Rimantadine: A Viral Replication Inhibitor

Poster Team: Roxanne Colwell, Courtney Horvat, Holly Mercado-Schoessow
E-Poster Team: Kristina Clark, Scott Wiersma, Khon Yang
Jmol Team: Adam McCarthy, Andy Rosicky
Faculty Advisors: Daniel Sém, Ph.D.; Frank Dailey, M.S., Ph.D.
School of Pharmacy, Concordia University Wisconsin, Mequon, WI, S3097

Abstract
The live intranasal FluMist vaccine is highly effective in preventing influenza A infections. It provides immediate protection to vaccinated individuals and the community around them. Rimantadine is in the adamantane class. Influenza A contains a pH-gated proton channel in the viral envelope formed by the M2 channel. Adamantane drugs inhibit movement of protons through the M2 channel, thereby inhibiting replication. These drugs are no longer recommended for use due to 99% resistance of influenza A (H3N2) to adamantane drugs.

Molecular Story
The main site of action for rimantadine is the M2 channel protein located on the viral envelope. Rimantadine consists of an adamantane group with an alpha methylamine group (Fig. 2). Rimantadine inhibits the M2 channel by binding directly to four sites on the outside of the transmembrane portion (Fig. 1) through hydrogen bonds and van der Waals interactions. The M2 channel has developed resistance to rimantadine through mutations that destabilize the channel, making it easier to open. Due to drug action and resistance, a patient was advised not to take rimantadine after recently receiving the live flu vaccine.

Introduction
A 46 year old male presented to his pharmacy with a new prescription for rimantadine to treat influenza A. He received the live intranasal FluMist vaccination the day before. The pharmacist informed him rimantadine is not recommended since he received the live flu vaccination. A patient should avoid rimantadine 48 hours prior to and two weeks after vaccination with the live attenuated intranasal spray influenza vaccine as it may inactivate the vaccine.

Further Drug Design
Resistance to rimantadine limits its clinical utility. There are several primary mutations of the M2 channel that confer drug resistance: L26F, V27A, A30T, S31N, G34E, and L38F. New adamantane drugs must be developed to overcome the resistance problem. Based on drug binding, it is clear that the adamantane group and positively charged amine are critical for binding. However, the positive amine group could also be located directly off the adamantane group as in amantadine. The primary change that medicinal chemists must consider is the addition of functional groups to the positively amine to enhance binding to the M2 channel. Compounds featuring a CH$_2$-heteroaryl group conjugated to the amine of amantadine show promise in inhibiting the function of the S31N mutant (Fig. 9). Specifically, the heteroaryl groups were isoxazole, 1,2,4-oxadiazole, and isoxazoline.

Summary
Rimantadine inhibits the influenza A M2 channel by binding on the outside of the transmembrane portion. Through hydrogen bonding, van der Waals interactions, and hydrophobic interactions it stabilizes the closed conformation. However, the influenza A virus has developed resistance to rimantadine through six primary mutations to the M2 channel. In the development of new drugs, large heteroaryl groups can be added to the core structure of rimantadine to overcome resistance.

References
2. Rimantadine Monograph. Leci-Cmp Online.

Fig. 1: Four orange rimantadine molecules bind between the four chains of the M2 channel backbone, inhibiting proton flow. Rendered from 2RLF.pdb.

Fig. 2: Chemical structure of rimantadine. Adamantane group shown in orange. Alpha-methyl amine shown in blue.

Fig. 3: Acidic pH activation of the M2 channel by protonation of His378, causing destabilization of the helix allowing for proton conduction. (Left) Py, HHis, DAsp, TH-transmembrane.

Fig. 4: Four orange rimantadine molecules binding in between the four chains of the M2 channel backbone. Rendered from 2RLF.pdb.

Fig. 5: Hydrogen bond interaction between the oxygen of Asp44 of the M2 channel and the nitrogen of rimantadine. Polar interactions between the rimantadine amine and Arg45 and Trp41. Rendered from 2RLF.pdb.

Fig. 6: Van der Waals interactions between one rimantadine molecule (orange) and Leu40, Ile42, and Leu43 on the chains of the M2 channel. Rendered from 2RLF.pdb.

Fig. 7: Mutations at Lys26, Lys38, and Lys31 cause resistance by destabilizing helical packing. Rendered from 2RLF.pdb.

Fig. 8: Mutations at Val27 enlarge the pore. Mutations of Ala30 and Gln34 destabilize helical packing, leading to resistance. One subunit not shown. Rendered from 2RLF.pdb.

Fig. 9: M2WJ332 is comprised of amantadine conjugated to isoxazole. It inhibits the M2 mutant S31N. From Wang, et al. 2013.

Fig. 10: Van der Waals interactions between one rimantadine molecule (orange) and Lys40, Lys42, and Lys43 on the chains of the M2 channel. Rendered from 2RLF.pdb.