Fine-tuning pKa's of Nucleoside Analogs to Increase Mutagenicity; a Strategy to Develop More Potent Lethal Mutagen with Anti-Viral or Anticancer Properties

Technology #17657

Applications

This technology is method for increasing mutagenicity of nucleoside analogs with potential applications as an anti-viral or cancer therapeutic.

Problem Addressed

Both viruses and cancers have relatively high rates of mutation, which facilitates rapid evolution of drug tolerance. However, there mutational burden is a delicate balance, and viruses and cancer cells need to sustain a mutation rate and that is favorable for evolution, while also maintaining genetic stability. Too high of a mutational burden can lead to catastrophic collapse of genetic integrity and complete loss of virus or cell viability known as “lethal mutagenesis.” Lethal hypermutation has therefore been proposed as an anti-viral and cancer therapeutic technique and there is at least one FDA approved drug, ribavirin, that uses lethal mutagenesis to treat hepatitis C and viral hemorrhagic fever. The pro-drug KP1212 is another example of a promising mutagenic drug candidate, however, KP1212 displayed only marginal anti-viral effects in clinical trials. This technology is a method for increasing the mutagenicity of nucleoside analogs to potentially maximize their therapeutic potential.

Technology

This technology can tune the mutagenicity of nucleosides analogs by changing the pKa of the molecule. In its active form, KP1212 is a cytidine nucleotide analog that causes G-to-A mutations. These inventors demonstrated that the KP1212 mutagenic capacity is highly dependent on pH. At physiological pH KP1212 is only marginally mutagenic, resulting in G-to-A mutation only about 10% of the time. Reducing pH *in vitro* significantly increases its mutagenic capacity, which demonstrates that the protonated form of KP1212 is more highly mutagenic. Additionally, this finding suggests that tuning the pKa of KP1212 to be protonated at physiological pH could greatly increase its mutagenic efficiency. Importantly, these results also indicate that tuning the pKa of nucleoside analogs could be a more general mechanism for changing the mutagenic properties of nucleoside analogs.

Advantages

- Increased mutagenesis of nucleoside analog KP1212 by tuning pH and pKa
- Generalizable strategy for tuning mutagenic capacity by changing pKa

Categories For This Invention:

Life Sciences

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Two-dimensional IR spectroscopy of the anti-HIV agent KP1212 reveals protonated and neutral tautomers that influence pH-dependen
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External Links:

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