Innovative Nanoparticles to deliver mRNA for Vaccination

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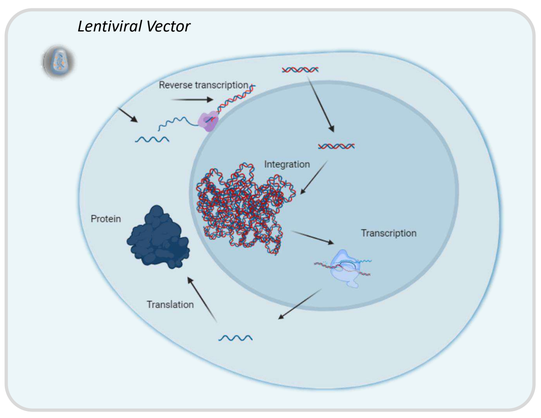
Abstract

The field of vaccination has experienced an unprecedented boost these last years through the development of nucleic **acids-based vaccine technologies** against COVID-19, demonstrating that nucleic acids can be used as vaccination platform against coronaviruses. However, this also highlighted the remaining challenges to design and develop more stable, efficient, and safer vectors to improve the immune protection induced and expand the application scope to other pathogens. **Synthetic vectors** such as Lipid NanoParticles (LNPs) can be used to vectorize mRNA coding antigens, taking advantage of RNA biosafety regarding genotoxicity. However, their low stability induces **issues in terms of stocking or *in vivo* use**. Furthermore, combining them with a system targeting specific cell populations remains challenging. Conversely, the vaccination **platforms derived from viruses** such as Adenoviral or Lentiviral Vectors (LVs) are **more stable**, conferring advantages for stocking and ***in vivo* efficacy**. Furthermore, LVs can be easily combined with a cellular targeting system. However, these vectors' viral sequences and DNA genomes **can induce biosafety issues**.

GEG Tech has designed a **new generation of nanoparticles combining the advantages of the LNPs and the viral vectors**. These new generations are constituted by viral packaging enabling good efficacy and stability, containing non-viral RNA, conferring a high biosafety level. We have demonstrated that these new nanoparticles efficiently enter human primary dendritic cells. We have also tested their ability to induce an immune response through different ways of administration using an Ovalbumin (OVA) mouse model. Finally, we have demonstrated that these new nanoparticles can induce high protection with a **Malaria mouse model**.

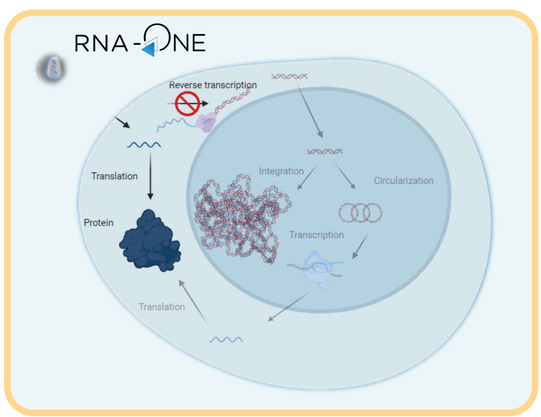
Design of a new Nanoparticle: RNA-ONE

RNA-ONE is derived from the lentivirus HIV-1 which contains a specific mutation into the reverse transcriptase coding sequence



Standard Lentiviral Vector cycle

After entry in the cell, RNA vector genome is reverse transcribed in DNA which is integrated into cell's genome.

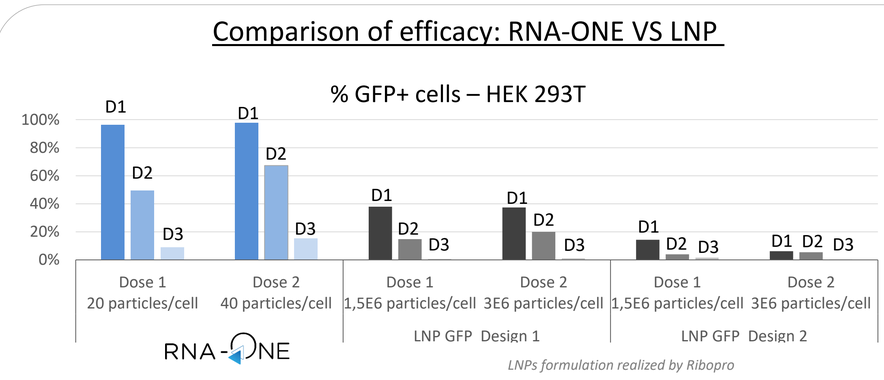


RNA-ONE cycle

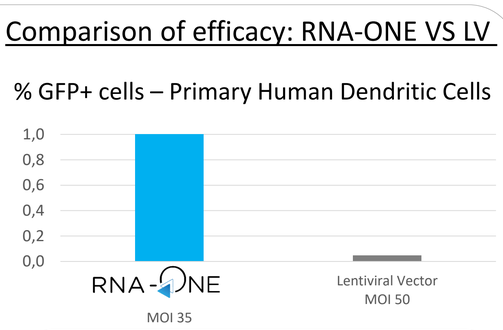
After entry in the cell, RNA vector genome is directly translated into protein without any DNA intermediate.

RNA-ONE is derived from lentiviruses. The reverse transcriptase has been specifically mutated and almost all viral sequences deleted. Consequently, this new nanoparticle enables to deliver mRNA with the lentiviral packaging, keeping the advantages in term of efficacy, stability and pseudotyping of lentiviruses.

RNA-ONE *in vitro* studies – Comparisons of efficacy with LNPs & Lentiviral Vectors

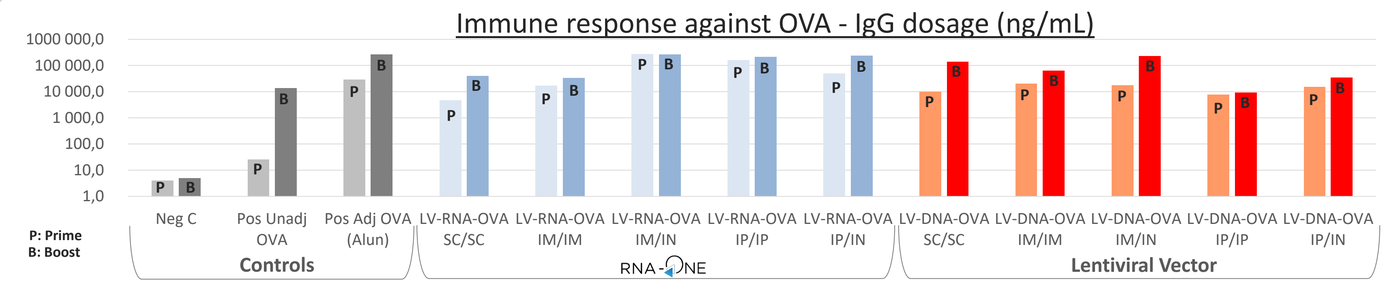


RNA-ONE efficacy is more than **two times higher than LNPs.**



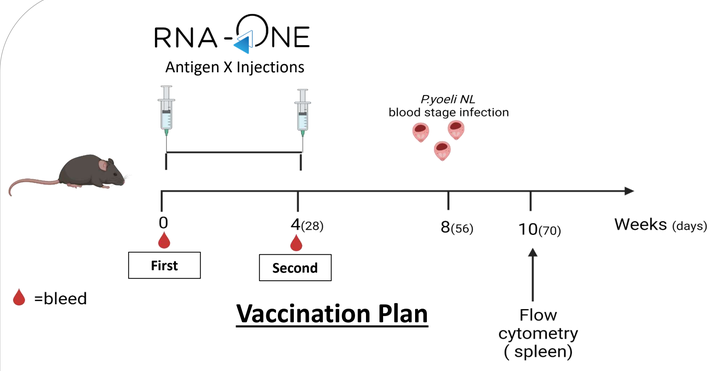
RNA-ONE efficacy is more than **10 times higher than LVs** to transduced primary dendritic cells.

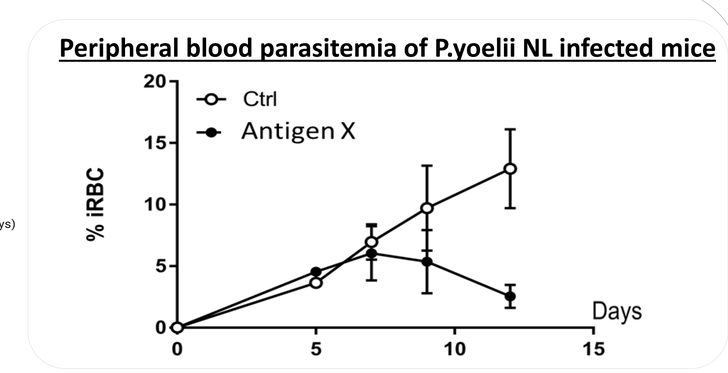
RNA-ONE encoding the ovalbumin is tested in mouse model

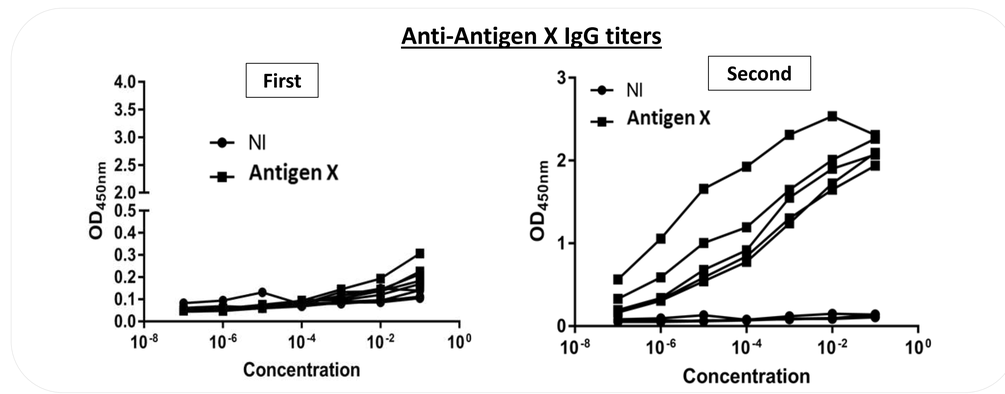


RNA-ONE is at least as effective as LVs to induce immune response against OVA through different routes of administration.

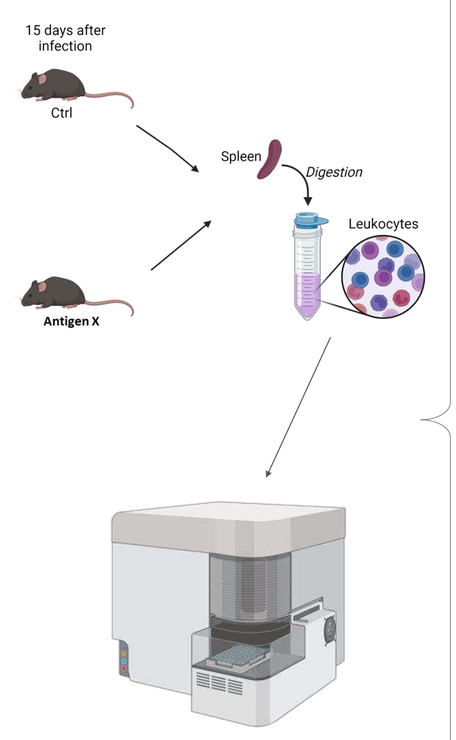
RNA-ONE encoding the Antigen X is tested in Malaria mouse model

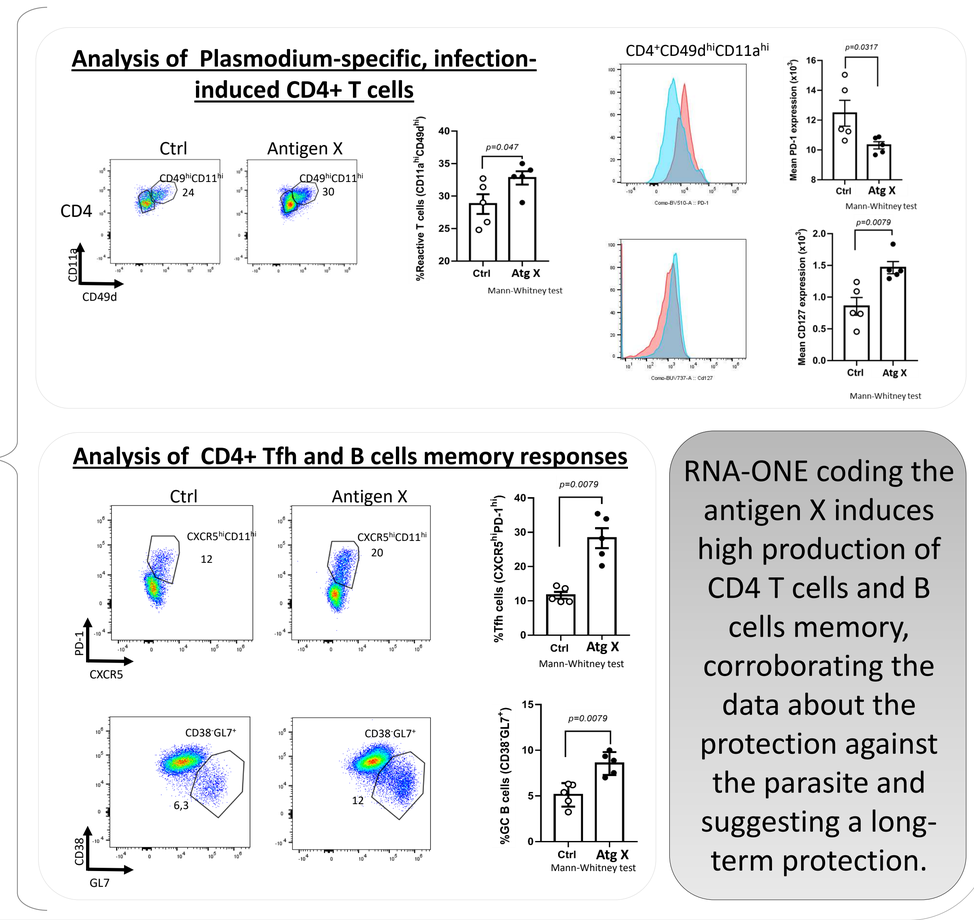






RNA-ONE coding the antigen X induces high production of specific IgG after the boost injection and an increased protection against the parasite two weeks after infection.





RNA-ONE coding the antigen X induces high production of CD4 T cells and B cells memory, corroborating the data about the protection against the parasite and suggesting a long-term protection.

RNA-ONE nanoparticles derived from the HIV-1 enable the delivery of mRNA with higher efficacy than LNPs to transduced/transfected cell lines, and than standard lentiviral vectors to transduced human primary dendritic cells. RNA-ONE OVA enables to induce a robust immune response against Ovalbumin through several administration routes. RNA-ONE Antigen X induces a strong protection against the parasite, combined with a good specific and memory immune response. These results show that RNA-ONE is a good candidate for vaccine platform, combining the strong efficacy of viral vectors with a high level of biosafety.