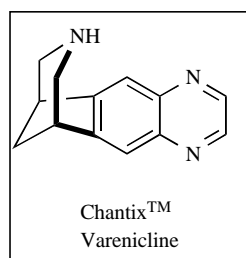


Molecule of the Month

Chantix™ – the first non-nicotine-containing medication for smoking cessation. Nicotine is a highly addictive, bioactive small molecule found in tobacco (e.g., cigarettes) which produces physical dependence [1]. Despite serious tobacco-related illnesses (cancer, respiratory disease and cardiovascular disease), most smokers fail to quit due to the addictive nature of nicotine [2]. Few pharmacotherapies are available for nicotine addiction, and those that are, nicotine replacement therapy and the antidepressant bupropion, have but modest long-term success [3]. An alternative, non-nicotine-containing approach centers on neuronal nicotinic acetylcholine receptors (nAChRs), and in particular, the $\alpha 4\beta 2$ nAChR is a target of interest for the development of smoking



cessation therapies due to its location on presynaptic terminals in the striatum and its role in modulating dopamine release [4]. In the mid 90s, Pontieri and Corrigan reported that the reinforcing effects of nicotine are mediated by high affinity $\alpha 4\beta 2$ nAChRs in the mesolimbic dopamine system [5,6]. Activation of $\alpha 4\beta 2$ nAChRs triggers mesolimbic dopamine release which elicits reward signal to higher cortical centers. Repeated abuse of nicotine triggers rapid and variable increases in dopamine release, facilitating both association and learning that leads to dependence [7]. Deletion of either the $\alpha 4$ or $\beta 2$ subunit of $\alpha 4\beta 2$ nAChRs led to an attenuation of the effects of nicotine and further supported the key role of mesolimbic $\alpha 4\beta 2$ nAChRs in nicotine addiction [3]. These data led to the hypothesis that a partial agonist of $\alpha 4\beta 2$ nAChRs would relieve the cravings and withdrawal symptoms in smokers trying to quit as well as reducing or eliminating the reinforcing element of tobacco [3, 8].

Achieving subtype selectivity within the nAChRs, which consist of many α and β subunit combinations, is a huge challenge, and developing a selective $\alpha 4\beta 2$ nAChR partial agonist through a classical HTS approach seems daunting. However, Pfizer delivered a potent partial agonist of $\alpha 4\beta 2$ nAChR Chantix™, also known as varenicline tartrate, which was approved by the FDA in 2006 for the cessation of smoking [3, 9]. The origin of Chantix™ can be traced back to a small, conformationally rigid plant alkaloid known as cytisine [10-13]. Equilibrium binding assays demonstrated that cytisine was selective for the $\alpha 4\beta 2$ subtype. In functional assays, cytisine showed greater potency at $\alpha 4\beta 2$ receptors than any other subtype; however, it does display a wide range of efficacy at multiple subunit congeners. In fact, cytisine, while a partial agonist at $\alpha 4\beta 2$, it is also a high efficacy agonist at $\alpha 7$ and at various $\beta 4$ variant. Studies demonstrated that structural manipulations of cytisine resulted in changes in efficacy at multiple neuronal nAChRs. The structure of Chantix™ is loosely based on cytisine, and it was the partial agonist activity of cytisine that led to the development of Chantix™. Chantix™ is an orally bioavailable, partial agonist of $\alpha 4\beta 2$ nAChR ($EC_{50} = 2.3 \mu M$, 13.4% of ACh max), but also activates other subtypes with a range of potencies and efficacies. Five separate clinical trials demonstrated the superior efficacy, tolerability and safety of Chantix™ relative to the other available pharmacotherapies. Indeed, after 12 weeks, 44% of

patients taking a 1 mg dose of Chantix™ quit smoking as compared to 17% on placebo. After 52 weeks, prevalence abstinence rates were 36.7% for Chantix™ as compared to 7.9% for placebo [3, 8-13]. The development of Chantix™, exclusively for the treatment of nicotine addiction, represents a huge advance for an unmet medical need, and once again highlights how a natural product inspired and facilitated the discovery of a major new pharmaceutical agent.

REFERENCES

- Rose, J.E.; Corrigan, W.A. Nicotine self-administration in animals and humans: similarities and differences. *Psychopharmacology* **1997**, *130*, 28-40.
- Balfour, D.J. The neurobiology of tobacco dependence: a clinical perspective on the role of dopamine projections to the nucleus. *Nicotine Tob. Res.* **2004**, *6*, 889-912.
- Rollema, H.; Chambers, L.K.; Coe, J.W.; Glowa, J.; Hurst, R.S.; Lebel, L.A.; Lu, Y.; Mansbach, R.S.; Mather, R.J.; Rovetti, C.C.; Snads, S.B.; Schaeffer, E.; Schulz, D.W.; Tingley, F.D. III; Williams, K.E. Pharmacological profile of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology* **2007**, *52*, 985-994.
- Everitt, B.J.; Robbins, T.W. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* **2005**, *8*, 1481-1485.
- Corrigan, W.A.; Coen, K.M. Nicotine maintains robust self-administration in rats on a limited schedule. *Psychopharmacology* **1989**, *99*, 473-478.
- Pontieri, F.E.; Tanda, G.; Orzi, R.; DiChiara, G. Effects of nicotine on the nucleus accumbens and similarly of those addictive drugs. *Nature* **1996**, *382*, 255-257.
- Dani, J.H.; Harris, R.A. Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nat. Neurosci.* **2005**, *8*, 1465-1470.
- Cohen, C.; Bergis, O. E.; Galli, F.; Lochead, A. W.; Jegham, S.; Biton, B.; Leonardon, J.; Avenet, P.; Sgard, F.; Besnard, F.; Graham, D.; Coste, A.; Oblin, A.; Curet, O.; Voltz, C.; Gardes, A.; Caille, D.; Perrault, G.; George, P.; Soubrie, P.; Scatton, B. SSR591813, a novel selective and partial $\alpha 4\beta 2$ nicotinic receptor agonist with potential as an aid to smoking cessation. *J. Pharm. Exp. Ther.* **2003**, *306*(1), 407-420.
- For detailed information on the FDA approval and five clinical trials of Chantix™ see: www.pfizer.com.
- Mihalak, K.B.; Carroll, F.I.; Luetje, C.W. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol. Pharm.* **2006**, *70*, 801-805.
- Reus, V.I.; Obach, R.S.; Coe, J.W.; Faessel, H.; Rollema, H.; Watsky, E.; Reeves, K. Varenicline: new treatment with efficacy in smoking cessation. *Drugs of Today* **2007**, *43*, 65-75.
- Oncken, C.A.; Gonzales, D.; Nides, M.; Rennard, S.; Watsky, E.J.; Coe, J.W. Varenicline: an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist as an aid to smoking cessation. *Medication Treatments for Nicotine Dependence* **2007**, 213-221.
- Coe, J.W.; Brooks, P.R.; Vetelino, M.G.; Wirtz, M.C.; Arnold, E.P.; Huang, J.; Sands, S.B. Davis, T.I.; Lebel, L.A.; Fox, C.B.; Shrikhande, A.; Heym, J.H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R.S.; Chambers, L.K.; Rovetti, C.C.; Schulz, D.W.; Tingley, F. D., III; O'Neill, B.T. Varenicline: An $\alpha 4\beta 2$ Nicotinic Receptor Partial Agonist for Smoking Cessation. *J. Med. Chem.* **2005**, *48*, 3474-3477.

Micah L. Breininger and Craig W. Lindsley

Indiana University, Bloomington Indiana
 Vanderbilt University, Vanderbilt University Medical Center
 Associate Professor of Pharmacology and Chemistry
 Robinson Research Building 804
 Nashville, TN 37232-6600,
 USA