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Webinaire

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Trans-amplifying RNA platform for vaccines and pandemic preparedness

In response to the Covid-19 pandemic vaccines were developed with unprecedented pace, largely thanks to synthetic mRNA. Before this pandemic, mRNA was mainly developed as a vaccine against cancer for individual patients requiring small RNA amounts. Accordingly, upscaling of production for supplying the global population was and still is a challenge. Future optimization of RNA vaccines should therefore aim to reduce doses of antigen coding RNA required to immunize a person. In this regard, a promising approach is to use mRNA that self-amplifies within cells after the injection.

In my talk, I will present the development of the trans-amplifying RNA (taRNA) platform, which is a bipartite vector system that we have engineered from alphaviral self-amplifying RNA (saRNA). It consists of two RNAs that are co-transfected, a long synthetic mRNA encoding the alphaviral replicase (an RNA-dependent RNA-polymerase), and a short antigen-coding RNA called trans-replicon (TR). The TR contains the 5'- and 3'-ends of saRNA acting as promoters for RNA amplification. Upon co-transfer with replicase-mRNA, replicase selectively amplifies the TR *in trans*. Furthermore, the TR may contain a subgenomic promoter controlling transcription of the antigen, or it can be designed without SGP, thereby resembling closely a conventional mRNA. We found that taRNA is a very powerful vector platform, leading to comparable *in vitro* expression as saRNA. When we immunized mice against influenza HA using synthetic mRNA, saRNA or taRNA we found comparable protecting immune response for 20 µg mRNA, 1.25 µg saRNA, and 20 µg taRNA. However, only 50 ng out of the 20 µg total taRNA amount consisted of the HA-coding TR, while the vast majority was replicase-coding mRNA that drove the TR-expression. Interestingly, *in vitro* capping and long poly-A tails were not required for TR expression and immune responses, offering options for simplified RNA production. Overall, taRNA is a very promising vaccine candidate. Its bipartite design may accelerate vaccine production, since the major constituent, the replicase mRNA, is able to amplify any antigen coding TR. Thus, it would be reasonable to produce replicase mRNA long before it is actually needed in a vaccine. The final production step being a compilation of the pre-produced and stocked replicase-mRNA, and newly manufactured low-doses of TR encoding antigens of emerging or seasonally varying pathogens. Thereby, we envision very short production times of a mass taRNA vaccine.

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