What’s the “Buzz” About?

- Zika virus (ZIKV) is a mosquito-born pathogen (Figure 1) that is linked to microcephaly in infants and Guillain-Barré syndrome in adults (3).
- ZIKV is in the same family as the West Nile Virus, the Flaviviridae; like all flaviviruses, ZIKV has an RNA genome that directs synthesis of viral proteins using the host cell’s protein synthesis machinery.
- Figure 2 (right) shows the sequence of steps in the ZIKV infection cycle:
  1. A virus particle binds to a specific cell surface receptor and enters the cell by endocytosis.
  2. The endosome is acidified, causing a conformational change on the capsid proteins that leads to translocation of the viral RNA genome from the endosome into the cytoplasm.
  3. The viral RNA is copied and moves to the endoplasmic reticulum where it is translated into protein.
  4. Viral polyproteins enter the maturation phase within the golgi apparatus.
  5. The infection cycle restarts.

- The 5’ end of the viral RNA possesses a “cap” of methylated bases that are used for protection against host cell defenses; ZIKV cannot reproduce if its RNA loses this 5’ cap.
- The cap is produced by a virally-encoded methyltransferase enzyme, the NS5 methyltransferase (MTase), which takes methyl groups from S-adenosyl methionine (SAM) and transfers them to specific locations on the 5’ end of the viral RNA.
- Inactivating the NS5 MTase with a small molecule inhibitor should be a viable treatment for ZIKV infections.

Function of NS5 Methyltransferase

- The 5’ end of the RNA is capped by the viral-encoded NS5 MTase enzyme, which transfers CH₃ groups from the SAM methyl donor to the guanine and adenine bases at the 5’ end of the RNA during transcription.

NS5 Substrates: SAM and unmethylated RNA

Modeling the Structure of NS5 Methyltransferase

- Jmol models of NS5 bound to SAM, and NS5 bound to hypothetical drug MO2

Moving Forward

- Process of creating an effective drug: Research on a drug’s affinity for a predetermined drug target, drug selection, years of clinical trials, FDA approval

- Drug Target: The NS5 from methyltransferase is a viable target for a drug because knocking out its activity (methylating the RNA cap) prevents the virus from replicating.

- SAM (S-adenosylmethionine) can be mimicked by our hypothetical inhibitor (MO2) due to both molecules possessing the same binding site on the enzyme. If the inhibitor binds, it will compete with SAM for binding to the protein.

- The next steps would be to test the designed inhibitor in the lab to see if it actually binds to the protein.