EARLY REGULATORY CONSIDERATIONS FOR RNA THERAPIES FOR RARE DISEASES

29-30 May 2025

CASSS Symposium: mRNA Therapy Products

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DISCLOSURE STATEMENT

I am the Vice President of Regulatory Affairs at Korro Bio, Inc, (Korro) where I am a full-time employee. Other than this disclosure, I have no additional financial interests or relationships to disclose. The comments and points made in this presentation are my own and are not the thoughts or opinions of Korro Bio.

RNA IS A HOT TOPIC!

RNA Editing Set to Take Off: Could DNA's Short-lived Cousin Overcome the Limitations of CRISPR Gene Editing?

By Willow Shah-Neville, LABIOTECH, February 12, 2024-UpdatedonApril 24, 2025
https://www.labiotech.eu/in-depth/rna-editing-reaches-clinic/

The NEW Symposium on mRNA explores how mRNA has become a new modality and how mRNA vaccines are applied.

RNA-based medicine: from molecular mechanisms to therapy

Anke Sparmann and Jörg Vogel

EMBO J (2023) 42: e114760 https://doi.org/10.15252/embj.2023114760

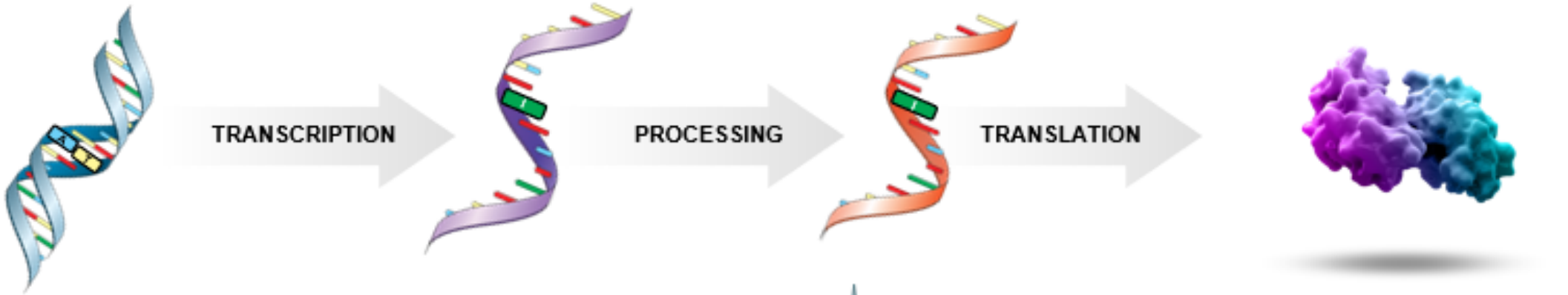
RNA Editing is the Next Frontier in Gene Therapy – Here's What You Need to Know

Published: November 21, 2024 2:07pm ES
https://theconversation.com/rna-editing-is-the-next-frontier-in-gene-therapy-heres-what-you-need-to-know-243938

RNA therapy: Rich History, Various Applications and Unlimited Future Prospects.

Kim, YK. RNA therapy: rich history, various applications and unlimited future prospects. *Exp Mol Med* **54**, 455–465 (2022). https://doi.org/10.1038/s12276-022-00757-5

RNA THERAPY - ABILITY TO EDIT RNA WITHOUT PERMANENTLY ALTERING THE GENOME



Edit a single A-to-I

Modifying gene expression

Edit a single A-to-I

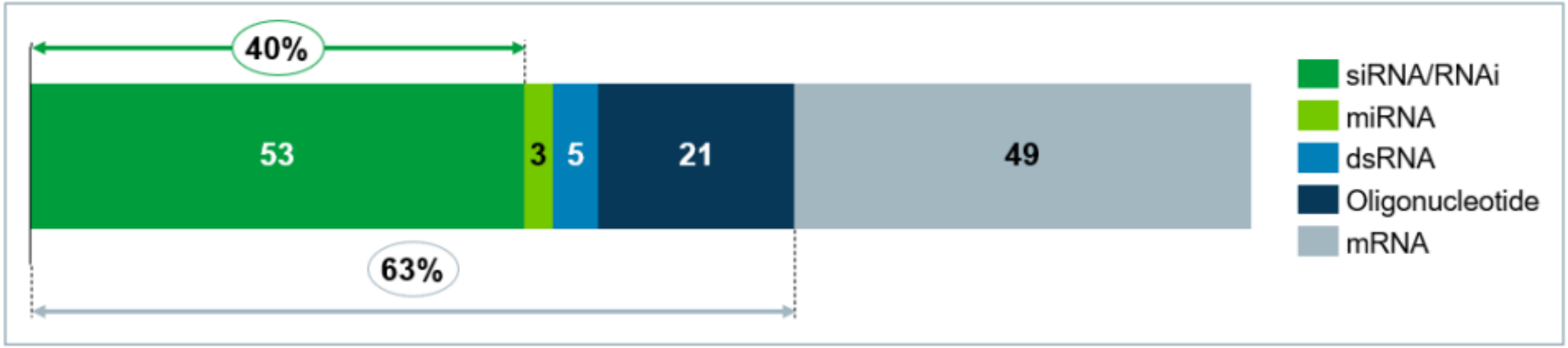
- **Repair** a G->A mutation to correct the protein
- **Generate a *de novo* protein** with preferred properties (can alter 12 amino acid sequences)

mRNA Approach

RNA THERAPY OPPORTUNITIES

As of 31 January 2024, there are an estimated 131 unique RNA-based therapies in clinical development across therapeutic areas.

Figure 1: Number of RNA-Based Therapies in Development, by Product Classification



Pipeline assessment conducted January 31, 2024.
dsRNA: Double Stranded Ribonucleic Acid; miRNA: Micro Ribonucleic Acid; mRNA: Messenger Ribonucleic Acid; RNAi: Ribonucleic Acid Interference

https://advisory.avalerehealth.com/wp-content/uploads/2024/06/20240522-Lilly-RNA-Based-Therapies-White-Paper-vFINAL.pdf#:~:text=RNA%2Dbased%20therapies%20differ%20by%20whether%20their%20mechanism,the%20synthesis%20of%20a%20novel%20therapeutic%20protein.

RNA THERAPY REGULATORY LANDSCAPE: EXAMPLES

US: FDA

- Gene therapy review falls under CBER/OTP
- RNA/ASO review falls under CDER
- IRBs and IBCs play a big role

Australia: Therapeutic Goods Administration (TGA)

- Human Research Ethics Committee(s) (HREC)

New Zealand: Medsafe

- Gene therapy review falls under Gene Technology Advisory Committee (GTAC)
- RNA/ASO review falls under Standing Committee on Therapeutic Trials (SCOTT)
- Health & Disability Ethics Committee(s) (HDEC)
- Māori and Locality Approval Required

Canada: Health Canada

- Research Ethics Board (REB)

Europe: EMA, MHRA, HPRA

- Ethics Committee(s) (ECs)

REGULATORY "ONION OF UNDERSTANDING" FOR RNA THERAPY

1. Health Authority
2. Division or Office Review Team
3. Ethics Committee (EC, REB, IRB, IBC)
4. Clinical Sites, PI/Physicians, KOLs
5. Patient Advocacy
6. Patients, Families & Caregivers

RNA THERAPY – CLEARING EARLY HURDLES: HEALTH AUTHORITIES

- Be clear with Health Authorities (HAs) across the board regarding DNA vs RNA
  - FDA, EMA, MHRA, Medsafe, TGA, Health Canada, etc.
  - Do Not Assume prior experience
- Be sure there is baseline understanding of what RNA *is* and what it *is not*
  1. Clearly differentiate RNA modifier versus DNA modifier
  2. Long lasting modification, but does not permanently modify DNA
  3. Temporary or Reversible therapy
  4. Ability to re-dose, if/when needed
  5. Less chance of off-target modifications
  6. Little concern about germline changes or heritable changes

RNA THERAPY – CLEARING EARLY HURDLES: ETHICS COMMITTEE, IRB, IBC

- Some Health Authorities share “approval” responsibilities with Ethics Committees (ECs)
- Important to be sure that the ECs understand the technology and MoA
- ECs are the decision makers in certain jurisdictions
- When not the decision makers, ECs/IRBs play crucial roles in the “approval” process at the IND/CTA stage
- Do not assume understanding or assume exposure to other RNA therapies
- Each step plays a critical role to getting started in the clinic/clinical study

RNA THERAPY – CLEARING EARLY HURDLES: SITES, KOLS, PHYSICIANS

Sites, PIs, Key Opinions Leaders (KOLs) also play a crucial role in successful submissions, clinical trials, and trial design

Site and PIs need to be comfortable with benefit:risk

Sites and PIs need to understand the technology to explain and discuss with patients & families

Physicians/PIs will have questions, opinions, input on Clinical Study Design

EXAMPLE: Site Declined then Accepted

RNA THERAPY – CLEARING EARLY HURDLES: PATIENTS, FAMILIES, CAREGIVERS, PATIENT ADVOCACY

- Clinical studies are nothing without participants/patients!
- Clear ICFs are critical
- PIs/Sites needing to understand RNA technology
- Rare Disease: Patient Advocacy is a critical element of support and knowledge sharing
- Involved Patient Advocacy groups EARLY in development
- Involve Patients and Patient Advocates in Protocol and Study Design discussions
  - Provides insight into concerns and how to address those concerns

RNA THERAPY OPPORTUNITY

Concerns still occur similar to traditional gene therapies:

- Biodistribution: Where does it go?
- Potential Off-target Effects: What is it doing there?
- Durability of Therapy: How long is it working?
- RNA as Base-editor vs DNA changes
- hERG study expected
- Genotoxicology study(ies)
- Reproductive Toxicity (especially in RNA re-dosing situations)
- CMC Considerations
  - Choose vendor(s) wisely
  - Be ready to move quickly

RNA THERAPY OPPORTUNITIES

- Ability to Leverage prior applications or “prior knowledge” to support the “platform” moving forward?
- Possible to cross reference previously conducted early nonclinical studies, for example, or prior Health Authority meetings where advice conveys across programs, in order to:

1) Reduce development cost and time to patients
   - Especially important in rare disease indications
2) Reduce burden on re-review by regulators (redundancy)
3) Reduce development missteps and provide a clear path forward for industry

SUMMARY

- RNA therapies are of great interest and many RNA therapies are under development
- Do not assume broad understanding of the differences between DNA therapy and RNA therapy
- Do not assume understanding or assume prior exposure to other RNA therapies
- In early development, it is important to have understanding from all decision makers: Health Authorities, ECs, IRBs, IBCs, Sites & PIs, and the Patients, Families and PAGs
- Early planning is essential: Nonclinical studies, Clinical Study design, and RNA Manufacturing should all be considered and early input obtained for a successful program with few bumps.
- Ability to Leverage prior applications or "prior knowledge" to support the "platform" ideal for regulators, developers, and patients alike

CONTACT & QUESTIONS

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