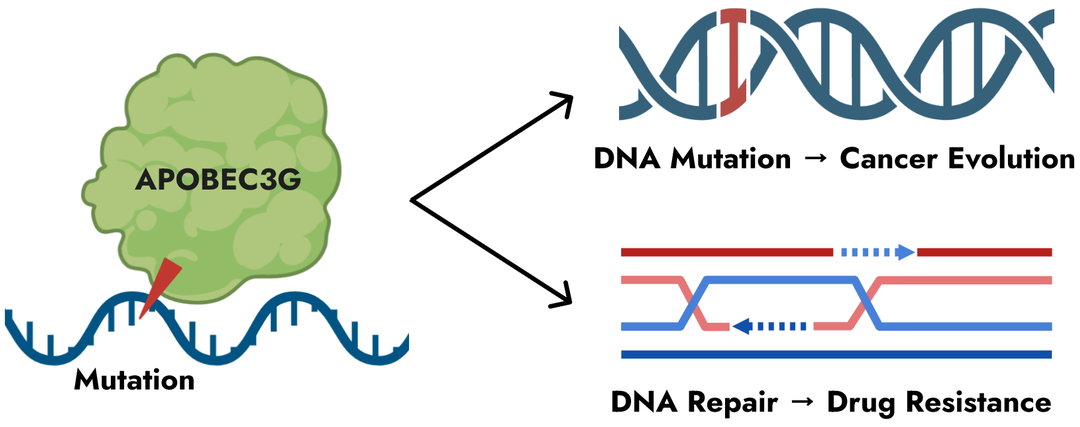
In silico Design of Novel 2'FANA Oligonucleotides to Inhibit APOBEC3G

Background

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3 (APOBEC3) is a family of proteins recently identified as the cause of >50% of endogenous mutations in cancer genomes[1].

APOBEC3G (A3G) contributes to cancer evolution and drug resistance in a range of cancers, including multiple myeloma and metastatic colorectal cancer[2-5].

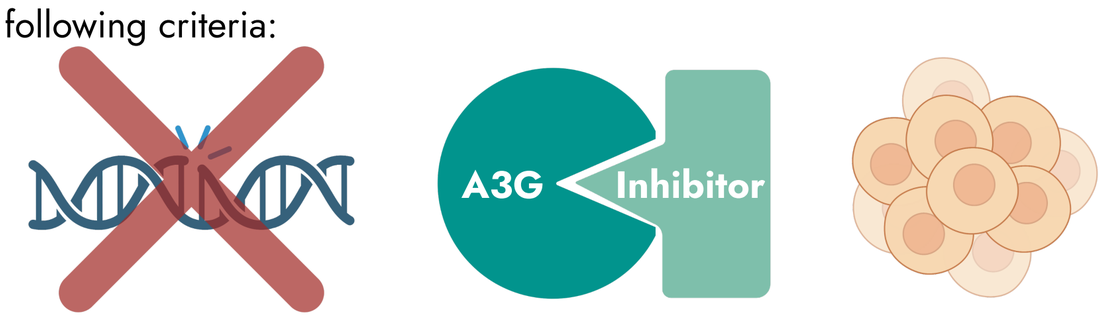


Existing inhibitors of A3G exhibit poor binding and low cell-stability, but generally utilize **deoxy-zebularine** (dZ), a structural analog of cytidine that inhibits A3G's mutation mechanism[6-8].

2'FANA is a type of sugar that can be used to build DNA-based drugs. These modifications can be used to confer increased binding potential and cell-stability, countering drawbacks of existing studies[6-10].

Design Considerations

Inhibiting A3G could expand cancer treatment options and help clinicians better treat patients. An inhibitor of A3G must meet the following criteria:



1. **Immutable**
   For an inhibitor to be effective it *must* prevent deamination
2. **Tight Binder**
   An inhibitor must potently bind A3G to limit processivity
3. **Cell-Stable**
   Endonucleases should not degrade the inhibitor

Methdology

Molecular dynamics simulations utilize biophysical principles to predict how biomolecules will behave in their environments. Inhibitor structures with different 2'FANA modifications were simulated in triplicate and then analyzed for structural changes and impacted interactions between the inhibitor and A3G. Our work aims to optimize 2'FANA placement.

Results

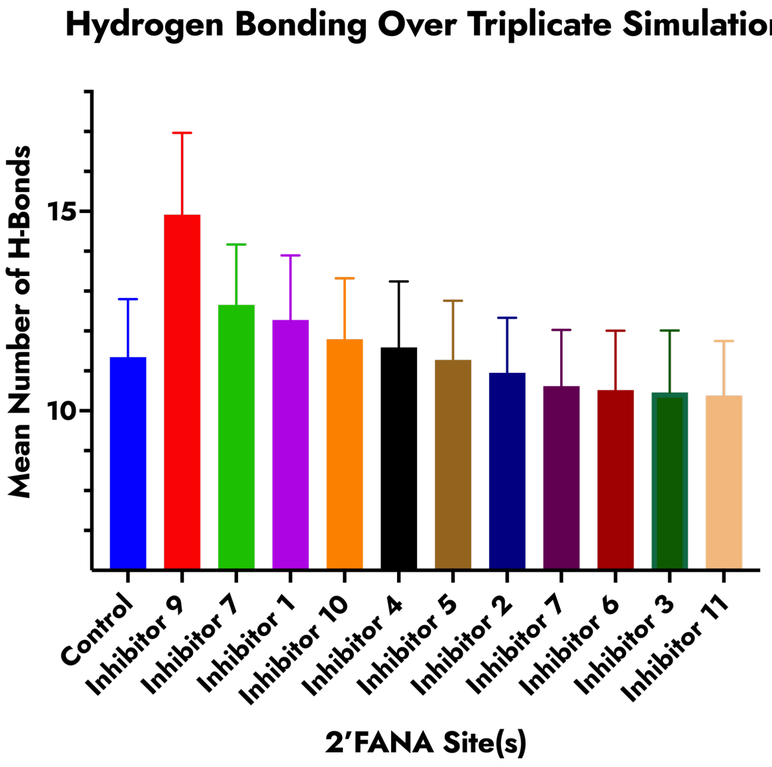


Figure 1. Mean number of hydrogen bonds formed between protein and each inhibitor. Standard deviation delineated by bars. Data obtained from VMD analysis. Figure created in GraphPad Prism.

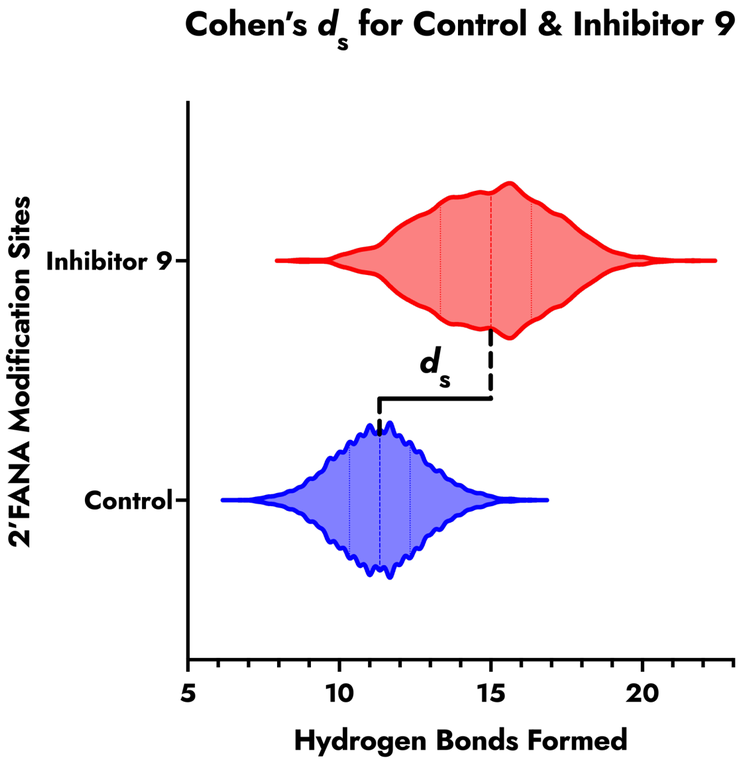


Figure 2. Violin plots of control inhibitor and Inhibitor 9. Cohen's d_s computed as the number of pooled standard deviations between sample means and shown graphically. Data obtained from VMD analysis. Figure created in GraphPad Prism.

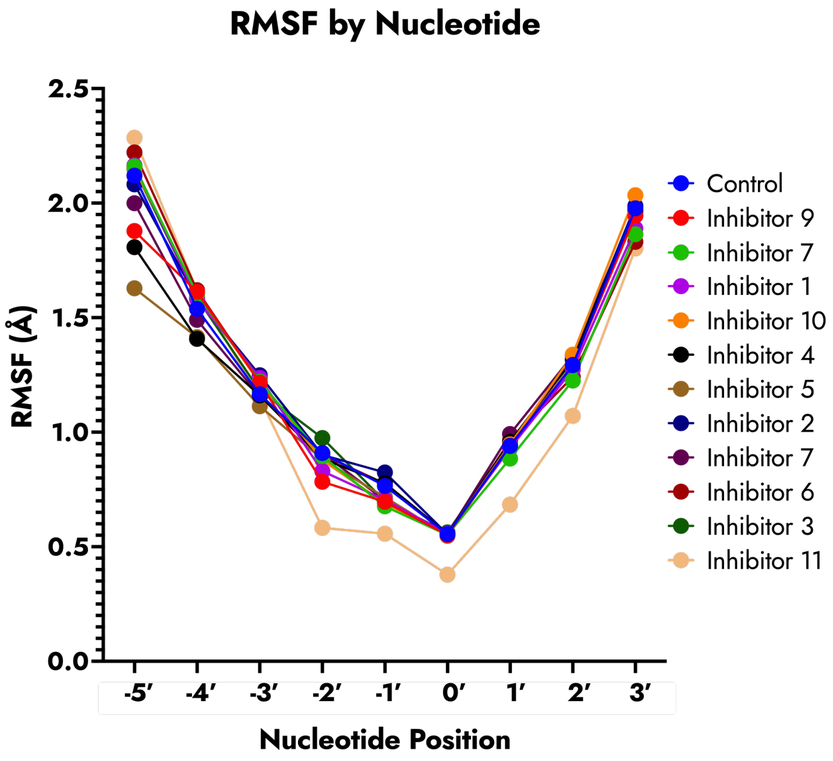


Figure 3. Root mean square fluctuation (RMSF) by nucleotide for each inhibitor. RMSF computed by averaging RMSF values at each position across triplicate simulations. Data obtained from VMD analysis. Figure created in GraphPad Prism.

Conclusion

A novel inhibitor of A3G with 2'FANA modifications to improve binding and cell-stability was identified using molecular dynamics simulations. Following *in vitro* and *in vivo* study, the application of Inhibitor 9 in cancer treatment could help prevent cancer evolution and drug resistance, thereby acting as a powerful addition to a therapeutic regimen. Moreover, our structural work could accelerate future 2'FANA work aimed at drug optimization via conformational alterations to oligonucleotide organization.

Our study outlines a drug candidate with the potential to improve prognosis for patients suffering from aggressive, deadly cancers.

References

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Unless otherwise indicated, all graphics were made in BioRender.