Developing 1 New Drug Takes >$2.5B & >10 Yrs

This approach is not adequate to develop new drugs to treat patients with rare disease quickly.
How Much Does It Cost To *Discover* A New Drug*?

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- A “lead” is a drug candidate that is ready to begin formal animal safety testing
- Traditional small molecule drugs take a long time and cost a lot of $ before they even get close to clinical testing
- Consequences:
  - It’s difficult and costly to begin clinical testing or try new drug ideas
  - It’s very risky to try to develop drugs for rare diseases, or small subsets of common diseases (“precision medicine”, or “personalized medicine”)

*Pfizer R&D metrics*
New Technologies Have Dramatically Accelerated Drug Discovery And Development

- 1975 - Kohler and Milstein discover how to produce monoclonal antibodies
- 1986 - The first antibody drug was approved by FDA (OKT3; mouse antibody)
- Generations of new innovations occurred, humanized antibodies
- 1997 - The first commercially successful antibody drug was approved (Rituxan)
- Now “biologics” are very widely used and successful drugs, can treat diseases that were previously untreatable with small molecules
- Still too expensive, slow for N of 1 therapeutics

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Nucleic Acid Drugs (ASO) Are Further Accelerating Drug Discovery And Development, Reducing Costs

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- No other drug platform can match the speed and low cost of ASO drug discovery
- ASO represent “rational drug design” – the sequence of the drug is designed to match that of the target RNA (or DNA)
- The same basic chemical building blocks are used for all drugs, and behave consistently
- The cost is within range for N of 1 therapeutic development
Mutations in DNA may cause disease if they alter proteins. Conventional drugs to treat disease work at the protein level. In 1978, Paul Zamecnik conceived of “antisense oligos” (ASO) – RNA or DNA drugs to treat disease “upstream” of proteins.

- Took 6 mos to make enough ASO for 1 experiment.
- His approach actually didn’t work.

In the mid 1980’s, Marv Caruthers invented automated DNA synthesis, leading to the birth of many antisense companies (e.g., Ionis). In 1993, Ryszard Kole conceived of and demonstrated ASO to alter RNA splicing in vitro (didn’t work in vivo). In 1998, the first ASO drug was approved (fomiversen – didn’t fxn as ASO).

In the 2000’s, generations of innovations, new chemistries, and designs were developed. Adrian Krainer showed in 2010 that splice-switching ASO can be designed to treat spinal muscular atrophy (SMA). In 2016, Nusinersen was approved by FDA to treat SMA, the first commercial success for ASO field.

- Proof of concept for ASO approach to treat many other fatal neurologic diseases.
Where do we go from here?

- What prevents customized ASO drugs from being developed for many (tens of thousands?) of rare disease patients?