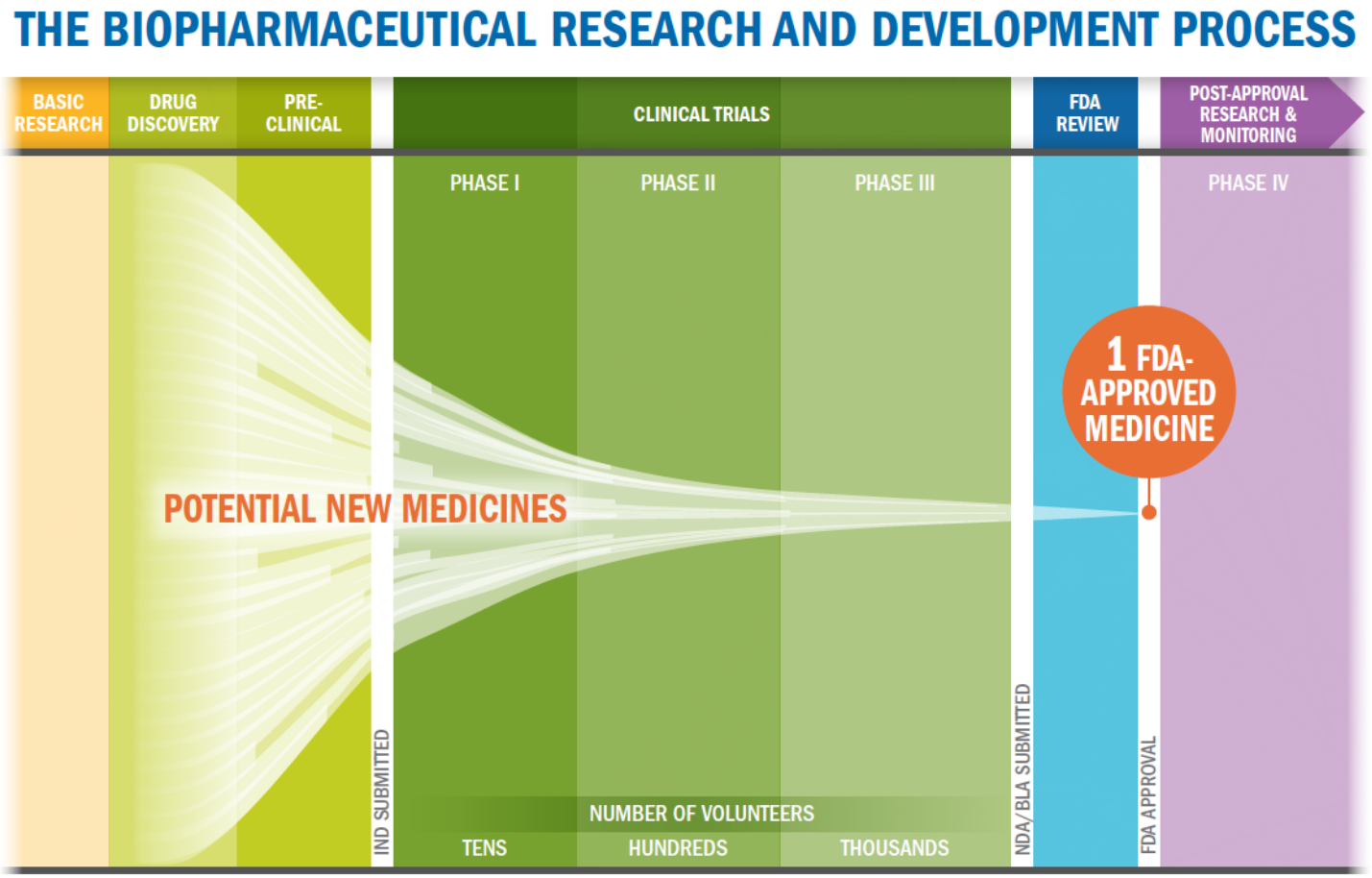
Developing 1 New Drug Takes >$2.5B & >10 Yrs



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*?

	Discovery FTE Years	Cycle Time	Cost to Discover a Lead
Small Molecule	70-90 FTEs total	4-5 years	~$25 million

- 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

	Discovery FTE Years	Cycle Time	Cost to Discover a Lead
Small Molecule	70-90 FTEs total	4-5 years	~$25 million
Antibody	20-30 FTEs total	2-3 years	~$8 million

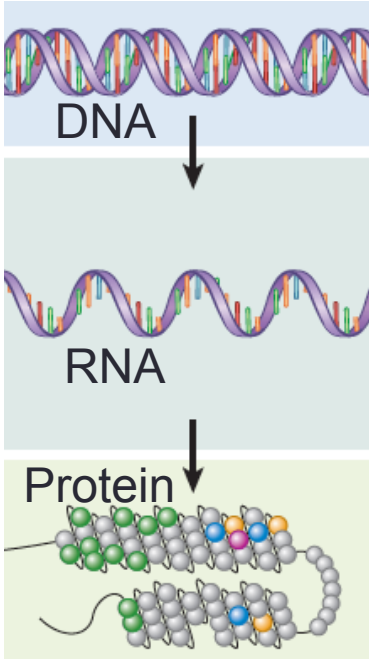
- 1975 - Kohler and Milstein discover how to produce monoclonal antibodies
- 1986 - The first antibody drug was approved by FDA (OKT3; mouse antibody)
- Generations of new innovations occurred, humanized antibodies
- 1997 - The first commercially successful antibody drug was approved (Rituxan)
- Now “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

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

	Discovery FTE Years	Cycle Time	Cost to Discover a Lead
Small Molecule	70-90 FTEs total	4-5 years	~$25 million
Antibody	20-30 FTEs total	2-3 years	~$8 million
Nucleic Acid Drugs (ASO)	<10 FTEs total	<0.5 year	<$3 million

- 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

From Biology to ASO Drug Development



- Mutations in DNA may cause disease if they alter proteins
- Conventional drugs to treat disease work at the protein level
- 1978 – Paul Zamecnik conceives 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
- mid 1980's Marv Caruthers - invents automated DNA synthesis, leading to the birth of many antisense companies (e.g., Ionis)
- 1993 – Ryszard Kole conceives of and demonstrates ASO to alter RNA splicing in vitro (didn't work in vivo)
- 1998 – first ASO drug approved (fomiversen – didn't fxn as ASO)
- 2000's – generations of innovations, new chemistries, designs
- 2010 Adrian Krainer shows that splice-switching ASO can be designed to treat spinal muscular atrophy (SMA)
- 2016 - Nusinersen approved by FDA to treat SMA
  - 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?