Director's Update
Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
Council of Councils Meeting
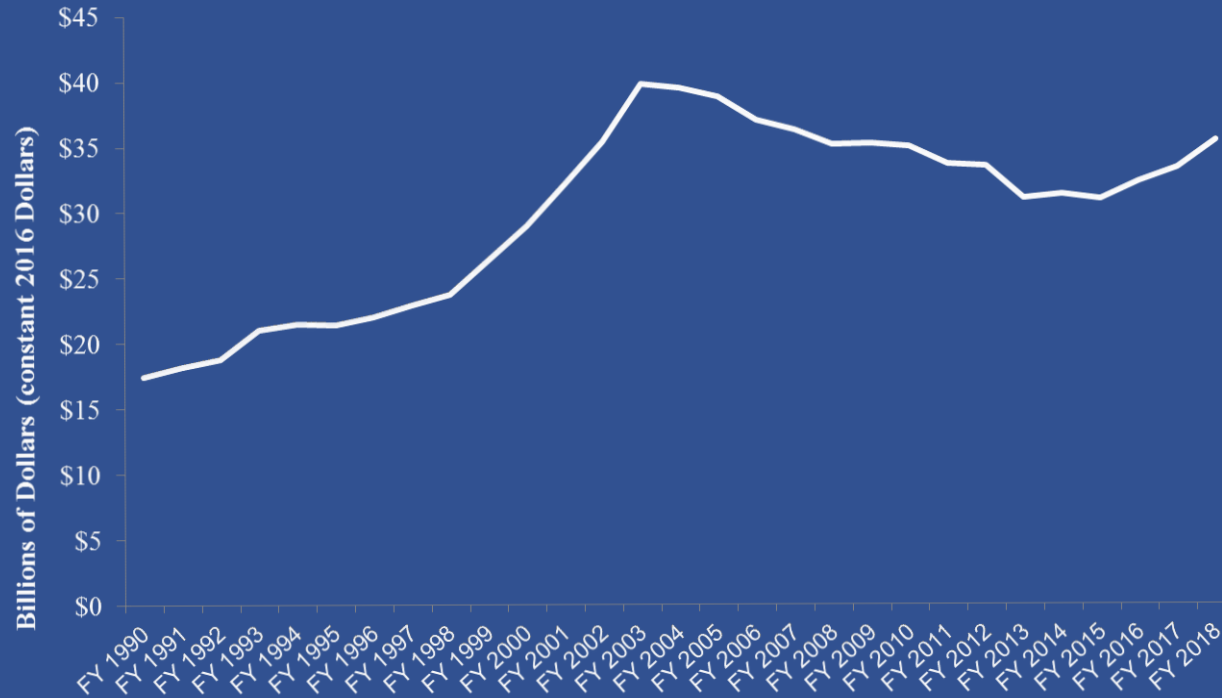### September 7, 2018

Changes in Leadership

- Retirements
  - Patricia Grady, Ph.D., R.N., FAAN, Director of the National Institute of Nursing Research (August 31, 2018)
  - James Battey, Jr., M.D., Ph.D., Director of the National Institute on Deafness and Other Communication Disorders (June 1, 2018)
- New Hires
  - Helene M. Langevin, M.D., C.M., Director of the National Center for Complementary and Integrative Health (November 2018)
  - Bruce Tromberg, Ph.D., Director of the National Institute of Biomedical Imaging and Bioengineering (January 2019)

National Institutes of Health Funding 1990-2018

Billions of Dollars (constant 2016 Dollars)

$45
$40
$35
$30
$25
$20
$15
$10
$5
$0

FY 1990, FY 1991, FY 1992, FY 1993, FY 1994, FY 1995, FY 1996, FY 1997, FY 1998, FY 1999, FY 2000, FY 2001, FY 2002, FY 2003, FY 2004, FY 2005, FY 2006, FY 2007, FY 2008, FY 2009, FY 2010, FY 2011, FY 2012, FY 2013, FY 2014, FY 2015, FY 2016, FY 2017, FY 2018

Note: Dollar values are adjusted to 2016 dollars using the Biomedical Research and Development Price Index (BRDPI), http://officeofbudget.od.nih.gov/gbiPriceIndexes.html.
Source: NIH Office of Extramural Research and Office of Budget source data (February 2, 2018).
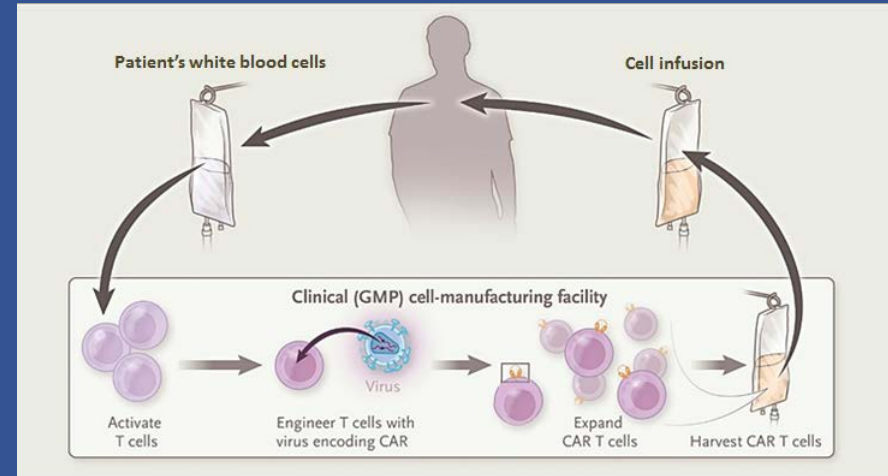
Topics for Today

- Precision Medicine and Cancer
- Accelerating Medicines Partnership
- NIH BRAIN Initiative
- Artificial Intelligence
- Gene Therapy
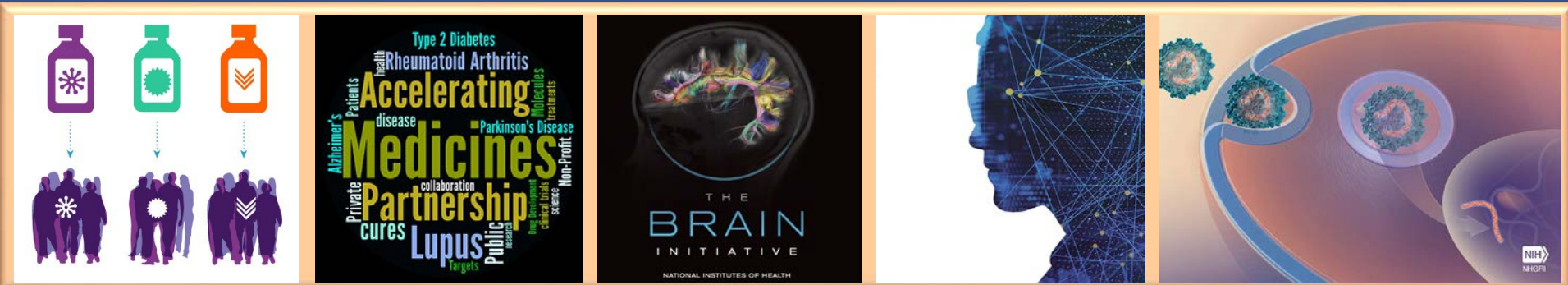
Cancer Genomics: Advancing Precision Medicine

- NCI's Molecular Analysis for Therapy Choice (NCI-MATCH) trial:
  - Are targeted therapies effective, regardless of cancer type?
    - Multiple treatment arms target specific mutations
    - Tumors sequenced; patient matched to study arm
  - Milestone: results from three study arms published
- Cancer immunotherapy

NATIONAL CANCER INSTITUTE
PRECISION MEDICINE
IN CANCER TREATMENT

Steven Rosenberg   James Allison   Carl June

Patient's white blood cells

Cell infusion

Clinical (GMP) cell-manufacturing facility

Activate T cells

Engineer T cells with virus encoding CAR

Virus

Expand CAR T cells

Harvest CAR T cells
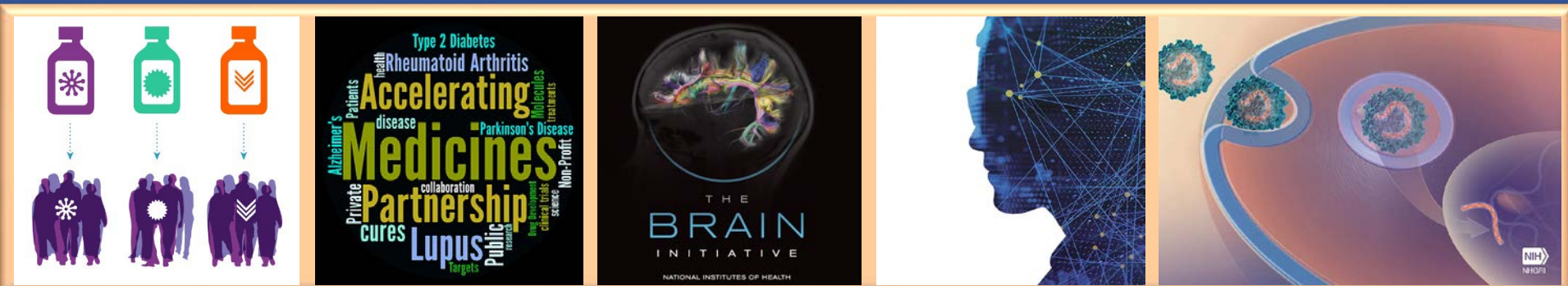
Cancer Moonshot: PACT

The Partnership for Accelerating Cancer Therapies

Rebecca G. Baker, PhD,* Axel X. Hoos, MD, PhD,† Stacey J. Adam, PhD,‡ David Wholley, M.Phil,‡
James H. Doroshow, MD,§ Douglas R. Lowy, MD,§
Lawrence A. Tabak, DDS, PhD,* and Francis S. Collins, MD, PhD*

- 5-year, $220M precompetitive public-private research partnership between NIH, FDA, FNIH, 12 companies
- Aims to speed development of immunotherapies for more types of cancer and more cancer patients

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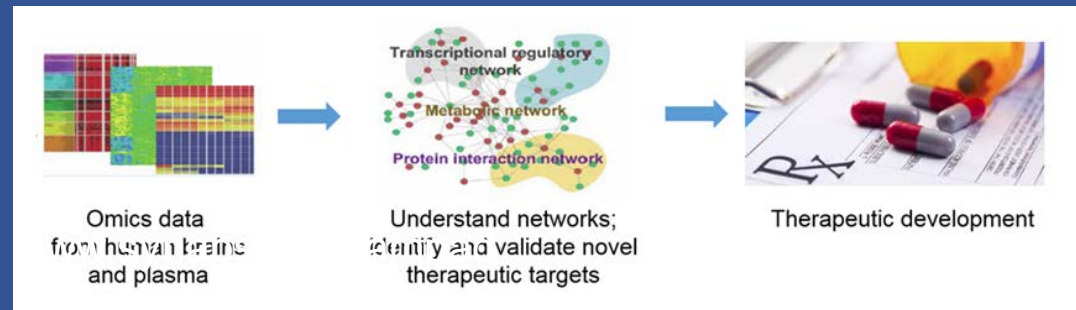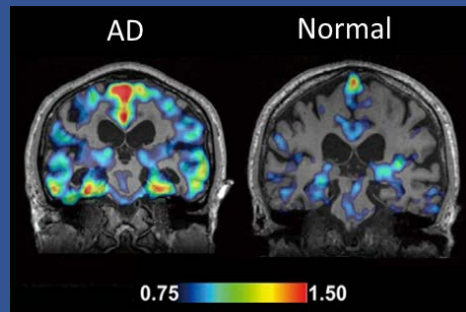- Gene Therapy

AMP: Overview

- NIH partnering with FNIH, FDA, 12 biopharmaceutical firms, multiple non-profits (including patient advocacy groups), to:
  - Increase the number of new diagnostics, therapies
  - Reduce time, cost of developing them
- Investing >$350M over five years on four projects:
  - Alzheimer's disease
  - Type 2 diabetes
  - Rheumatoid arthritis/Lupus
  - Parkinson's Disease
- Project management provided by FNIH
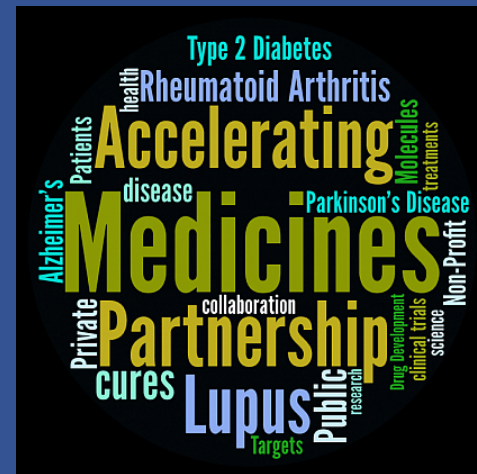
AMP: Alzheimer's Disease (AMP-AD)

$225M program aiming to shorten the time between discovery of potential drug targets and development of new AD drugs

- Projects:
  - Biomarkers
  - Target Discovery and Preclinical Validation
- Data available on AMP-AD Knowledge Portal

AD   Normal

0.75   1.50

Omics data from human brain and plasma

Transcriptional regulatory network
Metabolic network
Protein interaction network

Understand networks; identify and validate novel therapeutic targets

Therapeutic development

ACCELERATING MEDICINES PARTNERSHIP (AMP)

AMP: Type 2 Diabetes (AMP-T2D)

$59M+ program to link human genetic and phenotypic data to identify novel drug targets for T2D and its complications

- Knowledge Portal – online library and discovery engine – launched 2015
  - Integrates diverse genomic, clinical, molecular data – all confidential
  - Anyone with Google account can query
  - 38 datasets; 68 traits*
- Knowledge Portal Network provides genetic data on complex diseases

TYPE 2 DIABETES KNOWLEDGE PORTAL

In English | En Español

www.type2diabetesgenetics.org

ACCELERATING MEDICINES PARTNERSHIP (AMP)

*Aug. 2018

AMP: Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP-RA/SLE)

$42M+ program for single cell analyses of kidney and synovial biopsies from patients with SLE or RA

- Prioritized single-cell RNA profiling of as many tissue samples as possible
  - Existing funds provide for collection, not analysis
- Proposal: "Year 6" for additional high-priority analyses for discovery and biomarkers for patient stratification (~$8M)
  - Discovery: additional analyses of tissue cells
  - Biomarkers: analyses of paired blood, urine, skin (SLE)

RA Synovium: Integration of histology and scRNAseq data identifies three disease subtypes

SLE Kidney: scRNAseq reveals comprehensive clusters of tissue resident and disease-specific immune cells

ACCELERATING MEDICINES PARTNERSHIP (AMP)

AMP: Parkinson's Disease (AMP-PD)
Launched January 2018

$24M program to identify and validate diagnostic, prognostic, progression biomarkers

- Establish framework; develop knowledge portal
  - Gather, incorporate wealth of extant data; add new data
- Use portal to identify most promising biomarkers for new treatments
- Validate biomarkers – incorporating additional data as needed
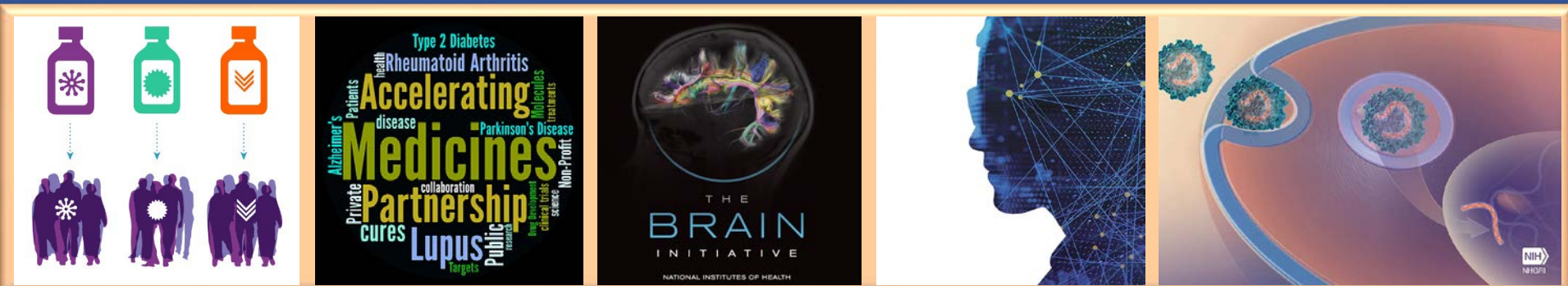- *Goal:* make long-needed progress in developing effective PD treatments

Data in AMP PD Portal: 3Q 2019

BioFIND
HBS
PDBP
PPMI

Whole Genomes
Transcriptomes
Clinical Data

Cloud Storage
BigQuery
Google Cloud Platform

amp-pd-researchers
Google Group
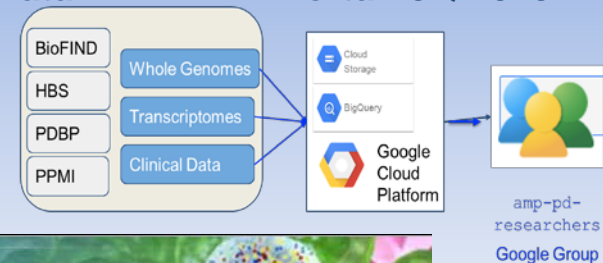
ACCELERATING MEDICINES PARTNERSHIP (AMP)

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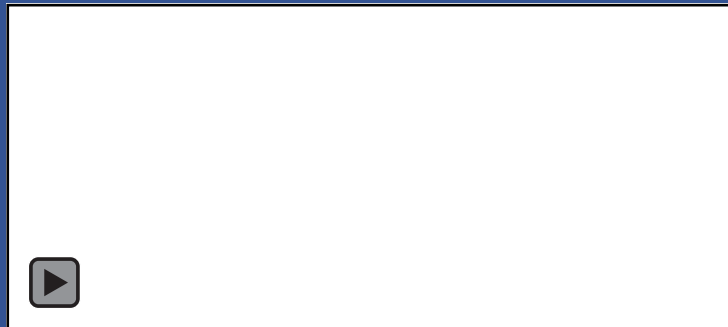- Artificial Intelligence
- Gene Therapy

Recent BRAIN Advances
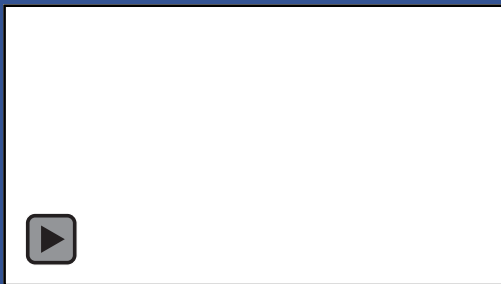
*Zebrafish larva's brain wiring –
reconstructed from 16,000 slices*
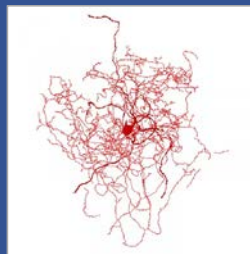PIs: F. Engert, J. Lichtman; Harvard

*Non-toxic cellular imaging method developed –
enables long-term study of neural circuits in mice.*
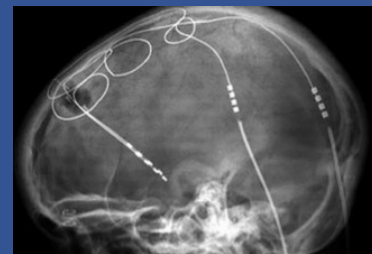PI: I. Wickersham, MIT

*Nanoscale neural probes created to avoid
immune response from body.*
PI: C. Chestek, U. Michigan

*New kind of brain cell
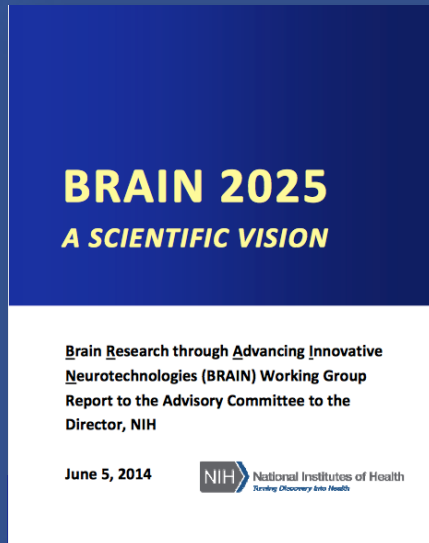discovered: rosehip neuron.*
PI: E. Lein, Allen Institute

*Deep brain stimulation improved to
incorporate feedback, adjust
stimulation from pacemaker.*
PI: P. Starr, UCSF

NIH and the U.S. BRAIN Initiative

BRAIN 2025
A SCIENTIFIC VISION

Brain Research through Advancing Innovative
Neurotechnologies (BRAIN) Working Group
Report to the Advisory Committee to the
Director, NIH

June 5, 2014   NIH National Institutes of Health
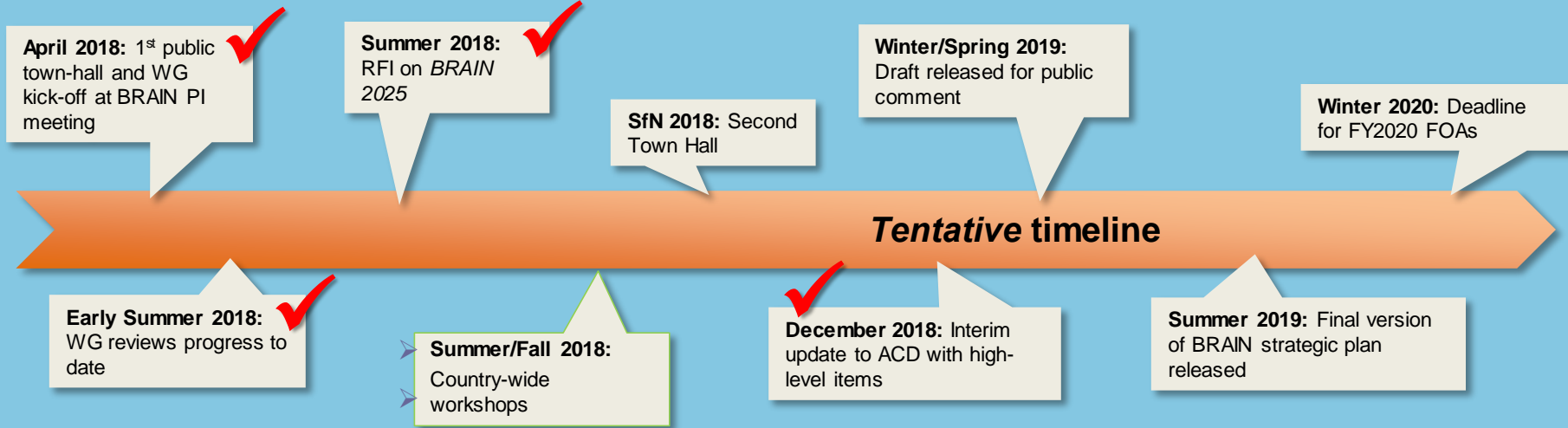*Turning Discovery Into Health*

- A focus on circuits, networks

- Measure fluctuating electrical, chemical patterns within circuits

- Understand how all of this
  - Helps generate our thoughts, actions
  - Improves diagnosis, treatment of disorders

www.braininitiative.nih.gov

Rapid scientific progress →
New NIH ACD BRAIN Initiative Working Group "2.0"
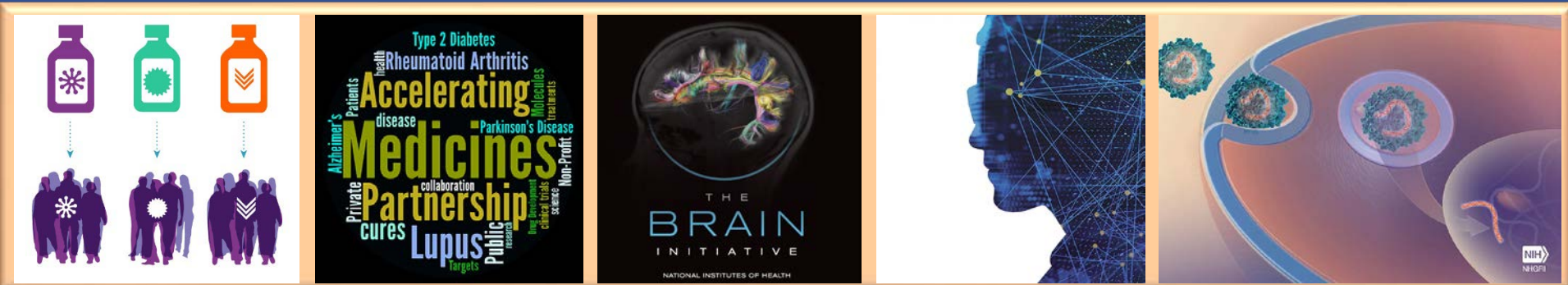
ACD WG 2.0 Timeline and Deliverables

Estimated Timeline for ACD BRAIN WG effort:

April 2018: 1st public town-hall and WG kick-off at BRAIN PI meeting

Summer 2018: RFI on *BRAIN 2025*

SfN 2018: Second Town Hall

Winter/Spring 2019: Draft released for public comment

Winter 2020: Deadline for FY2020 FOAs

Tentative timeline

Early Summer 2018: WG reviews progress to date

Summer/Fall 2018: Country-wide workshops

December 2018: Interim update to ACD with high-level items

Summer 2019: Final version of BRAIN strategic plan released

- Goals for new WG:
  - Update scientific vision laid out in BRAIN 2025 to guide 2nd half of Initiative
  - Identify valuable areas of new and continued technology development
  - Consider the Initiative's unique contributions

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ARTIFICIAL INTELLIGENCE
A program that can sense, reason, act, and adapt

MACHINE LEARNING
Algorithms whose performance improve as they are exposed to more data over time

DEEP LEARNING
Subset of machine learning in which multilayered neural networks learn from vast amounts of data

Source: www.codeproject.com/articles/1185501/How-to-Get-Started-as-a-Developer-in-AI

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Gene Therapy for Spinal Muscular Atrophy
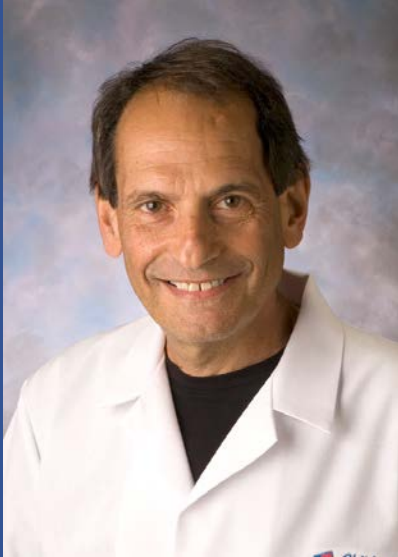
Jerry Mendell/Nationwide Children's Hospital, Columbus, OH
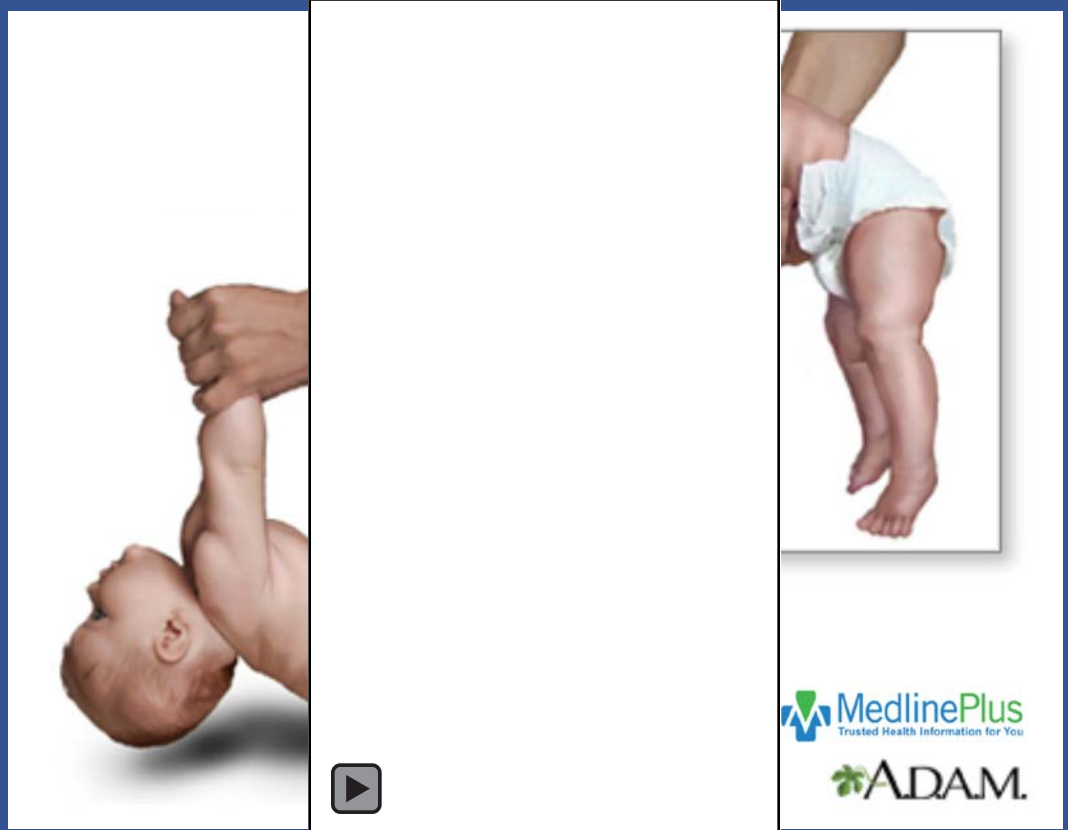
CRISPR-Cas9 and Gene Editing

- Basic science advance: from studies of yogurt, bacteria viruses
- Achieves targeted editing of genomes with enzyme (cas9) + guide RNA
  - Initial approaches created knockouts
  - Newer technologies can correct point mutations
- Producing mouse models has been greatly accelerated
- Has revolutionized basic molecular biology
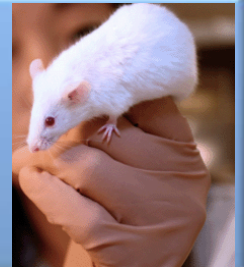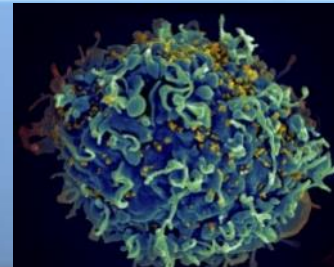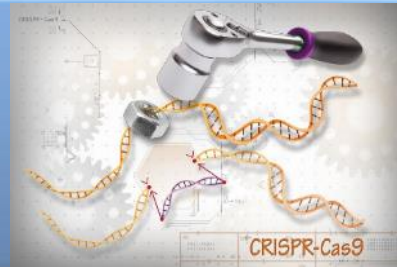
Toward the 1st Cure for the 1st Molecular Disease?

Sickle Cell Disease (SCD)

- *1910:* Disease described
- *1949:* Inheritance shown to be recessive
- *1957:* Genetic basis determined
- *1980:* Hemoglobin genes cloned
- *1998:* Hydroxyurea, first approved SCD drug
- *Recently:* Bone marrow transplants, but few patients have match
- *Today:* Gene transfer via viral vectors
- *Today:* CRISPR-Cas gene editing
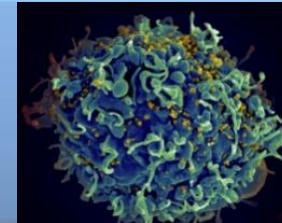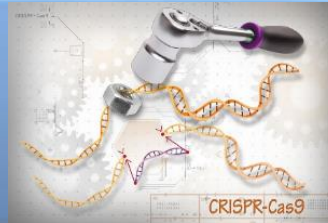
First CRISPR Clinical Trial Backed by U.S. Companies Launched

NIH U.S. National Library of Medicine

ClinicalTrials.gov

A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia

Study Description

Brief Summary:

This is a single-arm, open-label, multi-site, single-dose Phase 1/2 study in up to 12 subjects 18 to 35 years of age with transfusion-dependent β-thalassemia (TDT), non-β0/β0. The study will evaluate the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) using CTX001.

Condition or disease ⓘ	Intervention/treatment ⓘ	Phase ⓘ
Beta-Thalassemia	Biological: CTX001	Phase 1
Thalassemia		Phase 2
Genetic Diseases, Inborn		
Hematologic Diseases		
Hemoglobinopathies		

New NIH Program: Somatic Cell Genome Editing

Program will:

- Speed development of safe, effective editing tools for human patients

- Make tools widely available to researchers

- Reduce time, cost to develop new therapies

Francis S. Collins @NIHDirector · 8:03 AM - 25 Jan 2018

I just announced this at #wef18: #NIH's Somatic Cell Genome Editing research program will focus on accelerating dramatically the translation of technologies like CRISPR/Cas9 for treatment of as many genetic diseases as possible. bit.ly/2F78HBI #CFGenomeEditing

NIH to launch genome editing research program
Somatic Cell Genome Editing aims to develop tools for safe and effective genome editing in humans.
nih.gov
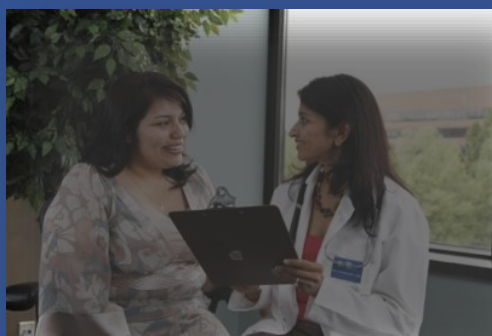
NIH... *Turning Discovery Into Health*

www.nih.gov/hope

directorsblog.nih.gov   @NIHDirector