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An Introduction to Preclinical Therapeutics Development

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DEE-P

September 21, 2020

National Center for Advancing Translational Sciences

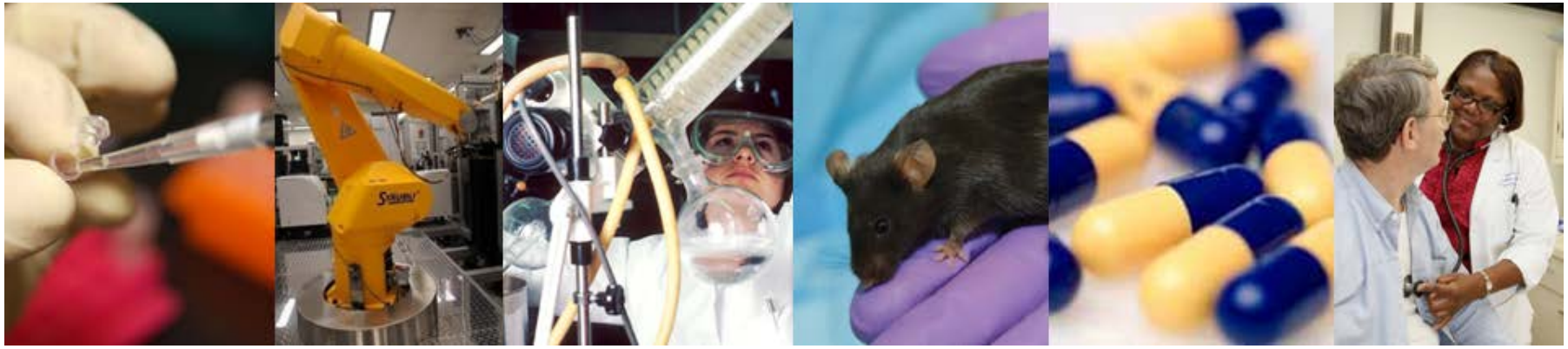
Introduction to Preclinical Therapeutics Development: Outline

- NIH: Who we are
- Precision medicine primer
- Preclinical development overview
- Keypoints
- Resources for you

Who We Are

- National Institutes of Health (NIH): US's medical research agency
  - Mission: "Turning Discovery into Health"
  - Largest public funder of biomedical research in the world
- 27 Institutes and Centers (ICs), e.g.,
  - National Institute of Allergy and Infectious Diseases (NIAID)
  - National Institutes of Neurological Disorders and Stroke (NINDS)
- National Center for Advancing Translational Sciences (NCATS)
  - Established in 2012
  - Only NIH Center focused on translational sciences
  - Translation = process of turning observations (e.g., lab, clinic) into interventions that improve health

NCATS Mission



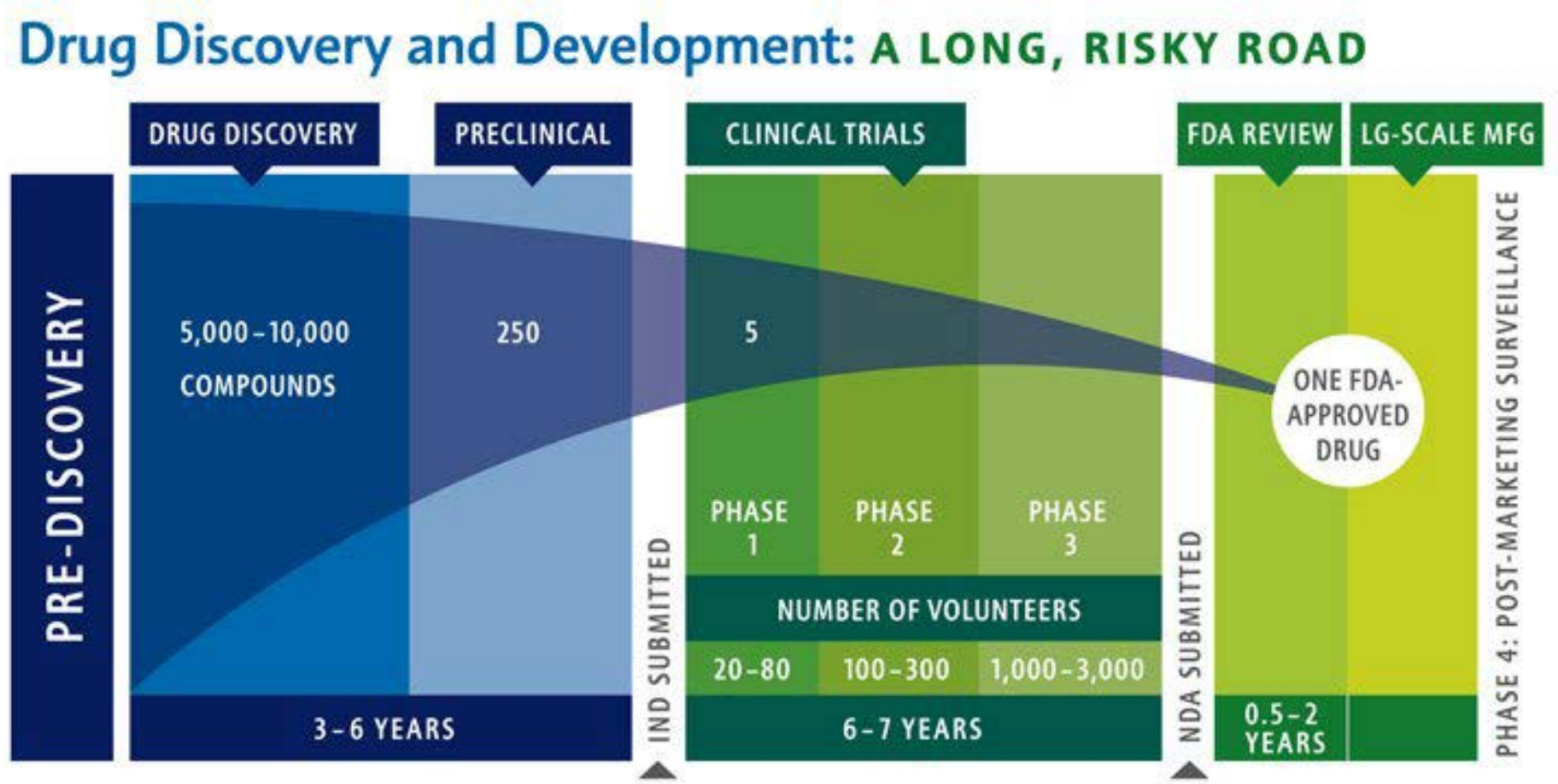
Answer critical research questions to transform the translation research process so that new treatments and cures for diseases can be delivered to patients faster

About NCATS: https://ncats.nih.gov/about

Office of Rare Diseases Research (ORDR)

Accelerating rare diseases research to benefit patients

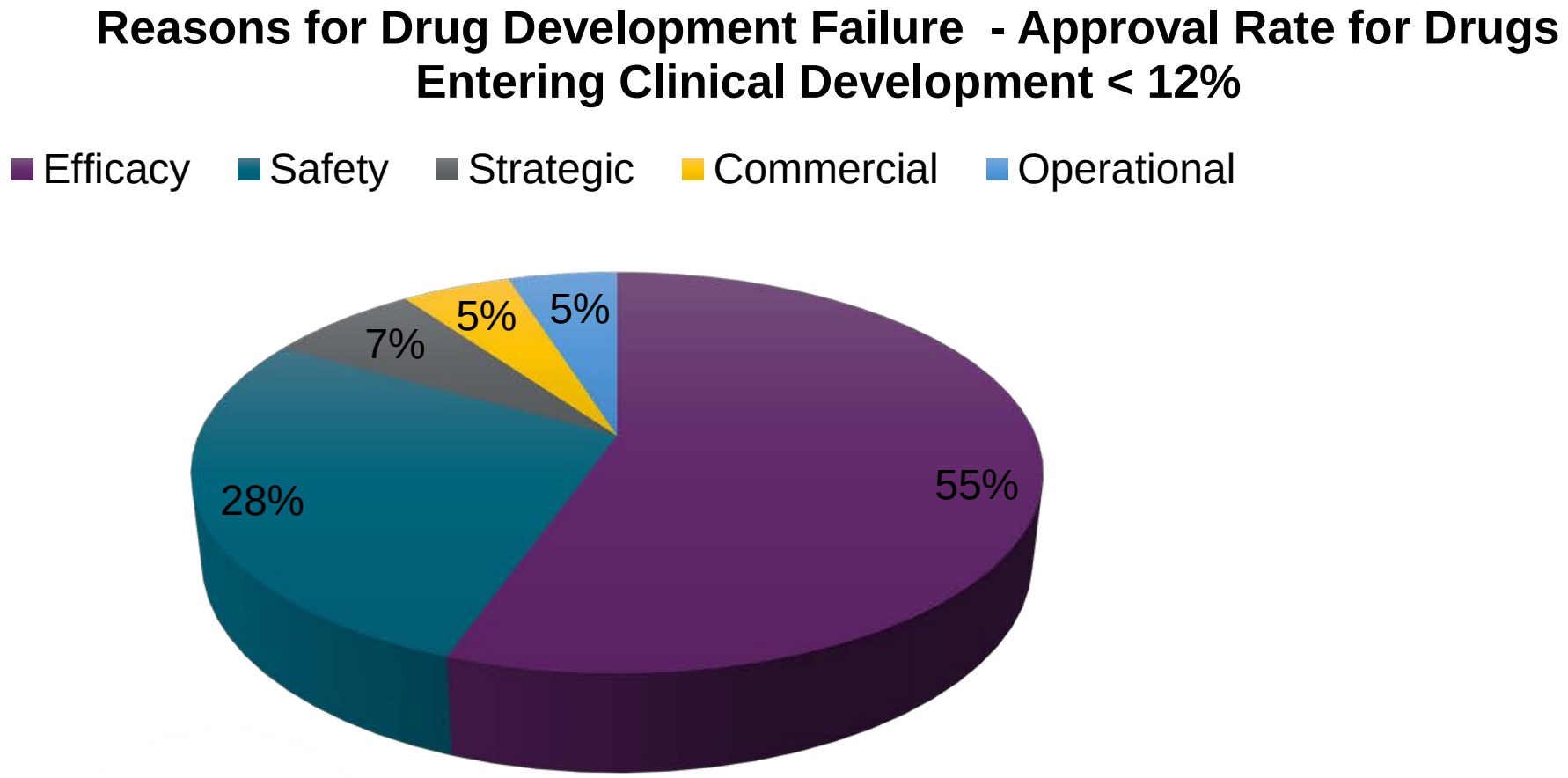
The Problem: Product Development Time and Costs: 10–15 Years and >$2.6 Billion USD



Sources:

- Pharmaceutical Research and Manufacturers of America, *Drug Discovery and Development: Understanding the R&D Process*, www.innovation.org
- DiMasi, JA and Grabowski, HG (2007), The Cost of Biopharmaceutical R&D: Is Biotech Different?, *Managerial and Decision Economics 28* : 469-479

Why Drugs Fail in Clinical Phase of Development



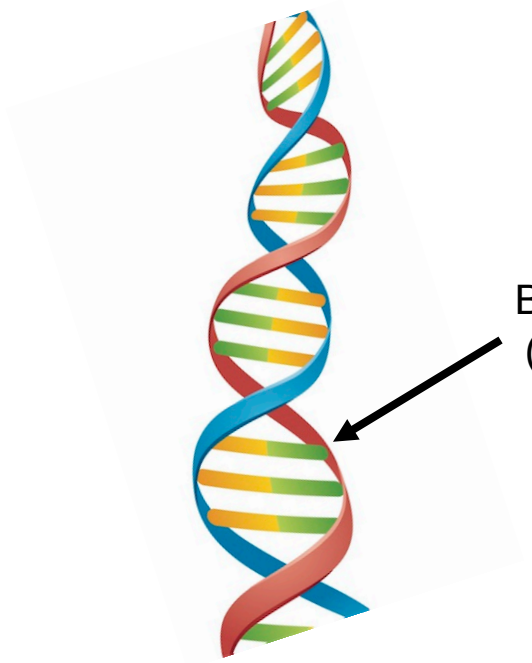
Sullivan T. March 21, 2019. https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html and *Arrowsmith and Miller, Nat Rev Drug Disc 12: 569 (2013)*

But first - A few words about modern rare disease drug development…

- ~7,000^{+} rare diseases
- ~80^{+}% genetic/inherited “single gene” disorders (monogenic)

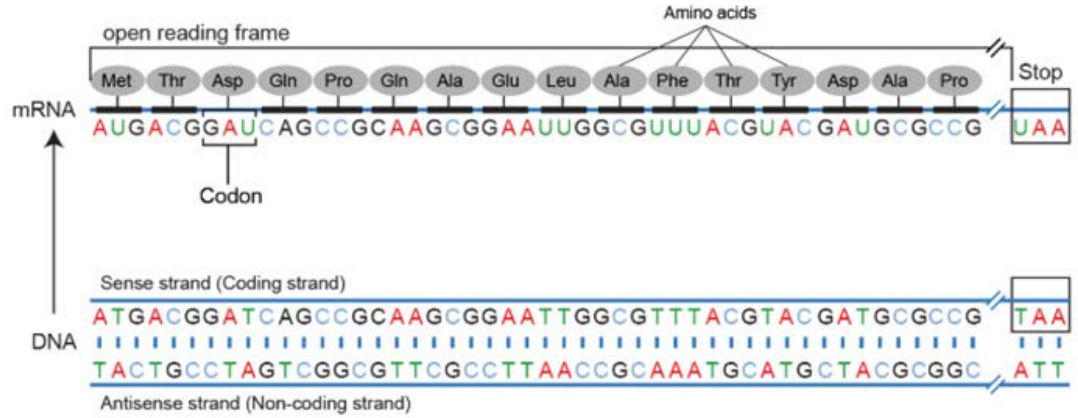
Genetics whirlwind refresher (puppies at the end)

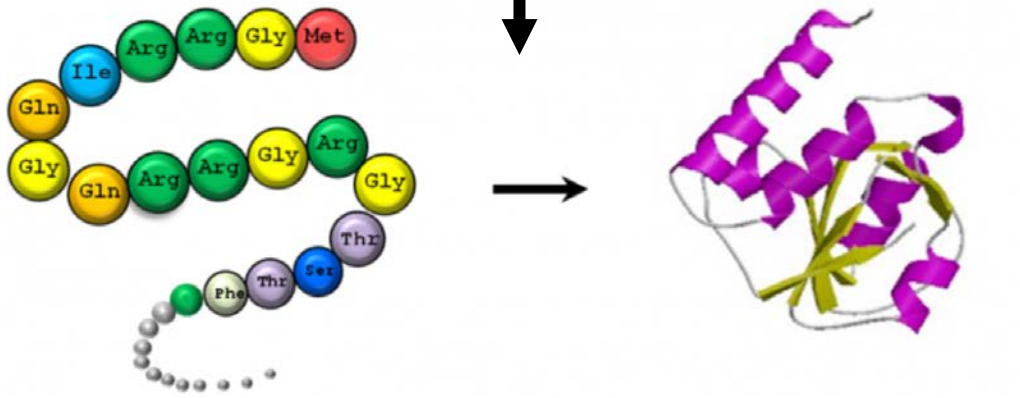
- Single gene aka monogenic disorder
- Caused by a deleterious change (mutation) in one gene



Base pairs
(A-T,G-C)

DNA double helix





3 bases/nucleotides = triplet/codon
Codes for an amino acid (aa)

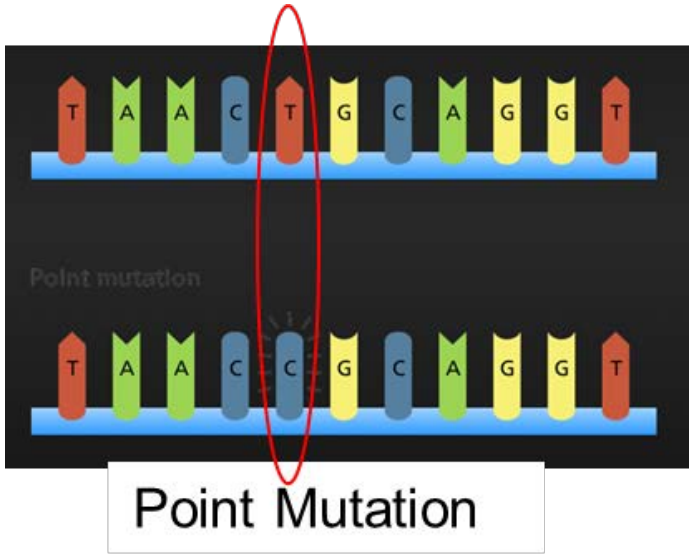
Many aas → protein, e.g, enzyme, structural

What Can Go Wrong?

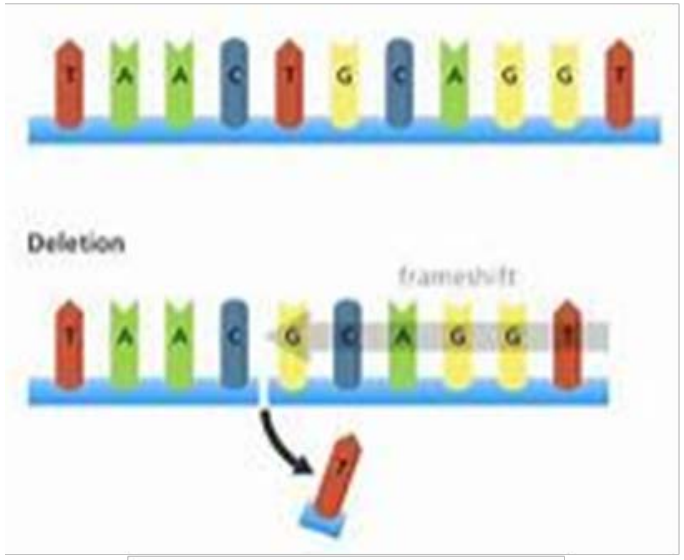
"Pathogenic variants"

Some examples

- Missense mutation: single base pair causes the substitution of a different aa in the protein
  - Sickle cell disease
- Nonsense mutation: premature stop codon
  - → truncated or absent protein
- Frameshift mutation: add or subtract a nucleotide
  - → alters the "reading frame"
- Gain of function mutation: enhanced or new activity on a protein
  - E.g., dominant, Hutchinson-Gilford Progeria
- And more….



Point Mutation



Frame shift

Bottom Line: It's in the Genes

- Many different underlying mutations
  - Considerable diversity within and between genetic diseases
- Thus, many different approaches to how to treat the disease, for example:
- Loss of function/deficiency state, e.g.,
  - add back enzyme/protein/gene, such as gene therapy, enzyme replacement therapy, drugs to enhance residual function, "read-through" drugs
  - Add or subtract elements upstream or downstream from the defect
- Gain of function → silencing/inhibition, e.g.,
  - Antibodies, drug-inhibitors
  - anti-sense oligonucleotides (AONs)
- Everything → gene editing
  - Active area of research, no approved therapies currently

Precision Medicine

- “an emerging approach for disease treatment and prevention that takes in to account individual variability in genes, environment, and lifestyle for each person”[1]
- “Interventions tailored to individuals or groups, rather than one-size-fits all approaches”[2,3]

- Aka “targeted therapy”
  - Take advantage of molecular differences in genes/cells/tissues for efficacy and/or safety of an intervention
  - E.g., target changes in cancer cells that help them grow, divide or spread

[1] https://ghr.nlm.nih.gov/primer/precision,medicine/definition

[2] https://www.cdc.gov/features/precision-medicine/index.html

[3] https://www.fda.gov/medical-devices/vitro-diagnostics/precision-medicine

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Clinical Development: Traditional Paradigm

- Knowledge

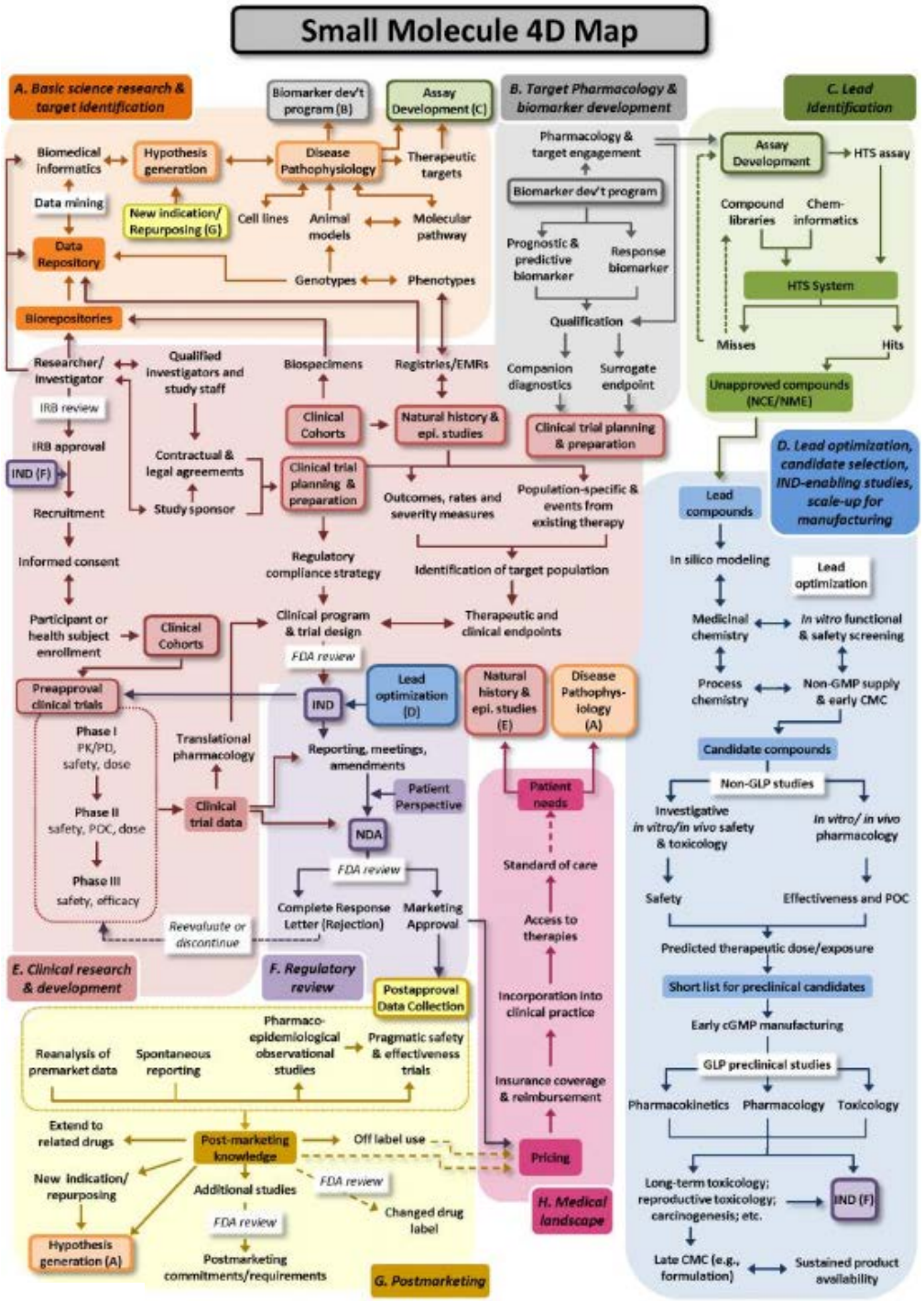
- Target identification
- Molecular screening
- Assays
- Biomarkers
- Drug discovery
- Candidate selection/ optimization
- Animal models
- Initial formulation
- Natural History Studies
- Clinical Outcome Assessments

- Animal testing/ toxicology
- ADME*

- IND*
- Human safety
- PK/PD
- Human efficacy

- NDA/BLA*
- "Therapy"
- Post-marketing surveillance

*ADME = Absorption, distribution, metabolism, excretion
IND = Investigational New Drug application
NDA = New Drug Application; BLA = Biologics Licensing Application



Clinical Development Overview

- "4D" Map*
  - Drug Discovery, Development and Deployment
- Dynamic representation of modern therapeutics development process*
- Development can start anywhere in the map
- Published in:
  - Nature Reviews Drug Discovery: https://pubmed.ncbi.nlm.nih.gov/29269942/
  - Clinical and Translation Science: https://pubmed.ncbi.nlm.nih.gov/29271559/

*https://ncats.nih.gov/translation/maps

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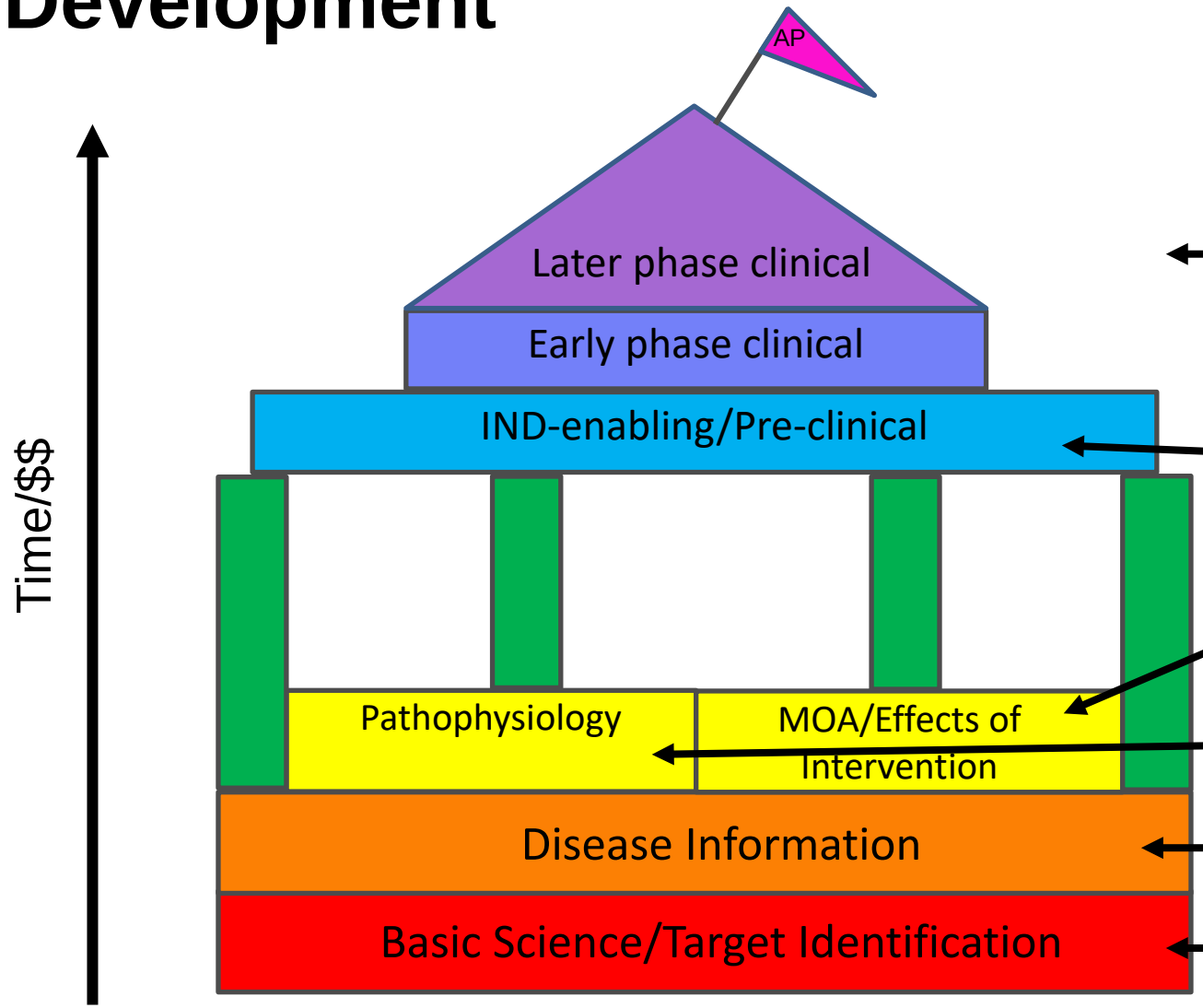
Foundational Science Building for Clinical Development



Human testing

Preliminary safety, first-in-human dose identification, formulation

How does the drug work, identify what can be measured and how, early product quality/characterization

What is going wrong, identify targets, identify drugs, test in models/modeling

Describe clinical features, not drug specific

Disease understanding, not drug specific

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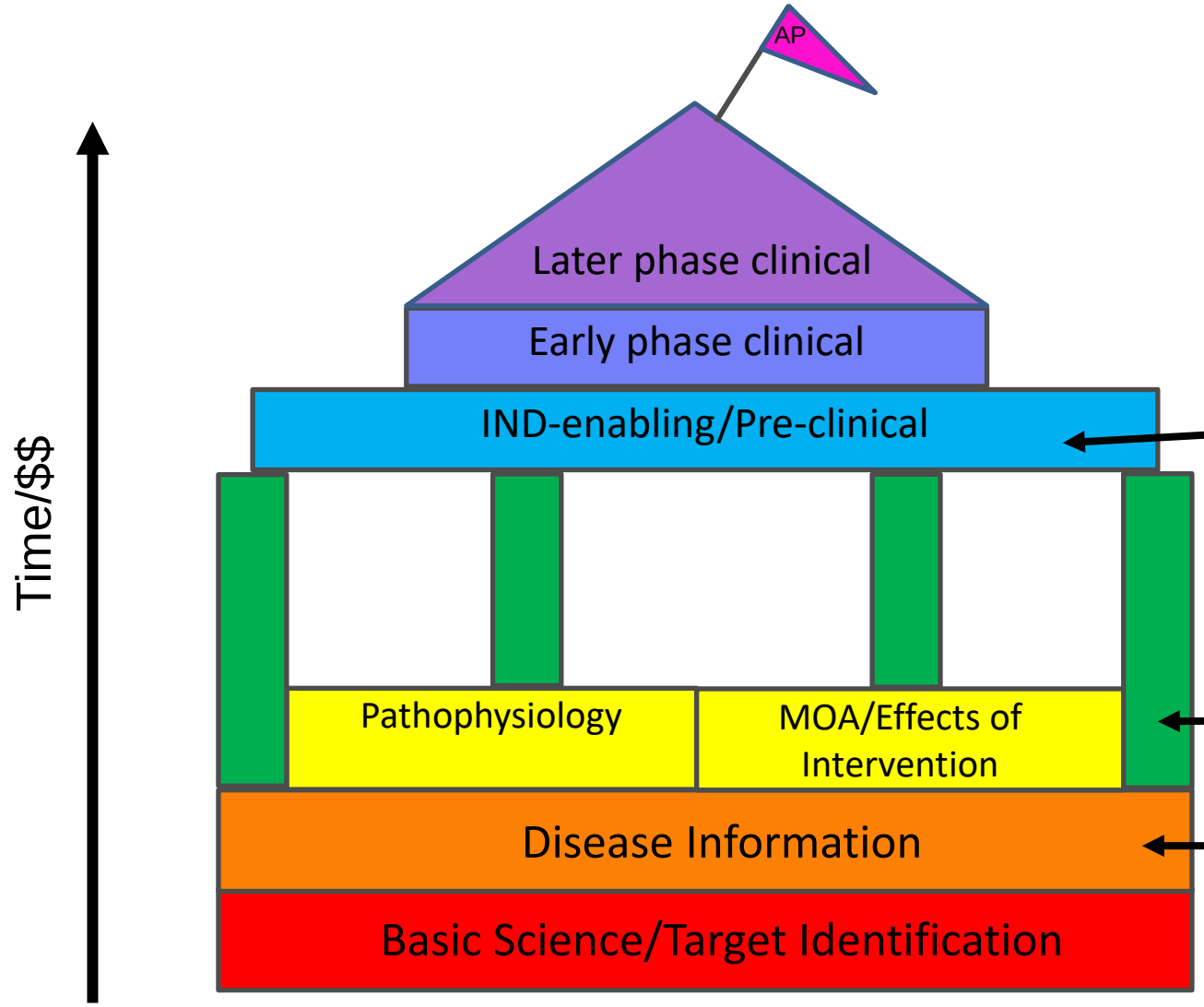
Foundational Science Examples



Animal testing and toxicology, ADME*

High throughout put screening, drug optimization, assays, animal models, and more

Natural history studies, registries, clinical outcome assessment identification and exploration

*ADME = absorption, distribution, metabolism, excretion

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What can patients do? A lot!

- Research process is long and unpredictable
  - Delays and resetting of timelines is very common (expected)
  - Setbacks = knowledge, not failure
- Many things can happen in parallel
  - Small investments at critical junctures can have big pay-offs
- Patients have special knowledge of their disease
  - Registries, natural history studies
    - Data quality and interoperability are important
  - Educate and bring together the community
- Scientific meetings are not just for scientists
  - Meet the researchers
  - Family “tracks” within meetings
  - Participate in research agenda setting process
- Share your stories – they matter and people will listen
- Rare Diseases Are Not Rare
  - 30 million people in the US with a rare disease, 350 million worldwide
  - Join with other groups – there is power in numbers

Resources for You

- NCATS
  - Toolkit for Patient-focused Therapeutics Development: https://ncats.nih.gov/toolkit
  - Rare Diseases Registry Program (RaDaR): https://registries.ncats.nih.gov/
  - Scientific Conference grants: https://ncats.nih.gov/funding/open/conference-grants
- FDA
  - Patient Affairs Staff: https://www.fda.gov/about-fda/office-clinical-policy-and-programs/patient-affairs-staff

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