Public funding of drug development: contributions of the US NIH

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Center for Integration of Science and Industry
Bentley University

Presentation to the Global Health Center Webinar Series
April 25, 2019

Bentley University, Waltham, MA

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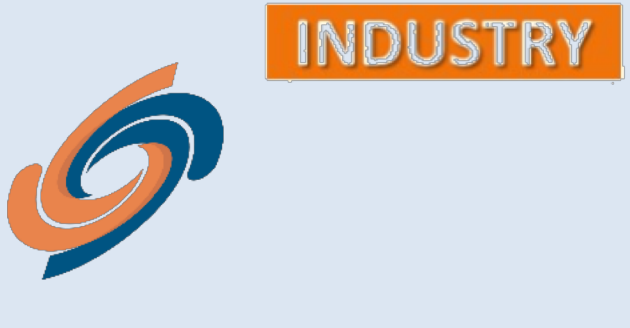
Center for Integration of Science and Industry at Bentley University

Our mission is to accelerate translation of scientific discoveries into public value through interdisciplinary dialogue

- Team-based research spanning business, pharmaceutics, data science, case studies
- Funded by National Biomedical Research Foundation



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Taking a systems approach to translational science from basic science to successful products and businesses

Ongoing projects include:

- Public sector (NIH) contributions to new medicines
- Decision models for translational science (TIME model, machine learning)
- Policies for accelerating translational science
- Business strategies for value creation in biotechnology
- R&D spending and profitability in biopharma and S&P 500 companies

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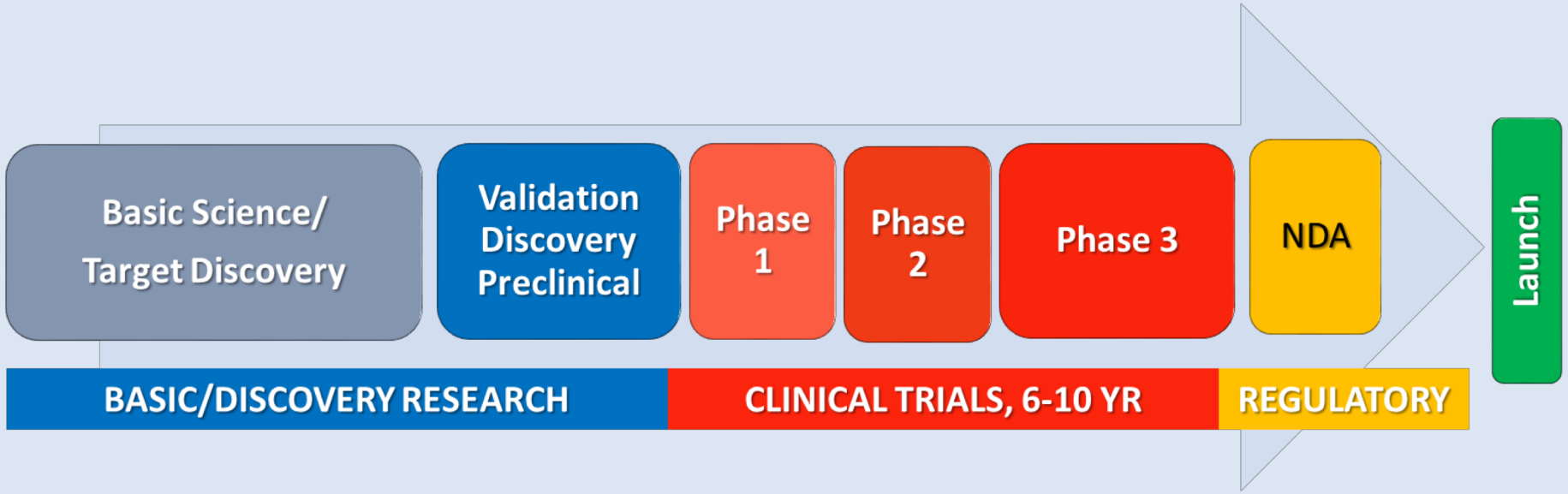
What is the public sector (NIH) contribution to new medicines?



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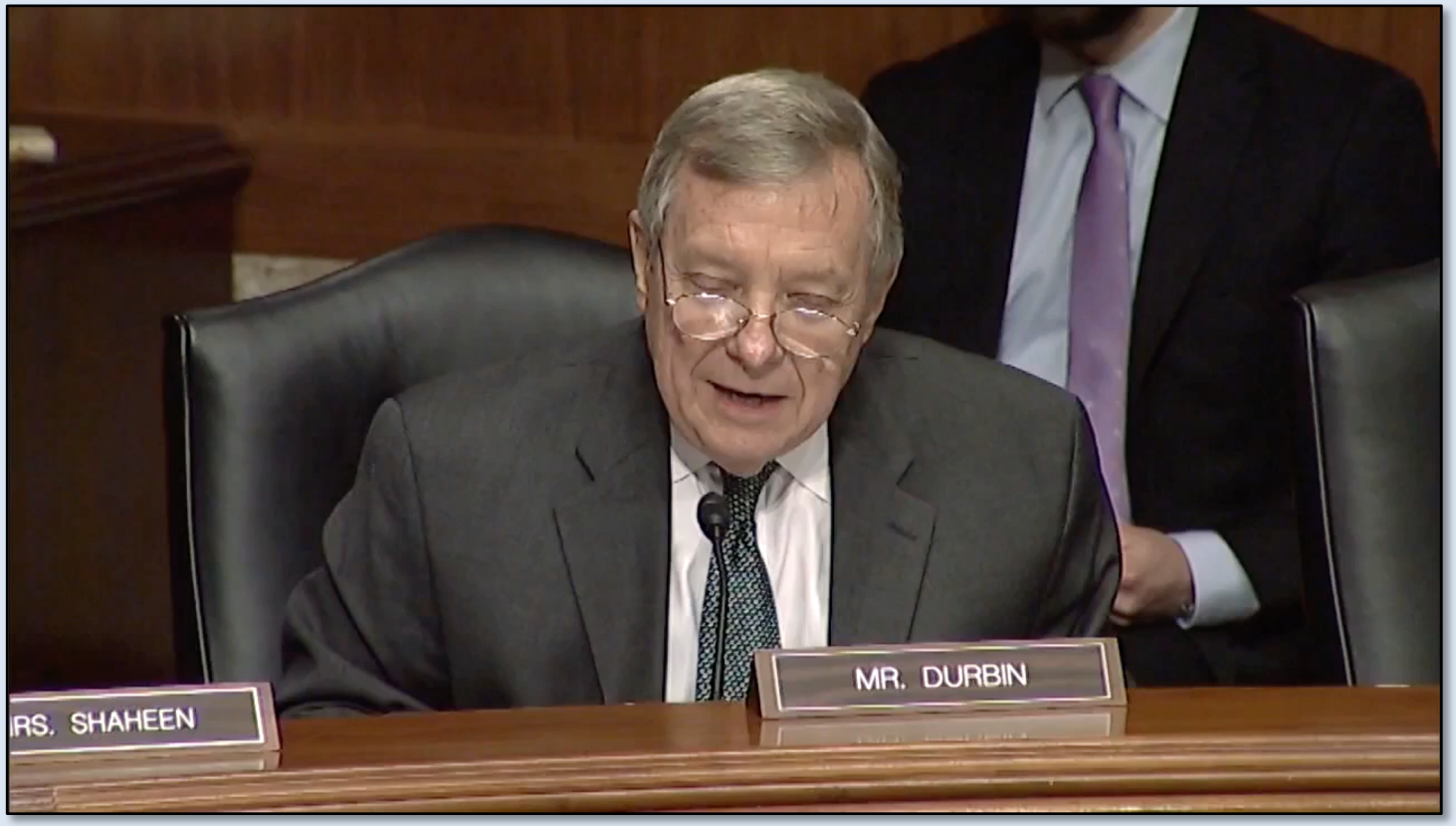
What contribution does the NIH make to new medicines?

Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies.

June 22, 2017

Senator Richard Durbin, (D-IL), question to Dr. Francis Collins, Director, National Institutes of Health



www.c-span.org/video/?430343-1/nih-officials-testify-fy-2018-budget-request

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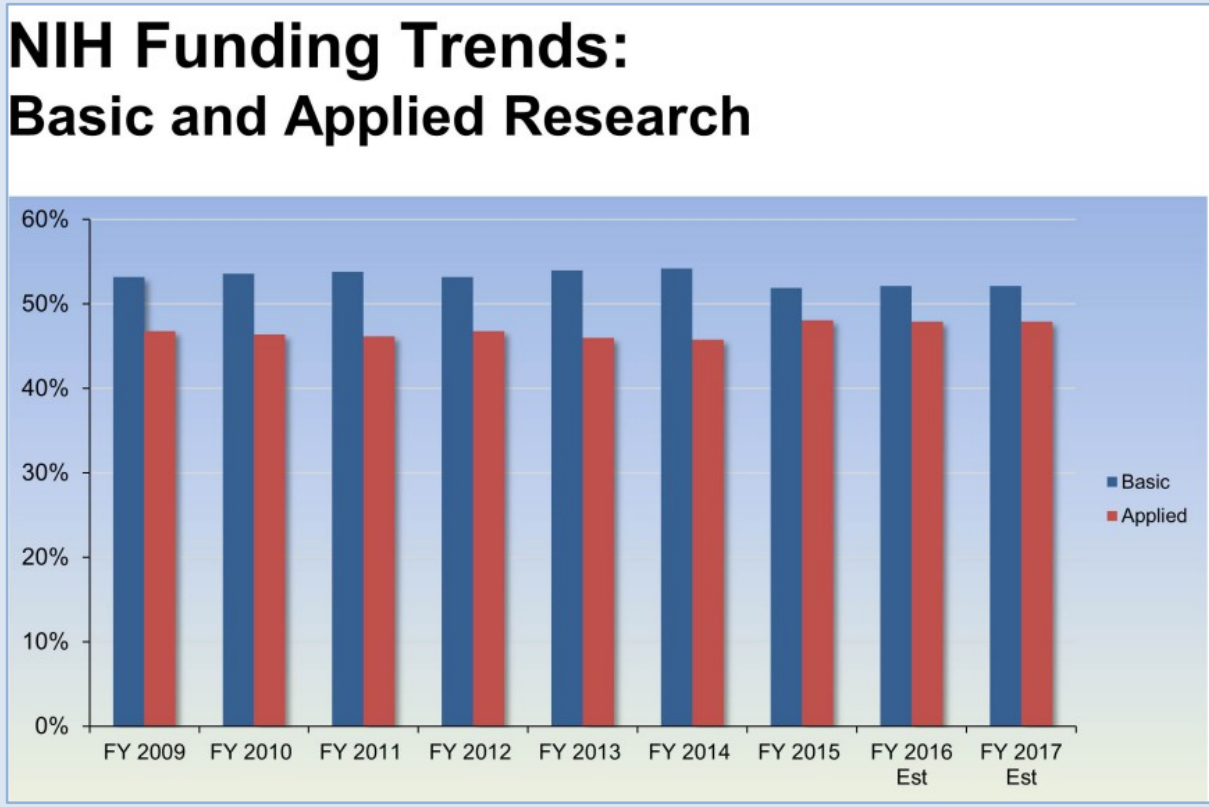
The government funds both basic and applied research

"**Basic research** is defined as systematic study directed toward fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications towards processes or products in mind. Basic research, however, may include activities with broad applications in mind."

Michael Lauer, NIH Deputy Director for Extramural Research



nexus.od.nih.gov/all/2016/03/25/nihs-commitment-to-basic-science/

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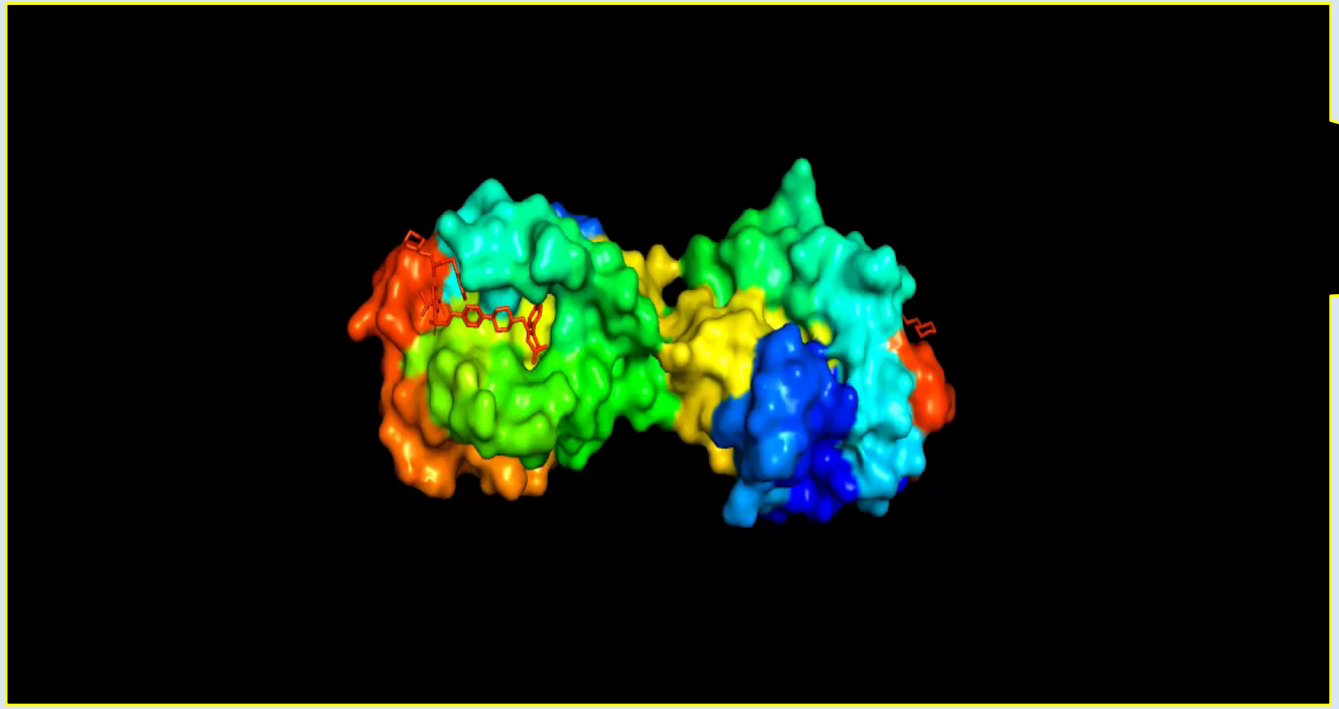
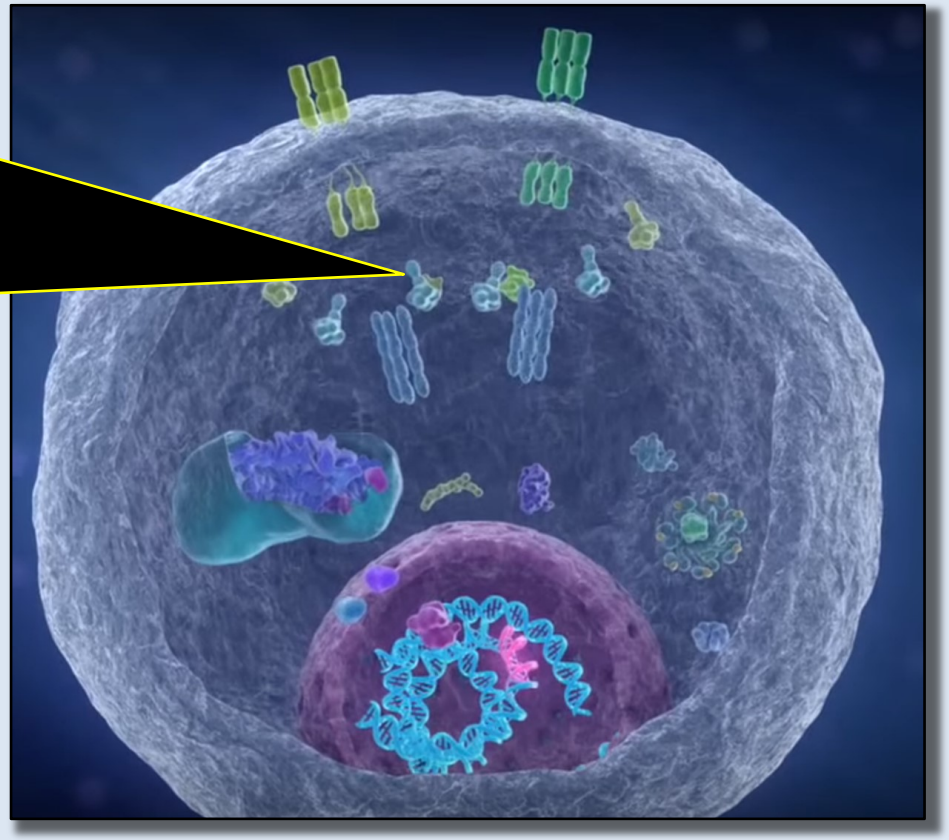
The mechanism of drug action involves binding to target proteins involved in disease process



www.ncbi.nlm.nih.gov/Structure/pdb/4LVT



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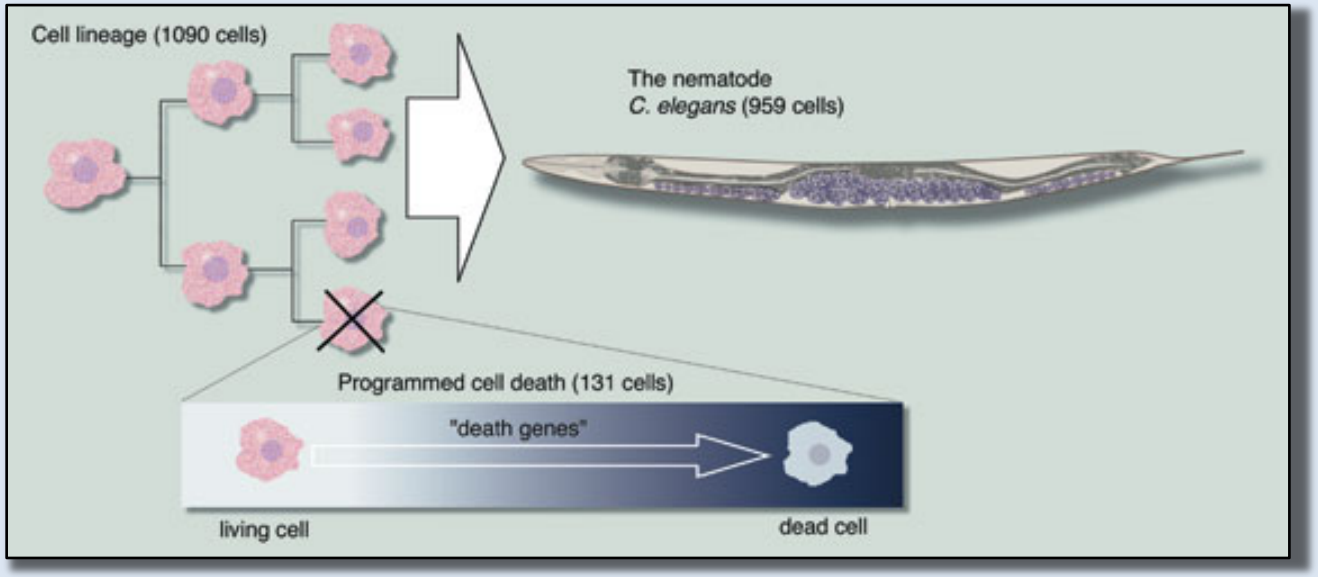
The biological targets for new medicines are discovered through basic science: *an example*

Discovery of apoptosis in *C. elegans* (worms)



www.nobelprize.org

An example:

- Programmed death (apoptosis) of cancer cells involves Bcl-2 protein
- Apoptosis discovered studying development of *C. elegans*
- Venetoclax/VenclextaTM (AbbVie) approved for leukemia (CLL), 2016
- Research on Bcl-2: >50,000 papers
- Research on Venetoclax: 286 papers

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Defining “Drug” and “Target” searches for new drugs approved 2010-2016

Structure of the human smoothened receptor bound to an antitumour agent.

Wang C[1], Wu H, Katritch V, Han GW, Huang XP, Liu W, Siu FY, Roth BL, Cherezov V, Stevens RC.

Author information

Abstract

The smoothened (SMO) receptor, a key signal transducer in the hedgehog signalling pathway, is responsible for the maintenance of normal embryonic development and is implicated in carcinogenesis. It is classified as a class frizzled (class F) G-protein-coupled receptor (GPCR), although the canonical hedgehog signalling pathway involves the GLI transcription factors and the sequence similarity with class A GPCRs is less than 10%. Here we report the crystal structure of the transmembrane domain of the human SMO receptor bound to the small-molecule antagonist LY2940680 at 2.5 Å resolution. Although the SMO receptor shares the seven-transmembrane helical fold, most of the conserved motifs for class A GPCRs are absent, and the structure reveals an unusually complex arrangement of long extracellular loops stabilized by four disulphide bonds. The ligand binds at the extracellular end of the seven-transmembrane-helix bundle and forms extensive contacts with the loops.

Target protein search

“TARGET only” search

Drug and Target protein search

“DRUG” search

Smoothened (SMO) receptor mutations dictate resistance to vismodegib in basal cell carcinoma.

Pricl S[1], Cortelazzi B[2], Dal Col V[3], Marson D[3], Laurini E[3], Fermeglia M[3], Licitra L[4], Pilotti S[2], Bossi P[4], Perrone F[5].

Author information

Abstract

Basal cell carcinomas (BCCs) and a subset of medulloblastomas are characterized by loss-of-function mutations in the tumor suppressor gene, PTCH1. PTCH1 normally functions by repressing the activity of the Smoothened (SMO) receptor. Inactivating PTCH1 mutations result in constitutive Hedgehog pathway activity through uncontrolled SMO signaling. Targeting this pathway with vismodegib, a novel SMO inhibitor, results in impressive tumor regression in patients harboring genetic defects in this pathway. However, a secondary mutation in SMO has been reported in medulloblastoma patients following relapse on vismodegib to date. This mutation preserves pathway activity, but appears to confer resistance by interfering with drug binding. Here we report for the first time on the molecular mechanisms of resistance to vismodegib in two BCC cases. The first case, showing progression after 2 months of continuous vismodegib (primary resistance), exhibited the new SMO G497W mutation. The second case, showing a complete clinical response after 5 months of treatment and a subsequent progression after 11 months on vismodegib (secondary resistance), exhibited a PTCH1 nonsense mutation in both the pre- and the post-treatment specimens, and the SMO D473Y mutation in the post-treatment specimens only. In silico analysis demonstrated that SMO(G497W) undergoes a conformational rearrangement resulting in a partial obstruction of the protein drug entry site, whereas the SMO D473Y mutation induces a direct effect on the binding site geometry leading to a total disruption of a stabilizing hydrogen bond network. Thus, the G497W and D473Y SMO mutations may represent two different mechanisms leading to primary and secondary resistance to vismodegib, respectively.

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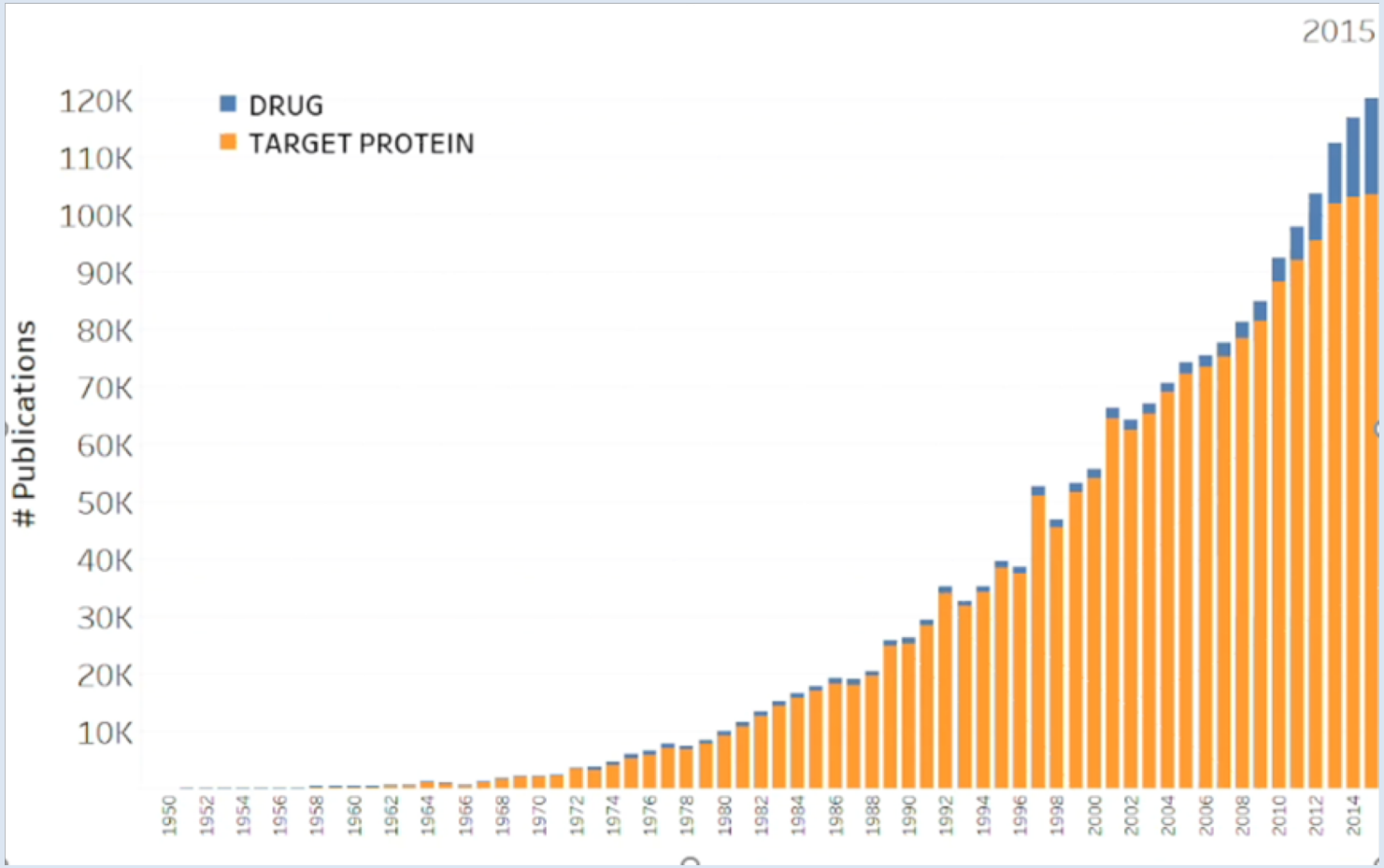
There are >2 million research publications related to drugs approved 2010-2016 or their target proteins



~ 95% identified in target search, but not drug search

600,000 publications cited NIH funding

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RePORTER associates PubMed publications with HHS funded Projects and Project Costs

RePORTER database includes:

- Human Health Service (HHS) funded projects, 1980-present
- PubMed IDs (PMID) for publications with HHS support
- Project costs (FY), 2000-present

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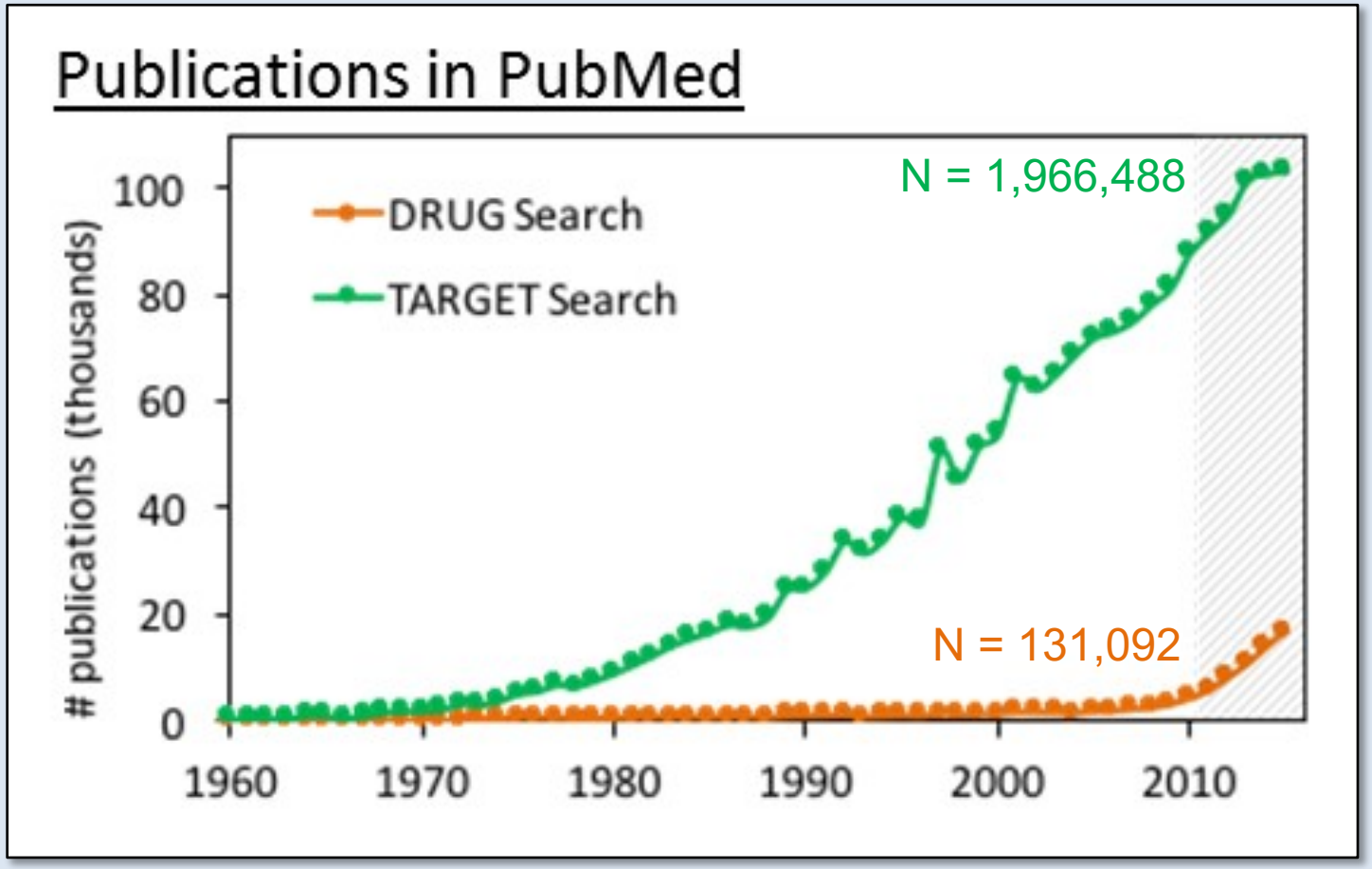
PubMed search for 210 drugs and 150 drug targets

PubMed
PMIDs

RePORTER
Link Table
PMID-Projects

RePORTER
Projects Table
Projects costs



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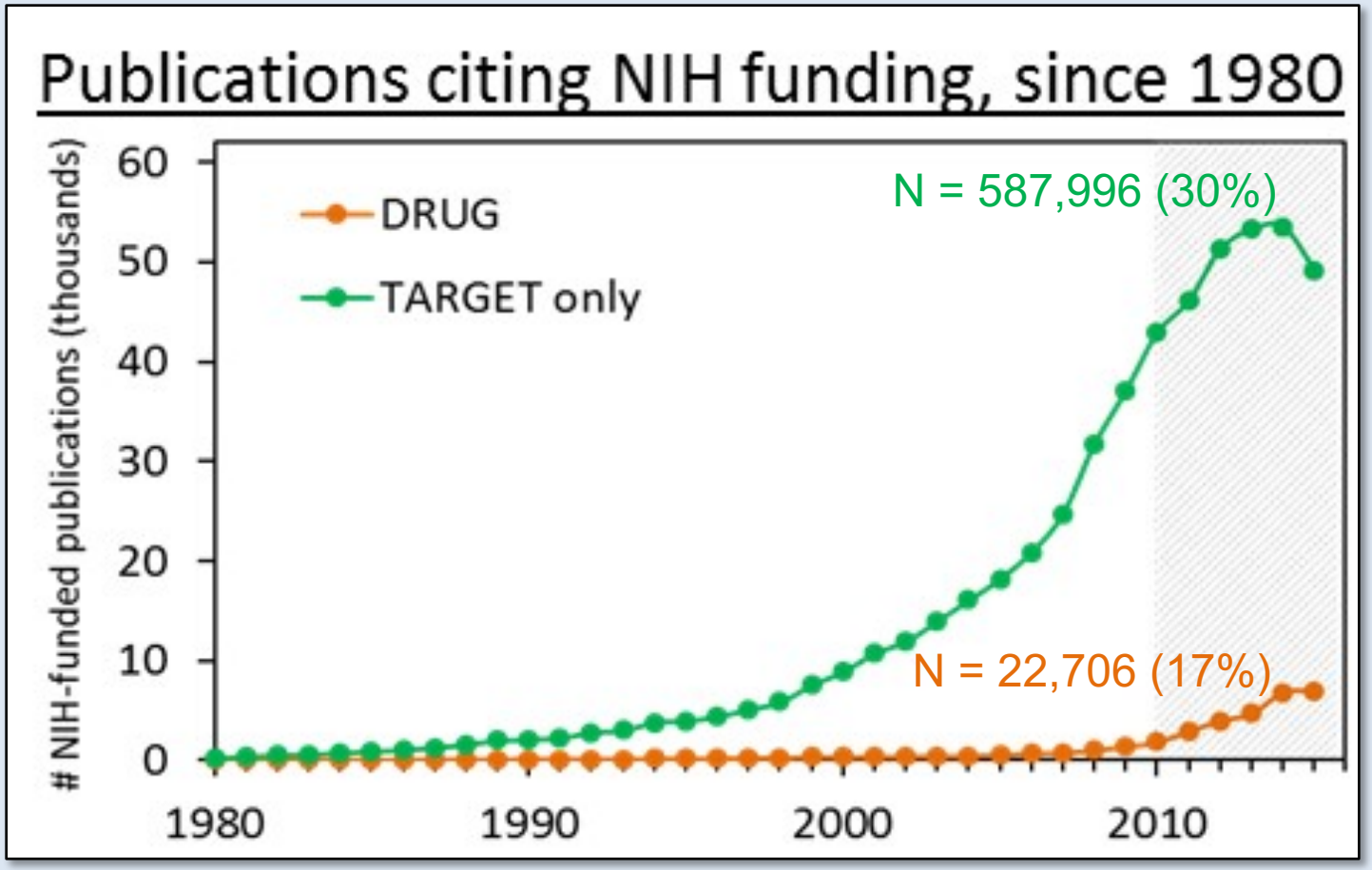
Linking PMIDs to Project numbers in RePORTER Link Table

PubMed
PMIDs

RePORTER
Link Table
PMID-Projects

RePORTER
Projects Table
Projects costs



Funding associated with all 150 targets and 198/210 drugs

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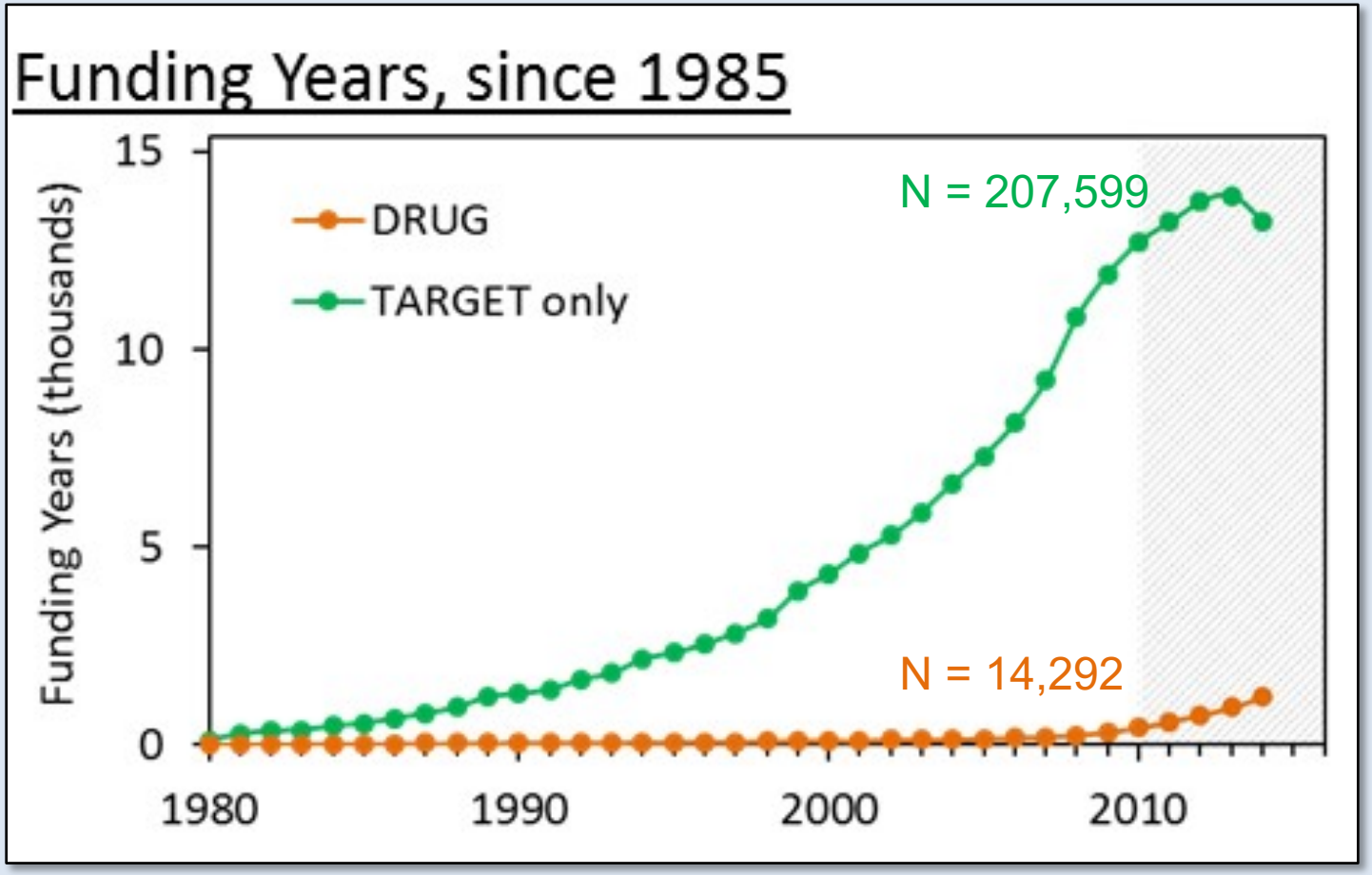
Linking PMID to fiscal of funding (Funding year)

PubMed
PMIDs

RePORTER
Link Table
PMID-Projects

RePORTER
Projects Table
Projects costs



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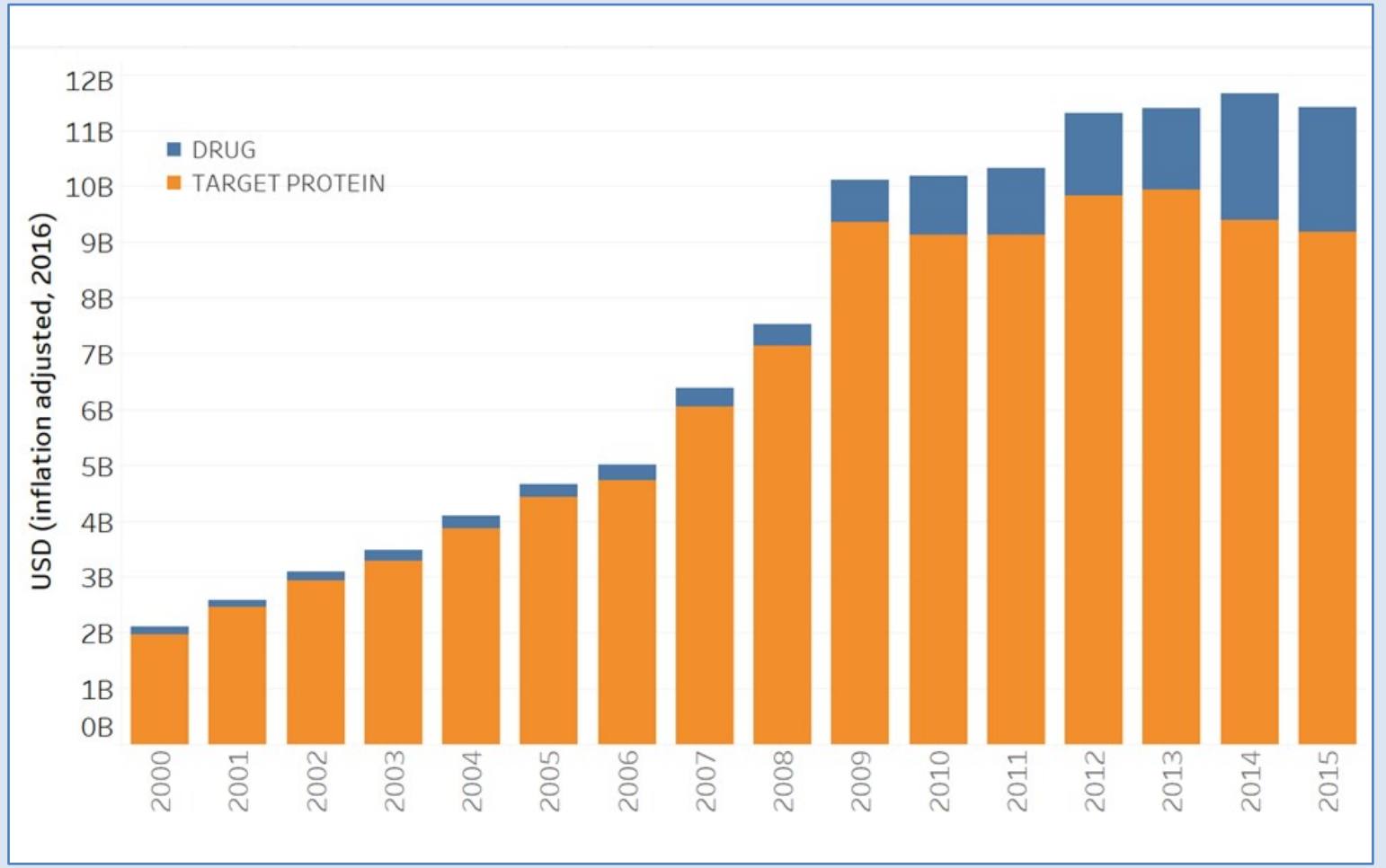
This research was supported by >$100 billion in NIH funding from FY 2000-2016



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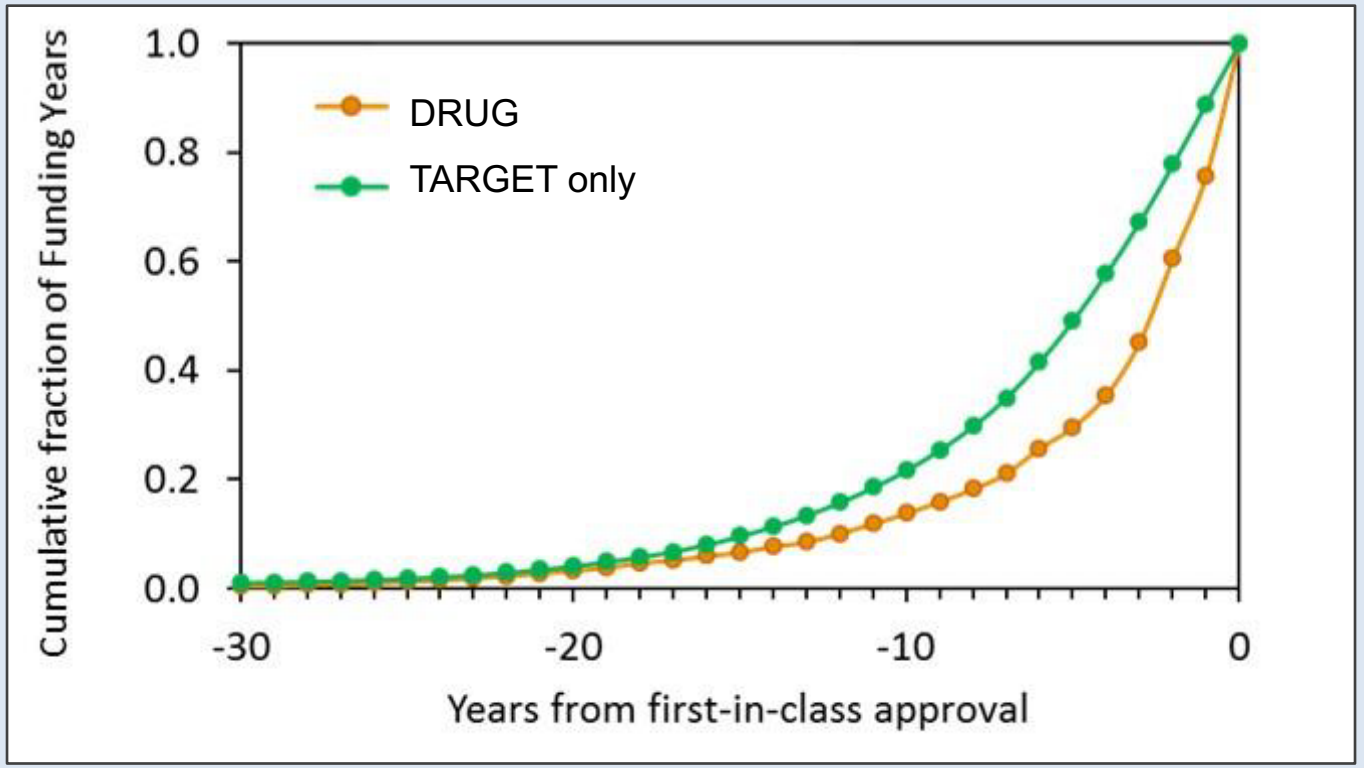
Isolated research done on first-in-class drug approvals



The cost of basic research leading to approval of novel "first-in-class" drugs was >$800 million

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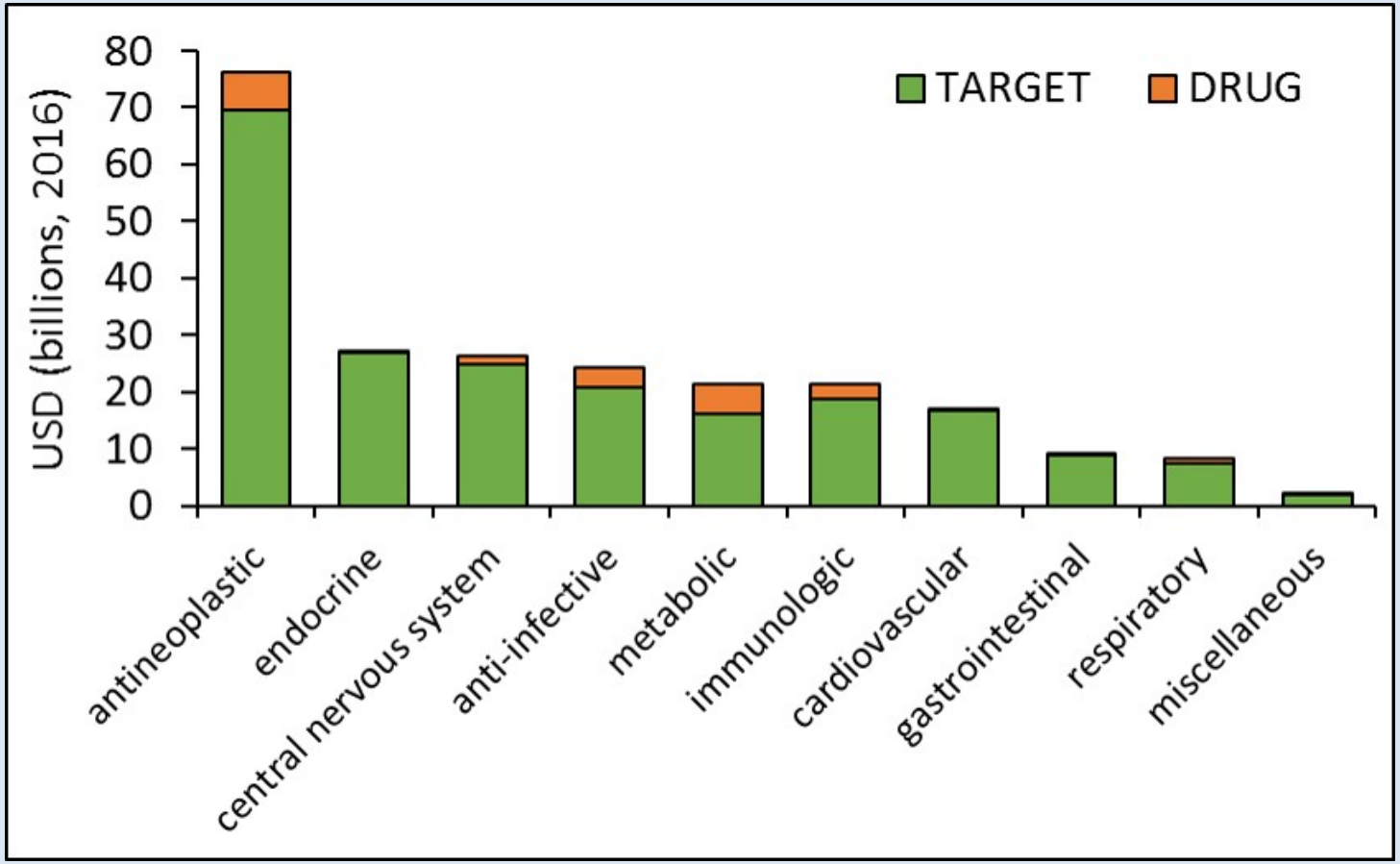
Predominantly more effort and spending on cancer drugs



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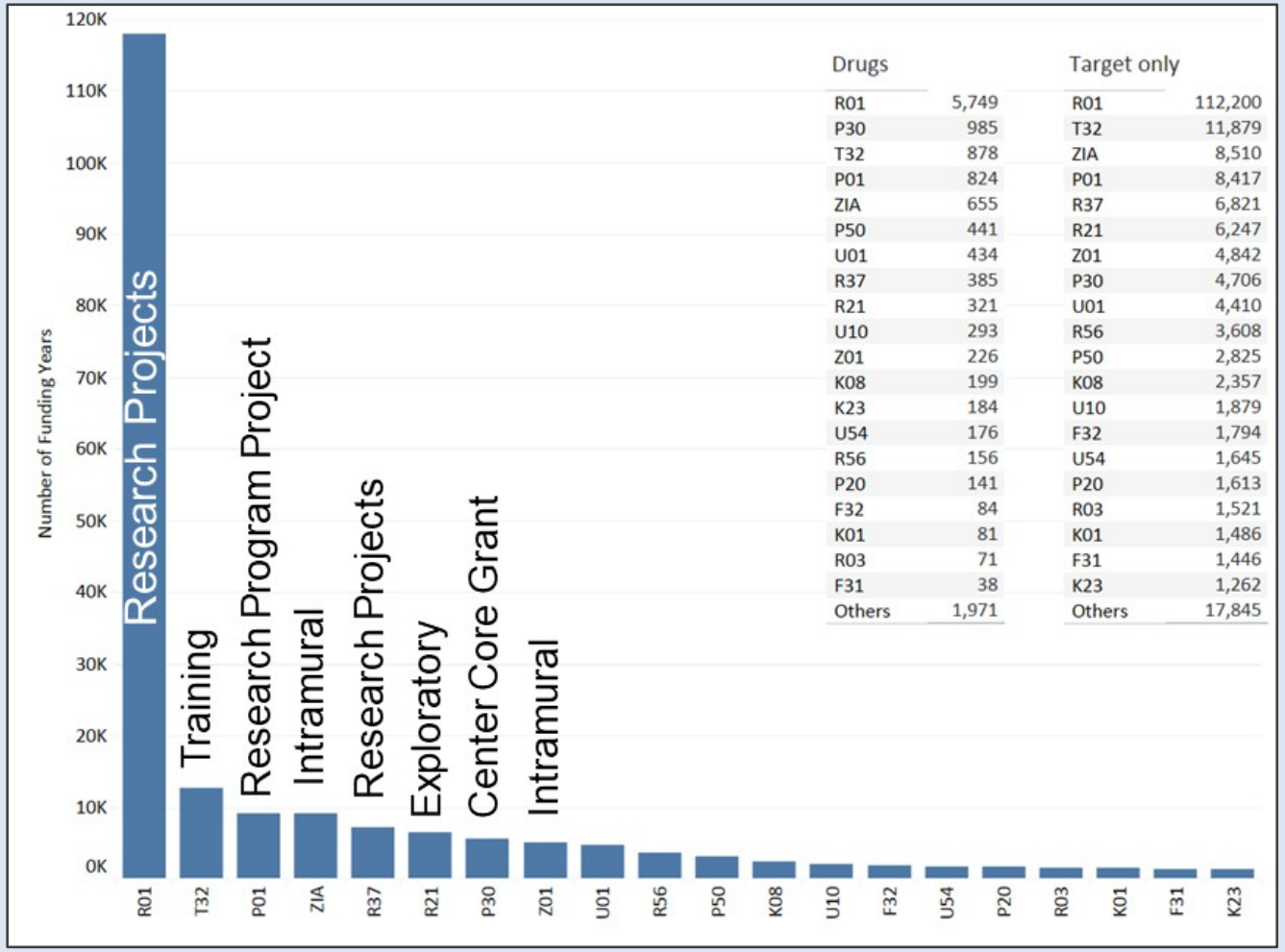
Cleary et al., PNAS www.pnas.org/content/early/2018/02/06/1715368115

Majority of all Projects and costs were for investigator-initiated research (R01s)



Drugs	
R01	5,749
P30	985
T32	878
P01	824
ZIA	655
P50	441
U01	434
R37	385
R21	321
U10	293
Z01	226
K08	199
K23	184
U54	176
R56	156
P20	141
F32	84
K01	81
R03	71
F31	38
Others	1,971

Target only	
R01	112,200
T32	11,879
ZIA	8,510
P01	8,417
R37	6,821
R21	6,247
Z01	4,842
P30	4,706
U01	4,410
R56	3,608
P50	2,825
K08	2,357
U10	1,879
F32	1,794
U54	1,645
P20	1,613
R03	1,521
K01	1,486
F31	1,446
K23	1,262
Others	17,845

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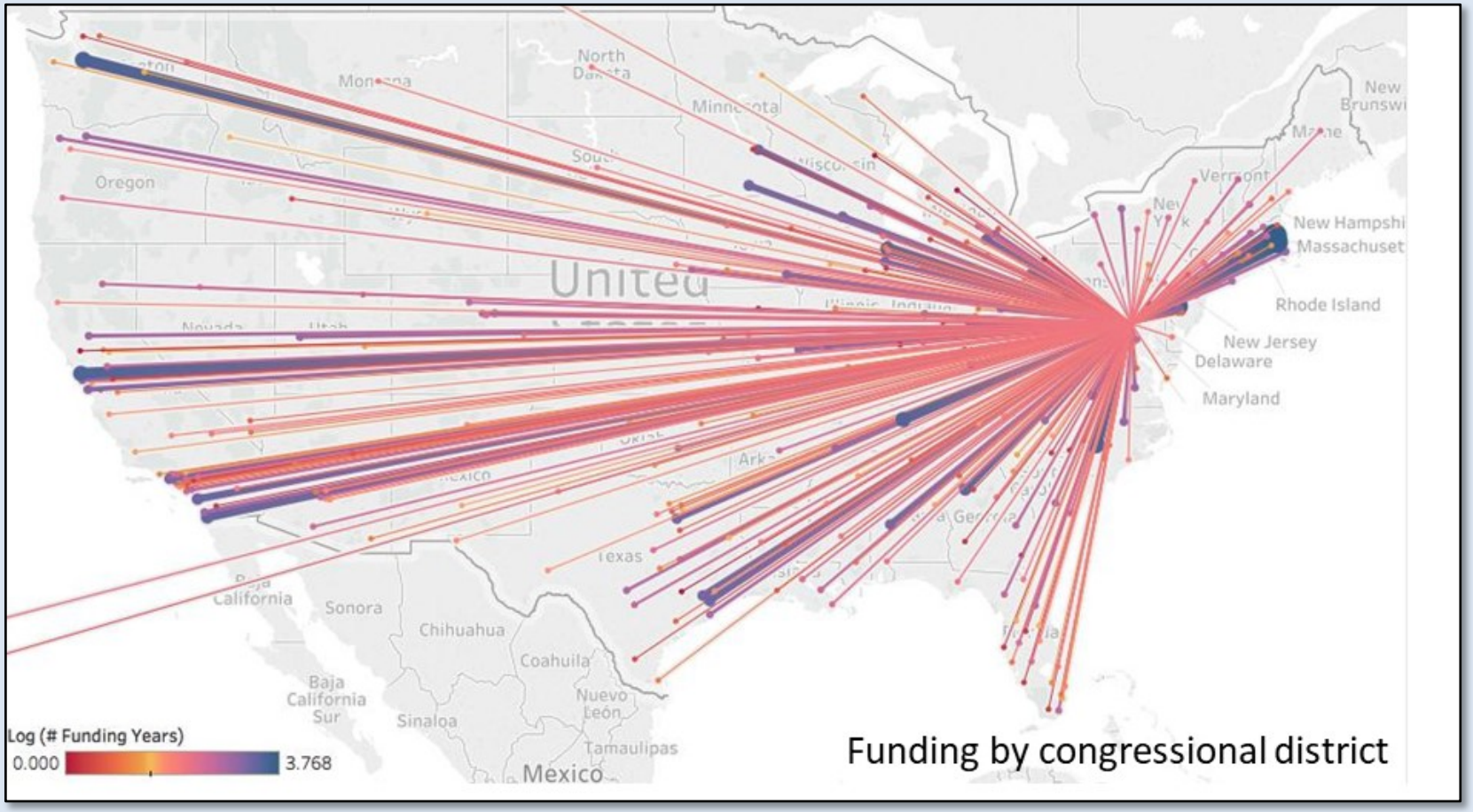
Cleary et al., PNAS www.pnas.org/content/early/2018/02/06/1715368115

NIH funded research leading to approved drugs occurred in every state



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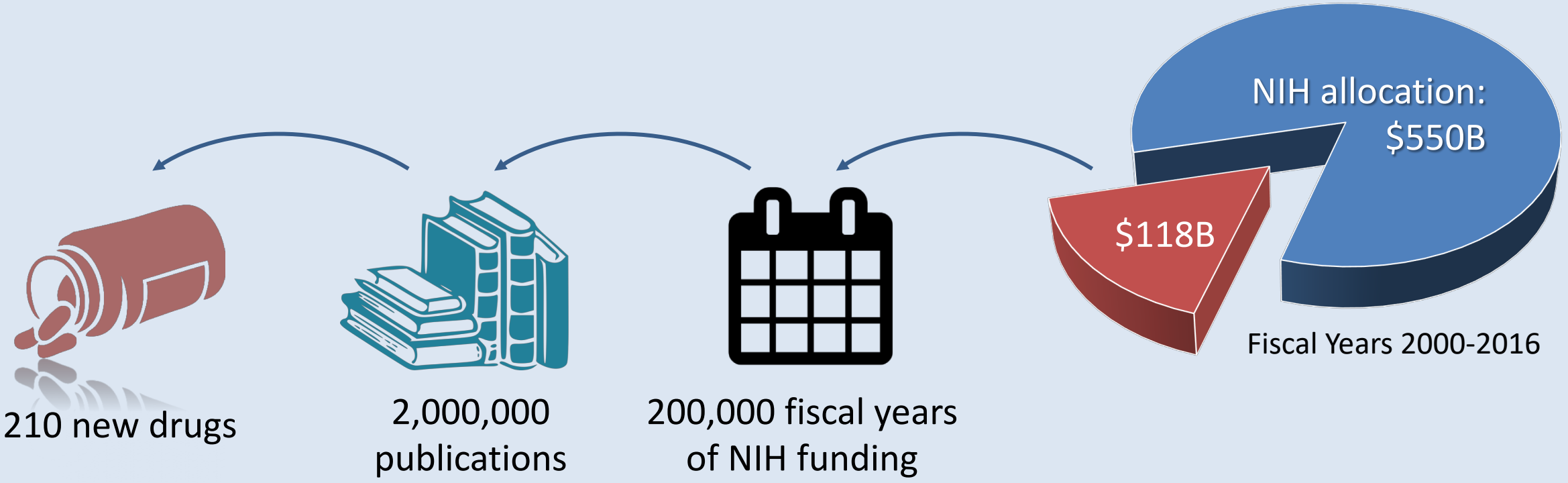
NIH funding contributed to basic research leading to every new drug approved 2010-2016



…demonstrates essential role of NIH funding for basic research in the pipeline of new medicines

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“Basic research: Building a firm Foundation for Biomedicine”

NIH Director's Blog

Basic Research: Building a Firm Foundation for Biomedicine

Posted on February 27th, 2018 by Dr. Francis Collins

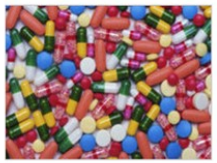
HEALTH CARE

Your Tax Dollars Fund Research on Hundreds of New Meds

U.S.News & WORLD REPORT

Feb. 15, 2018, at 12:00 p.m.

News) -- The U.S. National
100 billion on research that
Food and Drug
, a new study shows.
s for the development of
logical mechanisms or



IN THE LAB

NIH funding contributed to 210 approved drugs in recent years, study says

By MEGAN THIELKING @meggophone / FEBRUARY 12, 2018

How many new drugs rely on government-funded science? All of them

Data from 2 million scientific papers was used to show critical role of public funds in developing new drugs

Kelly Crowe · CBC News · Posted: Feb 23, 2018 4:00 AM ET | Last Updated: February 23

Canadian Broadcasting Corporation

Volume 96 Issue 8 | p. 17 | Concentrates
Issue Date: February 19, 2018

c&en CHEMICAL & ENGINEERING NEWS

NIH research contributed to all new FDA-approved drugs from 2010 to 2016, report says

By *Andrea Widener*

between 2010
paper by
NIH's publication

POLITICS ECONOMY ENVIRONMENT

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POLITICS, IDEAS & CIVIC LIFE IN MASSACHUSETTS

HEALTH CARE / OPINION

NIH funding provides the core foundation for new drugs

Proposed Trump cuts would slow progress in developing new cures

Congresswoman Katherine Clark
Bentley University, April 23, 2018

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Are taxpayers paying twice for medicines?

NATIONAL LAW REVIEW

Five Takeaways from the Senate Finance Committee's Hearing on Drug Pricing

The National Law Review, 04 Mar 2019

, the Senate Finance Committee heard testimony from top executives representin
profile drug manufacturers.

THE HUFFINGTON POST

Bernie Sanders And Ro Khanna Have A New Plan To Tackle Prescription Drug Rip-Offs

Huffington Post, 19 Nov 2018

The problem with prescription drugs is simple: The U.S. government bestows lon
monopolies on pharmaceutical companies...

The New York Times

'Paying Twice': A Push for Affordable Prices for Taxpayer-Funded Drugs

By Robert Pear

May 28, 2018

WASHINGTON — On Aug. 30, the Food and Drug Administration approved a radical new cancer treatment that harnesses a patient's immune system to attack tumor cells. The drug, known as Kymriah, grew out of research conducted and supported by the National Institutes of Health.

The New York Times

Opinion | How High Drug Prices Inflate C.E.O.s' Pay

New York Times, 26 Feb 2019

Opinion|How High Drug Prices Inflate C.E.O.s' Pay Pharmaceutical companies say their profits fund research and innovation in...

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Is the public acting as an early investor in the production of drugs, but receiving no ROI?

House Oversight and Reform Committee hearing examining the actions of drug companies in raising prescription drug prices.

January 29, 2019

Congresswoman Alexandria Ocasio-Cortez questions Dr. Aaron Kesselheim of Harvard University

https://www.youtube.com/watch?v=HIQk5B0il-A&t=113s

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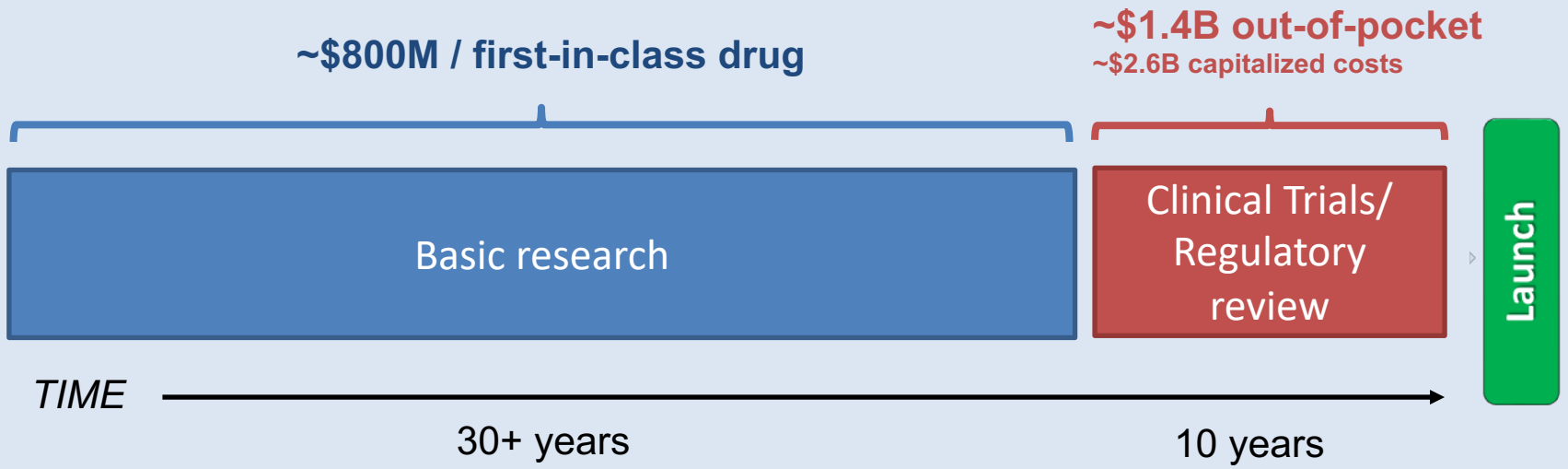
Costs incurred during the clinical development timeline exceed $3.5B/drug



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Acknowledgements

Bentley University:

Fred D. Ledley, M.D.
Jennifer Beierlein, Ph.D.
Laura M. McNamee, Ph.D.
Navleen Khanuja, M.S.

Washington University:

Michael Kinch, Ph.D.
Rebekah Griesenauer, Ph.D.
Ryan Moore

Michael Walsh, Ph.D.
Christopher Bresten, Ph.D.
David Oury, Ph.D.
Daniel Solar

Michael A. Boss, Ph.D., M.B.A.
Nancy Hsiung, Ph.D.

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PNAS

Contribution of NIH funding to new drug approvals 2010–2016

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Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved December 27, 2017 (received for review September 1, 2017)

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