Max-Planck-Innovation

Technology Offer

Compounds modulating frameshifting efficiency for antiviral therapy against HIV-1, SARS-CoV-2 and alphaviruses

Ref.-No.: MI 0707-5639-MG

Background

Many viruses use programmed ribosome frameshifting (FS) to increase genome-coding capacity and to regulate the stoichiometric ratio between viral proteins. Among them are human-pathogenic viruses HIV-1, SARS-CoV-2 and alphaviruses such as Semliki Forest virus (SFV). Synthesis of two major HIV-1 genes, gag and pol, requires –1FS. The ratio between Gag and Gag-Pol is crucial for virus propagation and its dysregulation is detrimental for replication, particle formation and infectivity of HIV-1. In SFV, –1FS defines the ratio between the two structural proteins, 6K and TransFrame which contribute to virus infectivity. Programmed FS in SARS-CoV-2 is crucial for the synthesis of the viral RNA-dependent RNA polymerase and downstream proteins.

Technology

Scientists from the Max-Planck-Institute for Multidisciplinary Sciences could show that FS efficiency is determined by the availability of $tRNA^{Leu}$ which reads the UUA codon in *cis*-acting elements (slippery sites) of viral mRNAs. The $tRNA^{Leu(UUA)}$ isoacceptor is rare in human cells, especially in $CD4^+$ T-lymphocytes, the primary target cells for HIV-1 infection in humans, whereas 45 % of all Leu in late expressing HIV-1 genes (including *gag* and *pol*) is encoded by this rare codon. The scientists revealed that an increase in $tRNA^{Leu(UUA)}$ concentration led to a significant reduction in overall –1FS efficiency and virus propagation, thus making modulation of FS efficiency by targeting rare codon decoders an ideal approach for antiviral therapy against retroviruses and alphaviruses.

Although a variety of viral therapeutics are available, art-established therapy options often suffer from several shortcomings which include the development of resistances and adverse effects. Therapeutics based on the $tRNA^{Leu(UUA)}$ which can be recognized by a ribosome and comprise the nucleotide sequence UAA or TAA and a binding site for the covalent attachment of Leu by an endogenous aminoacyl-tRNA synthetase would provide several advantages for antiviral treatment strategies. Owing to the universal conservation of the UUA codon within FS sequences across virus taxonomic categories, specific resistance mechanisms are less likely to emerge. This is of particular interest since many antiviral drug therapies that target less conserved structures suffer from the emergence of drug resistances through the development of unusual slippery sites that support different FS at levels sufficient for virus replication and pathogenicity despite the treatment.

We are now looking for a collaboration partner to further develop this project.

Publication

Korniy et al., 2019. Nucleic Acids Res. doi: 10.1093/nar/gkz202
Chang and Wen, 2021. Comput Struct Biotechnol J. doi: 10.1016/j.csbj.2021.06.015

Contact:

Dr. Mareike Göritz
Senior Patent- & License Manager
Chemist
Phone: +49 (0)89 / 29 09 19 - 32
eMail: goeritz@max-planck-innovation.de

Max-Planck-Innovation GmbH
Arnulfstr. 58
80335 München
www.max-planck-innovation.de