Facilitating Effective Oligonucleotide Drug Development Programs

Part I

• For ultra-rare diseases, including N=1+ conditions
  • Proposal: the OTS invites the FDA and other non-commercial stakeholders to join us at a workshop to advance this discussion, to be held in Bethesda in the first half of 2020.
  • Interested parties are invited to provide their preferred meeting dates at: https://doodle.com/poll/actt2k9e7mr2f2sq

Art Krieg, MD
Co-founder, Past President, Board Member, Oligonucleotide Therapeutics Society
Professor, University of Massachusetts RNA Therapeutics Institute
Intro to the Oligonucleotide Therapeutics Society (OTS)

- The Oligonucleotide Therapeutics Society (OTS) was incorporated in 2004 as a 501(c)6 nonprofit
  - Mission: “to foster academia and industry-based research and development of oligonucleotide therapeutics”
- Website: oligotherapeutics.org
- Our 500+ members represent >30 countries, and are roughly evenly divided between academia and industry.
- OTS has been conducting annual meetings for the past 15 years. The 2019 annual meeting, held last month in Munich, Germany, had ~600 attendees, 154 posters, 60 scientific presentations, and 33 travel awards for students and postdocs to attend
- Our official journal is *Nucleic Acid Therapeutics*
- We are on twitter as @OTSSociety
The dawn of oligonucleotide therapeutics (1989):

Early technologies were not suitable for most potential therapeutic applications:
- Weak affinity
- Many off-target effects
- No therapeutic index in most cases

Since 1989, >$5B have been invested into oligonucleotide technologies...

Figure adapted from Seth et al, J. Clin Invest. 129.3 (2019)
Multiple Innovations Have Advanced Oligonucleotide Therapeutics

- E.g., New chemistries:
  - New designs, platforms have led to 7 approvals:
    - Antisense oligonucleotides (ASO)
      - Gapmers (cleave targets; e.g., inotersen, mipomersen)
      - Mixmers (block targets; e.g., nusinersen, eteplirsen)
    - RNAi (siRNA) (e.g., patisiran)
    - Aptamers (e.g., pegaptanib)
    - Immune activating CpG TLR9 agonists (e.g., Heplisav)
    - mRNA
    - Gene editing (CRISPR, others)

Seth et al, J. Clin Invest. 129.3 (2019)

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Current state:
- 7 approved oligonucleotide therapeutics
- >140 in clinical development
State of the Art Today: Oligonucleotide Therapeutics Are A Robust Platform For Drug Development

- Companies will drive development for diseases affecting >1000 people

- There is no commercial incentive to develop oligos for ultra-rare diseases

- ASO can be applied to treat many ultra-rare diseases very rapidly, with limited resources...
Mila’s Story: The Promise of Personalized ASOs

How many Mila’s are there? Thousands? Tens of thousands? More?

- From diagnosis of a life-threatening disease to a personalized therapeutic in <1 yr!
- Early evidence of patient benefit
- ASO therapies may benefit many more patients
- The OTS invites the FDA and other stakeholders to join with us in a workshop in early 2020 to discuss these issues
- Doodle poll to select workshop date: https://doodle.com/poll/actt2k9e7mr2f2sq
Proposed Workshop: Facilitating The Development Of Oligonucleotide Therapeutics For Ultra-rare Diseases

- Expected size: 40-80 attendees
- Duration: 1 day
- Location: TBD in Bethesda, MD area
- Objectives:
  - Define a process to connect patients/families/physicians with appropriate resources
  - Formulating guidelines for appropriate new programs
    - Criteria for patient enrollment driven by science
    - Process of patient selection driven by risk/benefit
    - Protocols for oligo screening, CMC, safety testing
    - Pathway to approval for patient dosing, monitoring, follow-up
  - Establish guidelines, protocols in dialogue with FDA
Promoting Effective Oligonucleotide Drug Development Programs

Part II

• For The Treatment of Early Stage Cancer
  • the potential role of new surrogate endpoints in accelerating the development of novel cancer immunotherapies

Art Krieg, MD
Founder and Chief Scientific Officer, Checkmate Pharma*

*AK is a shareholder, employee, and patent holder for Checkmate Pharma
Cancer immunotherapies can “cure” some patients with some types of advanced cancers!

- Patients would benefit from approved immunotherapies for early stage cancer (e.g., neoadjuvant, adjuvant) where success rates are higher than in advanced cancer.

- Key challenge: the pathway to approval of new treatments for early stage cancer has been very long:
  - Survival endpoint can require ~ 5yrs to demonstrate
  - Few companies are able to invest in such long-term programs

- Proposal: Identification of surrogate endpoints that are likely to predict benefit in neoadjuvant and adjuvant trials to support accelerated review and approval:
  - Pathologic CR – increasing evidence supports extended disease-free survival in patients achieving pCR (e.g., breast cancer)

NOTE: this is a topic of ongoing discussions with multiple stakeholders and FDA, e.g., Approaches to Neoadjuvant Treatment in Melanoma Public Workshop, co-hosted by FDA and MRA, November 6, 2019
Questions?
DNA-Sensing Immune Pathways

Clinical Trials

Oligos in clinical trials and approved (03/2019)
Many oligo platforms are in development

Oligo Class Trending
Clinical Compounds: 2009 - Present