Table 34: mRNA - Vaccines and Beyond

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Scope:

The mRNA technology has shaped the treatment modalities for multiple diseases such as cancer, genetic disorders, infectious diseases, and more beyond the COVID-19. mRNA vaccines have taken the field to combat the COVID-19 pandemic by design optimization of mRNA and nanoparticle carriers like lipid nanoparticles (LNPs) for effective shuttling of the mRNA safely inside tissues. However, the therapeutic efficacy of mRNA depends on multiple factors e.g. the mRNA design, efficient delivery using nanocarriers, nanoparticle formulation, stability, biological barriers, and reactogenicity.

The scope of this mRNA vaccine forum addresses fundamental considerations for mRNA structures, mRNA LNP carriers, formulation technologies, the delivery challenges, and how to improve the process parameters to overcome heterogeneous barriers in the delivery. The focus is to improve the therapeutic efficacy of mRNA formulations while engineering intelligent designs for mRNA nanocarriers.

Questions for Discussion:

1. Can the chemical and thermostability of mRNA be optimized through mRNA design?
2. What is the structure-function relationship of mRNA-LNPs?
3. Where does mRNA localize inside LNPs and the cell after being released?
4. What are the driving mechanisms of endosomal escape? How much mRNA is released from LNPs in endosomes?
5. What are the key factors that impact the endosomal escape and transfection efficiency?
6. Can LNPs be stored at a wide temperature range without compromising stability for storage and transportation over a long time?
7. What are the safety considerations of mRNA vaccines?

Discussion Notes:

- Stability of LNP and mRNA . Both are equally important and have their own considerations and quality attributes that need to maintain
- Key parameters to consider for analytical characterization
- Sourcing of lipids and if they are interchangeable and impact on stability and performance. Supply of lipids and what aspects need to consider for manufacturing such as vendors, long term availability , need for back up vendors who are qualified
- Urgency for cancer vaccines

- Global vaccine needs local manufacturing. How can technology be transferred to low-income countries so that vaccines can be made locally in those countries? What are the alternatives to expensive lipid materials?
- Quality of lipids are critical – raw materials need to be qualified to ensure lot to lot consistency
- Small companies have limitations for long term delivery and may not be able to deliver high quality consistently
- The lipids are critical as they determine the key quality attributes of the LNP. The lipids and the ratio determine the characteristics
- The process of manufacturing is important – any changes can impact the final characterization - Change in one parameter may affect the LNPS as the process is complex
- Important aspects - The delivery and release of the mRNA to the endosomes is determined by the formulation conditions such as the pH, buffers and the lipids. – the mechanism / how much mRNA will be released. There are analytical tools to measure this -
- Can dye labeled fluorescence can be used similar to what has been with SiRNA. The moment of the LNP can be trapped to understand these mechanisms - There are publications
- Conjugating the radiolabel – or the surface of the LNP to evaluate the release mechanism are being developed.
- A change in the formulation or manufacturing process can impact the potency . animal studies can demonstrate the change in stability at certain dose levels
- Stability – physicochemical and thermostability
- Three aspects for a stabilized mRNA is a balance between the mRNA design , Lipids and process need to be considered.
- Any changes in the lipids later in the process may require nonclinical tox studies which may delay programs
- Stability of mRNA - can we make it more stable without a vehicle - capping / design of the mRNA , poly A tail etc. The process needs to be streamlined from the plasmid to the mRNA drug substance.
- Comparison between SiRNA and mRNA and what lessons can be applied
- Issues related to production in Africa – low resources and cost of goods
- Is it feasible to produce mRNA that is lyophilized – difficulties related to the process and if the characteristics will be maintained - The process adds more complexity with the process that may change the structure - the freeze thaw is OK but the primary and secondary drying and reconstitution destroying the mRNA and the LNP.
- Multi dose formulations have been used with a preservative traditionally, however it is possible to deliver within 4-6 hours
- New container closures that can contain even 100 doses is possible for mass immunization within a short period of time

- Are there alternates to the LNP for mRNA - not much known right now but important to consider for future
- New disease targets and the opportunity to use mRNA vaccines