Hot Topic Discussion

The rise of RNA Nanotherapeutics: Current Trends & Future Challenges

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What are RNA therapeutics?

Adapted from: Heart 103, 812-817 (2017)
RNA therapeutics: a brief history

Adapted from: Nature 574, S2-S3 (2019)

- 1985: i.m. injection of mRNA leads to protein production
- 1990: Fire and Mello prove siRNA can suppress gene activity in C. elegans
- 1995: Fire and Mello prove siRNA can suppress gene activity in mammalian cells
- 2000: RNAi is demonstrated in mammalian cells
- 2005: siRNA expression shown to cause liver damage and death
- 2010: First use of RNAi in humans for phase I trial: melanoma
- 2015: Approval of patisiran and inotersen

- 1985: Influenza virus proof of concept for RNA-based vaccines
- 1990: Fomivirsen, first ASO, approved by the FDA
- 1995: Pegaptanib, first RNA aptamer approved by the FDA
- 2000: RNAi used to target hepatitis C virus in mice
- 2005: Fire and Mello receive the Nobel Prize

Adapted from: Nature 574, S2-S3 (2019)
Commercial Landscape for RNA therapies for Cancer - $41B in capita
Cancer RNA therapeutics are on the rise

Adapted from: Kaczmarek et al. Genome Medicine (2017) 9:60
# Current Technologies used for RNA delivery

<table>
<thead>
<tr>
<th>Delivery vehicle</th>
<th>Type of RNA in clinical trials</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naked RNA</td>
<td>siRNA, ASO, mRNA</td>
<td>No additional materials or synthesis required</td>
<td>Prone to degradation, Immunogenic</td>
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<tr>
<td></td>
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<td>Difficulty entering cell, Poor circulation half-life</td>
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<tr>
<td>Nanoparticle</td>
<td>siRNA, ASO, mRNA</td>
<td>Increased half life, Protection from nucleases, Aids in endocytosis and endosomal escape</td>
<td>Elevated risk of toxicity with introducing excipient materials</td>
</tr>
<tr>
<td>Conjugate</td>
<td>siRNA, ASO</td>
<td>Defined chemical structure, Ability to target specific receptors, Limited toxicity due to lack of excipient materials</td>
<td>High doses required, Dependent on chemical modifications for RNA stability</td>
</tr>
</tbody>
</table>

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Kaczmarek+, *Genome Med.* 2018
Current Technologies used for RNA delivery

Clinical Trials

- Cancer
- Other
- Lipid
- Naked

- Liposome
- Lipoplex
- Lipid nanoparticle

DOTMA

DOTAP

Cationic lipids

Dlin-MC3-DMA

C12-200

New generation ionizable lipids
Routes of administration for RNA delivery

- Intravenous
- Intrathecal
- Intramuscular
- Intradermal
- Intranodal
- Eye drops
- Enema
- Autologous DC therapy
- SubQ
- Intravitreal
- Nebulization
- Other
The Challenges of RNA Delivery


clearance + targeting + penetration
Approaches to address challenges in RNA Delivery

- Intracellular barriers:
  - Membrane penetrating
  - Endosomal escape

- Extracellular barriers:
  - Active targeting
  - Particle size/shape
  - TME normalization

- Systemic barriers:
  - Stealth nanoparticles
  - Differential organ targeting
  - Nanoprimeing
What needs to happen for RNA delivery to make a difference in oncology?

- Delivery vehicle improvement
- Scale up challenges
- Patient stratification
- Other challenges?