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

SCAN ME

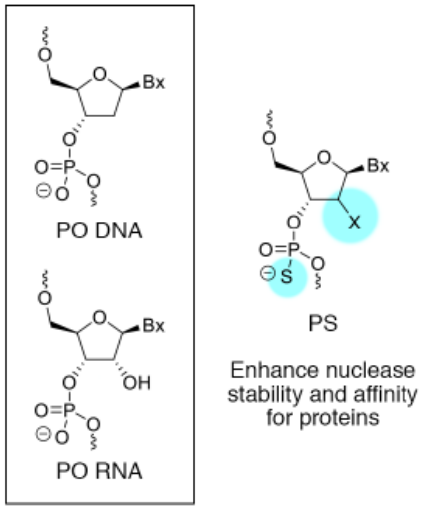
Art Krieg, MD
Co-founder, Past President, Board Member, Oligonucleotide Therapeutics Society
Professor, University of Massachusetts RNA Therapeutics Institute

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 @OTSociety

A Brief History Of Oligonucleotide Drug Development

The dawn of oligonucleotide therapeutics (1989):



Enhance nuclease stability and affinity for proteins

Early technologies were not suitable for most potential therapeutic applications:

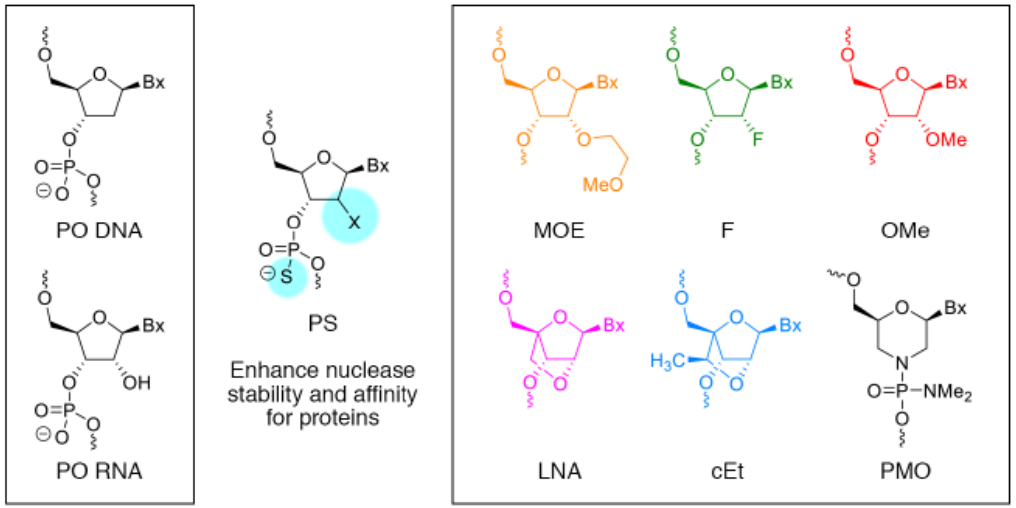
- Weak affinity
- Many off-target effects
- No therapeutic index in most cases

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:



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

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)

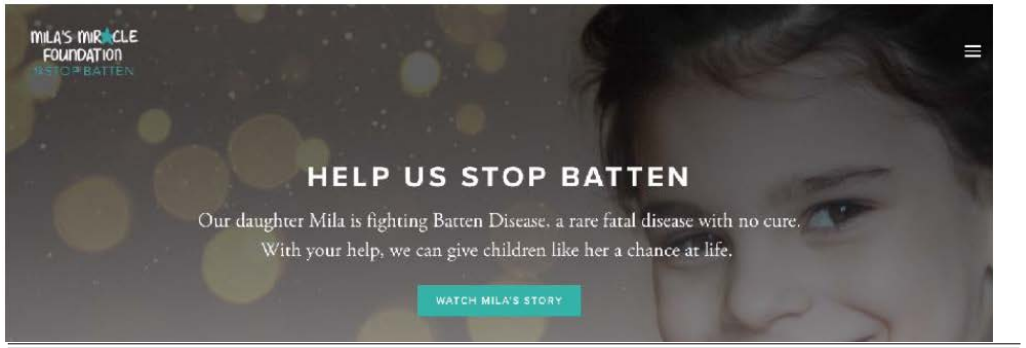
Current state:
7 approved oligonucleotide therapeutics
>140 in clinical development

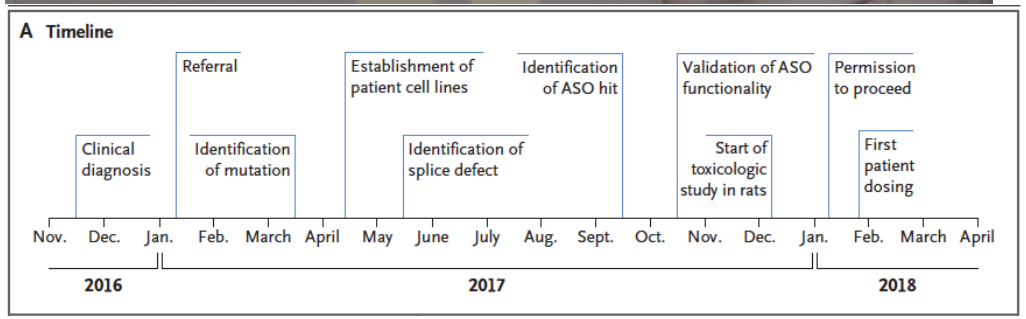
State of the Art Today: Oligonucleotide Therapeutics Are A Robust Platform For Drug Development

- 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?





The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu

- 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

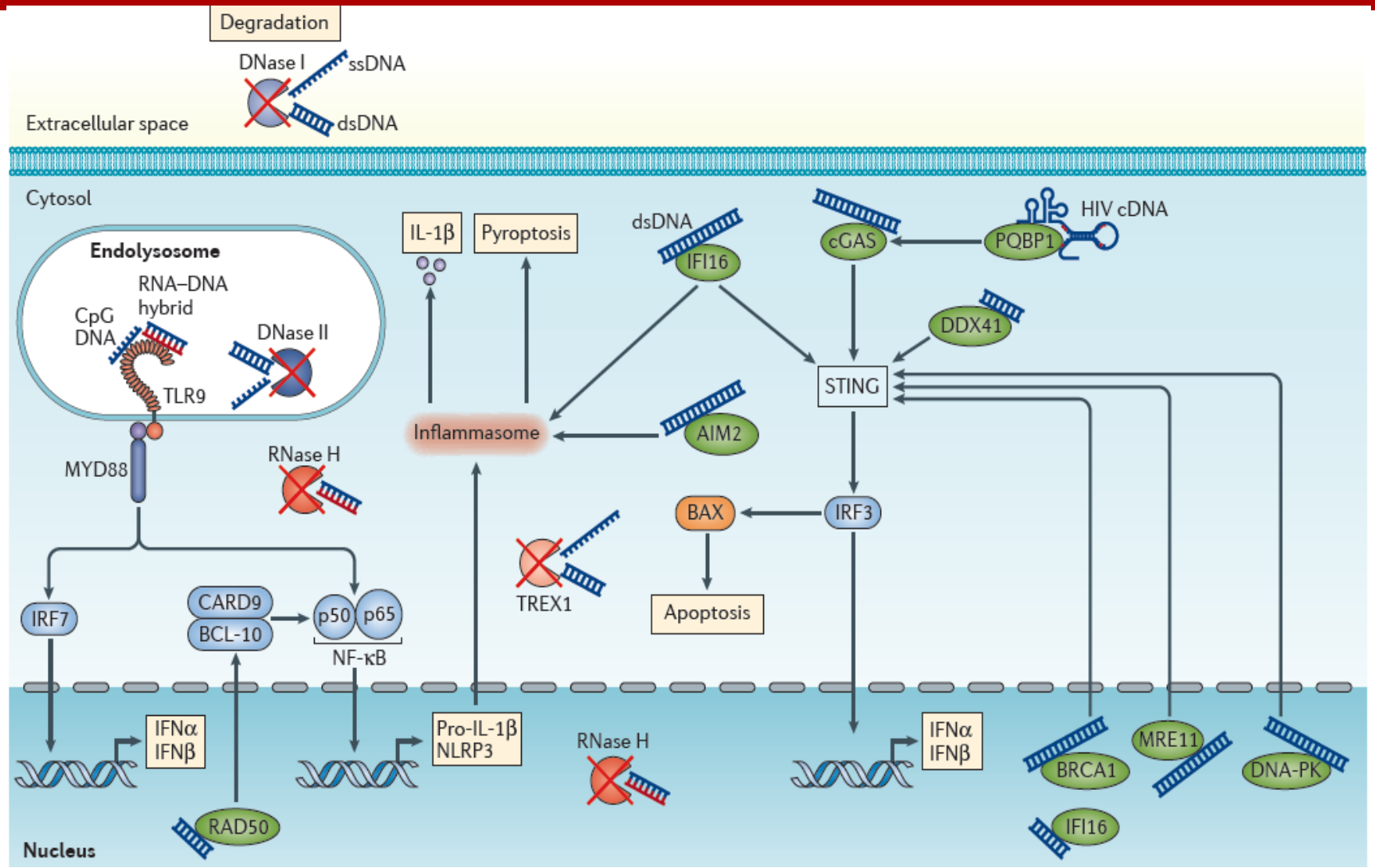
Cancer immunotherapies can "cure" some patients with some types of advanced cancers!

- **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?

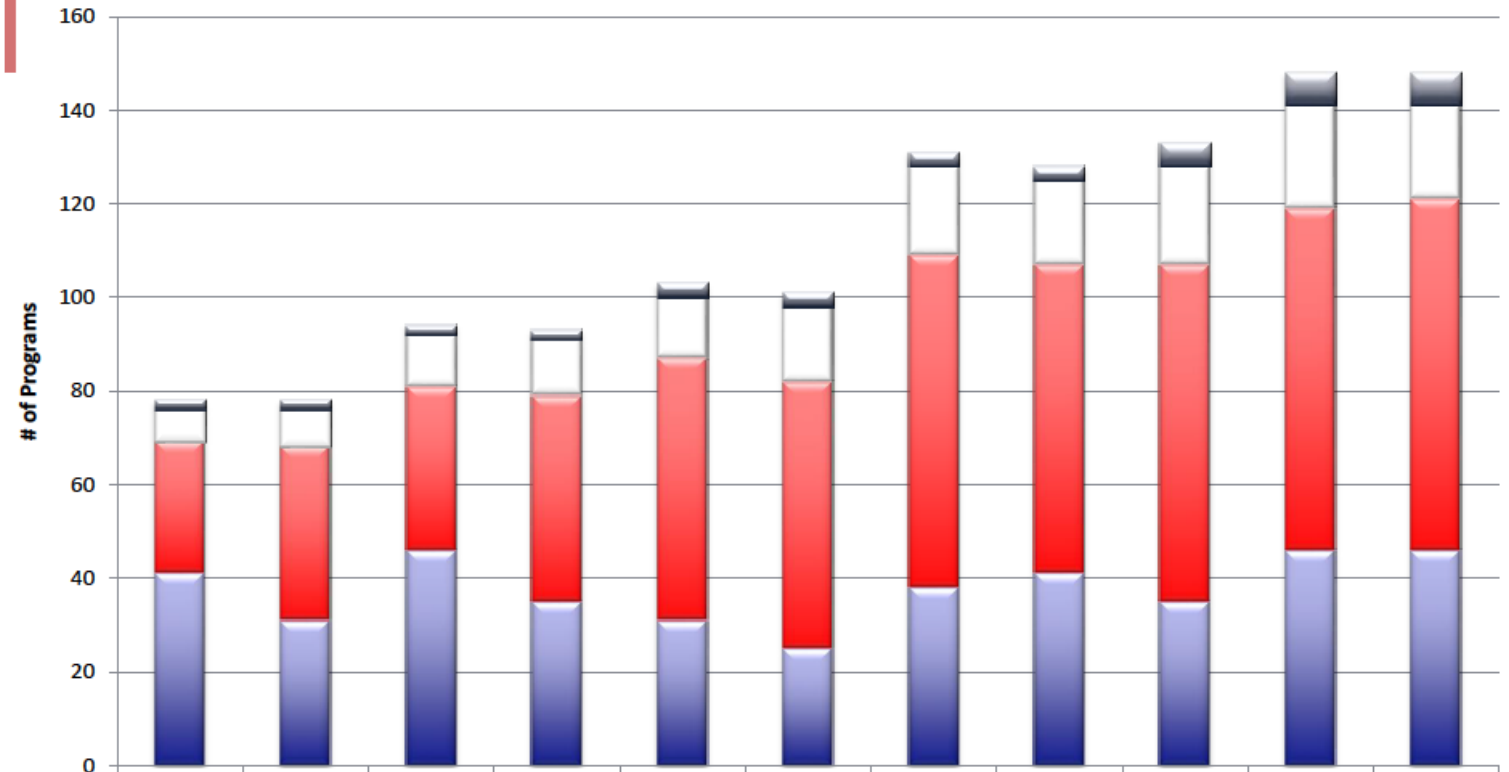
DNA-Sensing Immune Pathways



Schlee and Hartmann, Nature Rev. Immunol, 2016

Clinical Trials

Oligos in clinical trials and approved (03/2019)



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019 (To Date)*
Approved	2	2	2	2	3	3	3	3	5	7	7
Phase III	7	8	11	12	13	16	19	18	21	22	20
Phase II	28	37	35	44	56	57	71	66	72	73	75
Phase I	41	31	46	35	31	25	38	41	35	46	46

Many oligo platforms are in development