaningful reductions in the incidence of CINV associated with moderately to highly emetogenic chemotherapy compared with the prior standard regimen of a 5-HT₃ receptor antagonist and dexamethasone, and was well tolerated.^{20–26}

Aprepitant for control of postoperative nausea and vomiting

The control of postoperative nausea and vomiting (PONV) has recently been reviewed.²⁷ Similar to CINV, PONV has a delayed phase response known as postdischarge nausea and vomiting (PDNV). PONV and PDNV impact recovery after anesthesia immediately after surgery and at later times (24–72 h) after surgical interventions when day-care patients are sent home, at which time there is no simple access to rescue medications or medical care. Given the broad preclinical spectrum of antiemetic control observed preclinically with the SPAs and their unique clinical efficacy in the delayed phase of CINV, clinical studies were undertaken to compare their efficacy to 5-HT₃ receptor antagonists, the previous standard of care.²⁸ These studies demonstrated the efficacy of aprepitant as monotherapy for the prevention of postoperative nausea and vomiting, and it was approved for this indication in 2006.

Aprepitant: learning about the biology of chemotherapy-induced emesis

The development of aprepitant provided new insights into the pharmacological and pathophysiological mechanisms involved in emesis. Both peripheral (glossopharyngeal and vagal nerves) and central (cortical and cerebellar) pathways can activate neuronal nuclei in the brainstem and trigger a sequence of events that results in the vomiting reflex (Fig. 3A). The 5-HT₃ receptor antagonists are thought to exert their actions predominantly on the peripheral terminals of vagal afferents in the gastrointestinal tract and in the chemoreceptor trigger zone (CRTZ) that lays in the area postrema outside of the blood–brain barrier to block the activating effects of serotonin released during chemotherapy. The CRTZ signals to another area, the nucleus

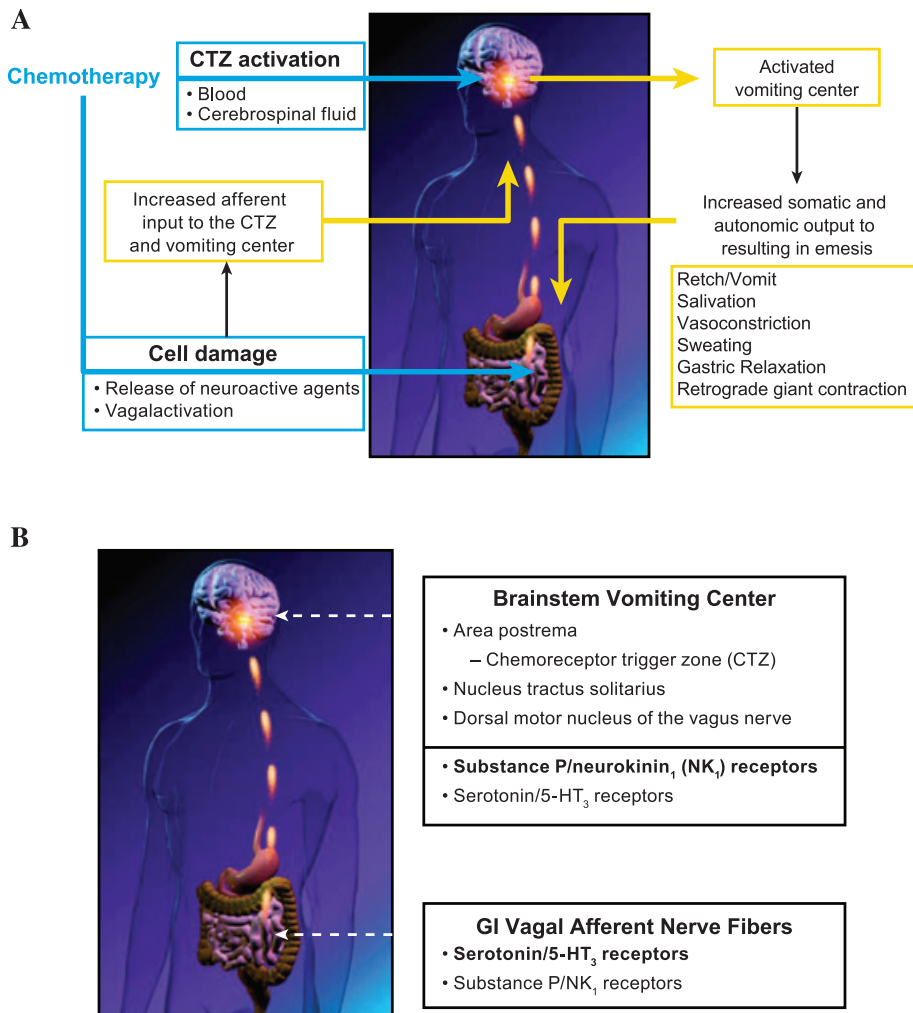


Figure 3. (A) Mechanism of chemotherapy-induced emesis. (B) Sites of action of 5-HT₃ and NK-1 receptor antagonists. Graphics by Kirk Moldoff.

tractus solitarius (NTS), in the brain stem that also receives emetogenic stimuli from higher brain centers (e.g., cortical and vestibular) as well as gastrointestinal vagal afferents, and is thought to orchestrate the patterns of central activity underlying CINV and PONV. Preclinical studies suggest that it is here within the NTS that SPAs such as aprepitant exert their strongest antiemetic properties through central inhibition of the emesis pattern generator (Fig. 3B). This central site of action is the likely explanation for the unique broad antiemetic pharmacological profile of the SPAs, indicating that substance P acting at central NK-1 receptors is one of the final common mechanisms involved in activation and coordination of the vomiting reflex.²⁹

The acute and delayed clinical time course of CINV has previously been linked to serotonin release and inflammation by the clinical effectiveness of 5-HT₃ antagonists and steroids, respectively. The discovery of the SPAs and clinical experience with aprepitant has furthered our understanding and provided substantial evidence for involvement of substance P throughout the CINV response. The prolonged efficacy profile of aprepitant, including the delayed phase, indicates that substance P acting at central NK-1 receptors becomes increasingly important with time in the pathophysiology of the overall CINV response.³⁰ These observations support the clinical rationale for combination therapy with 5-HT₃ receptor antagonists (e.g.,

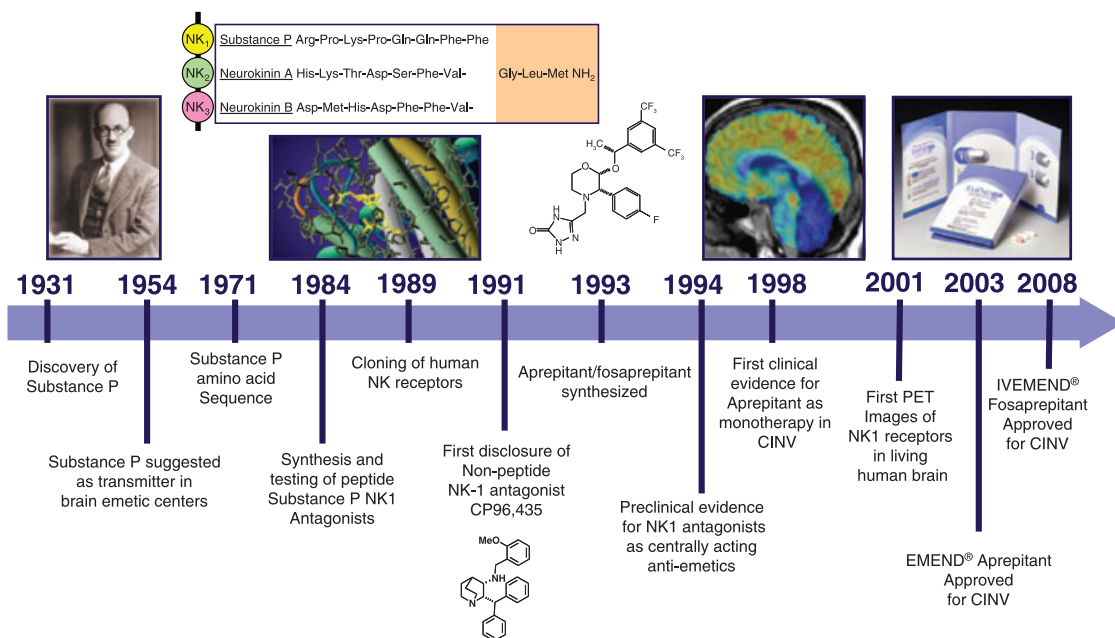


Figure 4. Substance P: 70 years from discovery to therapeutic utility. The photograph of Gaddum is reprinted by permission from Macmillan Publishers Ltd: *Nature* 406, 831 (24 August 2000), copyright 2000.

ondansetron), steroids (e.g., dexamethasone), and SPAs such as aprepitant to optimize control of CINV.

Current and future challenges in the aprepitant program

Ongoing discovery and development efforts in the program aim to identify simplified dose regimens of aprepitant. In August 2010, a single-dose formulation of fosaprepitant for IV administration was approved in the European Union for use instead of the 3-day oral regimen of aprepitant, together with a 5-HT₃ receptor antagonist and a corticosteroid. Additionally, in November 2010, the FDA approved a single-dose formulation, EMEND for Injection 150 mg, for patients receiving highly emetic chemotherapy. This new regimen provides a more simple treatment to patients who will not need to worry about taking capsules of EMEND on days two and three, ensuring compliance with therapy and improving convenience for both patients and healthcare professionals.

The incidence of cancer in pediatric patients is still a concern despite the availability of treatments for the different tumors and the resilience of the patients. There are no clear guidelines for antiemetic therapy in pediatric cancer patients since the avail-

able scientific data are very limited; this allows pediatric cancer patients to go through their chemotherapy treatment with suboptimal therapy for prevention of CINV. An age-appropriate formulation of aprepitant (powder for suspension) is currently under research and development to extend its benefits to pediatric patients.

Conclusion

Aprepitant today represents the culmination of more than 80 years of research into the pharmacology and physiology of substance P and more than 20 years of drug discovery and development toward identifying a safe, potent, orally active, and brain-penetrant SPA³¹ (Fig. 4). Its discovery and development has dramatically improved the quality of life for patients with cancer who must undergo multiple cycles of chemotherapy. Aprepitant is the first and only substance P/NK-1 receptor antagonist available for the prevention of CINV in cancer patients. Aprepitant, in combination with a 5-HT₃ receptor antagonist and dexamethasone, optimizes protection against CINV in both the acute and delayed phases compared to the prior standard of care, and is now recommended as first-line therapy for patients about to be treated with moderately or highly emetogenic chemotherapy.

Conflicts of interest

The authors are employees of Merck Sharp & Dohme Corp.

References

1. von Euler, U.S. & J.H. Gaddum. 1931. An unidentified depressor substance in certain tissue extracts. *J. Physiol. (Lond.)* **72**: 74–87.
2. Amin, A.H., T.B.B. Crawford & J.H. Gaddum. 1954. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol. (Lond.)* **126**: 596–618.
3. Chang, M.M., S.E. Leeman & H.D. Niall. 1971. Amino acid sequence of substance P. *Nat. New Biol.* **232**: 86–87.
4. Tregear, G.W., H.D. Niall, J.T. Potts Jr, *et al.* 1971. Synthesis of substance P. *Nat. New Biol.* **232**: 87–89.
5. Fong, T.M., S.A. Anderson, H. Yu, *et al.* 1992. Differential activation of intracellular effector by two isoforms of human neurokinin-1 receptor. *Mol. Pharm.* **41**: 24–30.
6. Snider, R.M., J.W. Constantine, J.A. Lowe, *et al.* 1991. A potent nonpeptide antagonist of the substance P (NK1) receptor. *Science* **251**: 435–437.
7. Bountra, C., K. Bunce, T. Dale, *et al.* 1993. Antiemetic profile of a non-peptide neurokinin NK1 receptor antagonist, CP-99,994, in ferrets. *Eur. J. Pharmacol.* **249**: R3–R4.
8. Tattersall, F.D., W. Rycroft, R.J. Hargreaves, *et al.* 1993. The tachykinin NK₁ receptor antagonist CP99,994 attenuates cisplatin induced emesis in the ferret. *Eur. J. Pharmacol.* **250**: R5–R6.
9. Watson, J.W., J.F. Gonsalves, A.A. Fossa, *et al.* 1995. The antiemetic effects of CP-99,994 in the ferret and the dog: role of the NK1 receptor. *Br. J. Pharmacol.* **115**: 84–94.
10. Andrews, P.L.R. & J.A. Rudd. 2004. The role of tachykinins and the tachykinin NK1 receptor in nausea and emesis. In *Handbook of Experimental Pharmacology*. P. Holzer, Ed.: 359–440. Springer. New York.
11. Tattersall, F.D., W. Rycroft, M. Cumberbatch, *et al.* 2000. The novel NK₁ receptor antagonist L-754,030 and its water soluble phosphoryl prodrug L-758,298 inhibit acute and delayed cisplatin-induced emesis in ferrets. *Neuropharmacology* **39**: 652–663.
12. Tattersall, F.D., W. Rycroft & B. Francis. 1996. Tachykinin NK₁ receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology* **35**: 1121–1129.
13. Hale, J.J., S.G. Mills, M. MacCoss, *et al.* 1998. Structural optimization affording 2-(R)-(1-(R)-3, 5-bis (trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl) methylmorpholine, a potent orally active, long-acting morpholine acetal human NK-1 receptor antagonist. *J. Med. Chem.* **41**: 4607–4614.
14. Frank, R. & R. Hargreaves. 2003. Clinical biomarkers in drug discovery and development. *Nat. Rev. Drug Discov.* **2**: 566–580.
15. Bergstrom, M., R.J. Hargreaves, H.D. Burns, *et al.* 2004. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol. Psychiatry* **55**: 1007–1012.
16. Brands, K.M.J., J.F. Payack, J.D. Rosen, *et al.* 2003. Efficient synthesis of NK1 receptor antagonist aprepitant using a crystallization-induced diastereoselective transformation. *J. Am. Chem. Soc.* **125**: 2129–2135.
17. Olver, I., S. Shelukar & K.C. Thompson. 2007. Nanomedicines in the treatment of emesis during chemotherapy: focus on aprepitant. *Int. J. Nanomedicine.* **2**: 13–18.
18. Hale, J.J., S.G. Mills, M. MacCoss, *et al.* 2000. Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water soluble prodrugs. *J. Med. Chem.* **43**: 1234–1241.
19. Cocquyt, V., S. Van Belle, R.R. Reinhardt, *et al.* 2001. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur. J. Cancer* **37**: 835–842.
20. Chawla, S.P., S.M. Grunberg, R.J. Gralla, *et al.* 2003. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* **97**: 2290–2300.
21. Poli-Bigelli, S., J. Rodrigues-Pereira, A.D. Carides, *et al.* Aprepitant Protocol 054 Study Group. 2003. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* **97**: 3090–3098.
22. Hesketh, P.J., S.M. Grunberg, R.J. Gralla, *et al.* Aprepitant Protocol 052 Study Group. 2003. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J. Clin. Oncol.* **21**: 4112–4119.
23. Herrstedt, J., H.B. Muss, D.G. Warr, *et al.* Aprepitant Moderately Emetogenic Chemotherapy Study Group. 2005. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* **104**: 1548–1555.
24. Warr, D.G., P.J. Hesketh, R.J. Gralla, *et al.* 2005. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J. Clin. Oncol.* **23**: 2822–2830.
25. Grote, T., J. Hajdenberg, A. Cartmell, *et al.* 2006. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. *J. Support. Oncol.* **4**: 403–408.
26. de Wit, R., J. Herrstedt, B. Rapoport, *et al.* 2004. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur. J. Cancer* **40**: 403–410.
27. George, E., C. Hornuss & C.C. Apfel. 2010. Neurokinin-1 and novel serotonin antagonists for postoperative and

- postdischarge nausea and vomiting. *Curr. Opin. Anesthesiol.* **23**: 714–721.
28. Gan, T.J., C.C. Apfel, A. Kovac, *et al.* 2007. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth. Analg.* **104**: 1082–1089.
29. Hornby, P.J. 2001. Central neurocircuitry associated with emesis. *Am. J. Med.* **111**: 106S–112S.
30. Hesketh, P.J., S. Van Belle, M. Aapro, *et al.* 2003. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur. J. Cancer* **39**: 1074–1080.
31. Pendergrass, K., R.J. Hargreaves, K.J. Petty, *et al.* 2004. Aprepitant. An oral NK1 antagonist for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy. *Drugs Today* **40**: 853–863.