DOE and NIH Partnerships Cancer and Brain

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Crescat scientia; vita excolatur

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Cancer, Brain and Supercomputing

Three White House Initiatives

- National Strategic Computing
- Precision Medicine
- BRAIN

Cancer, brain research, and supercomputing

By contributing to health research, the Department of Energy could transform its approach to designing the next generation of high-performance computers.

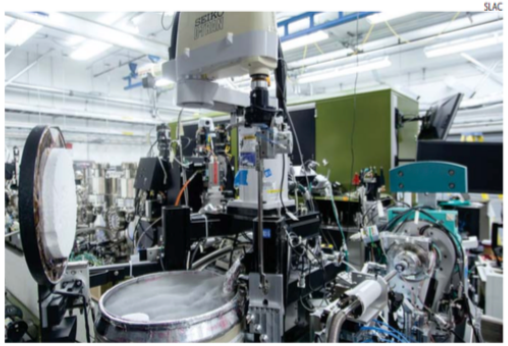
When computers capable of working at the exascale level (10^{18} floating-point calculations per second) come on line, they will be brought to bear on figuring out how another, quite different computer, the human brain, works. With that goal in mind, Energy secretary Ernest Moniz and National Institutes of Health director Francis Collins are exploring how to bring the Department of Energy, which houses the nation's leading supercomputers, into the presidential initiative known as BRAIN (Brain Research through Advancing Innovative Neurotechnologies; see PHYSICS TODAY, December 2013, page 20).

The brain is just one area of biomedical research that could benefit from the computational and physical sciences expertise at DOE and its national laboratories. In December Moniz asked his Secretary of Energy Advisory Board (SEAB) to look for ways to increase DOE's contribution to biomedical sciences. A SEAB task force, cochaired by former NIH and National Cancer Institute (NCI) director Harold Varmus and former DOE undersecretary Steven Koonin, will report to him in September.

The BRAIN Initiative will require advances across several scientific fields. "We need better ways of detecting and recording neural signals," says Roderic Pettigrew, director of NIH's National Institute of Biomedical Imaging and Bioengineering. "Then we need analytical tools to interpret those signals. We need ways of deciphering meaningful signals from noise, an area DOE scientists are accustomed to dealing with."

Another area of focus is the modeling of what goes on in the brain, resolved in three dimensions and in time. "People often don't think of the time domain of medical data," notes Pettigrew, the designated liaison to DOE. "But life is temporal, and biological dimensions change in the time domain. Proteins fold and unfold, protein receptors go from inactive to active state."

SLAC



A HIGHLY AUTOMATED, ROBOTIC X-RAY CRYSTALLOGRAPHY SYSTEM at SLAC's Linac Coherent Light Source x-ray laser. The metal drum at the lower left contains liquid nitrogen for cooling crystallized samples. This setup was used to explore the molecular machinery involved in brain signaling in atomic-scale detail.

In October representatives from the two agencies held a jointly sponsored BRAIN workshop at Argonne National Laboratory that coincided with a major neuroscience conference in nearby Chicago. Reports from those discussions were delivered to Moniz and Collins but haven't been made public.

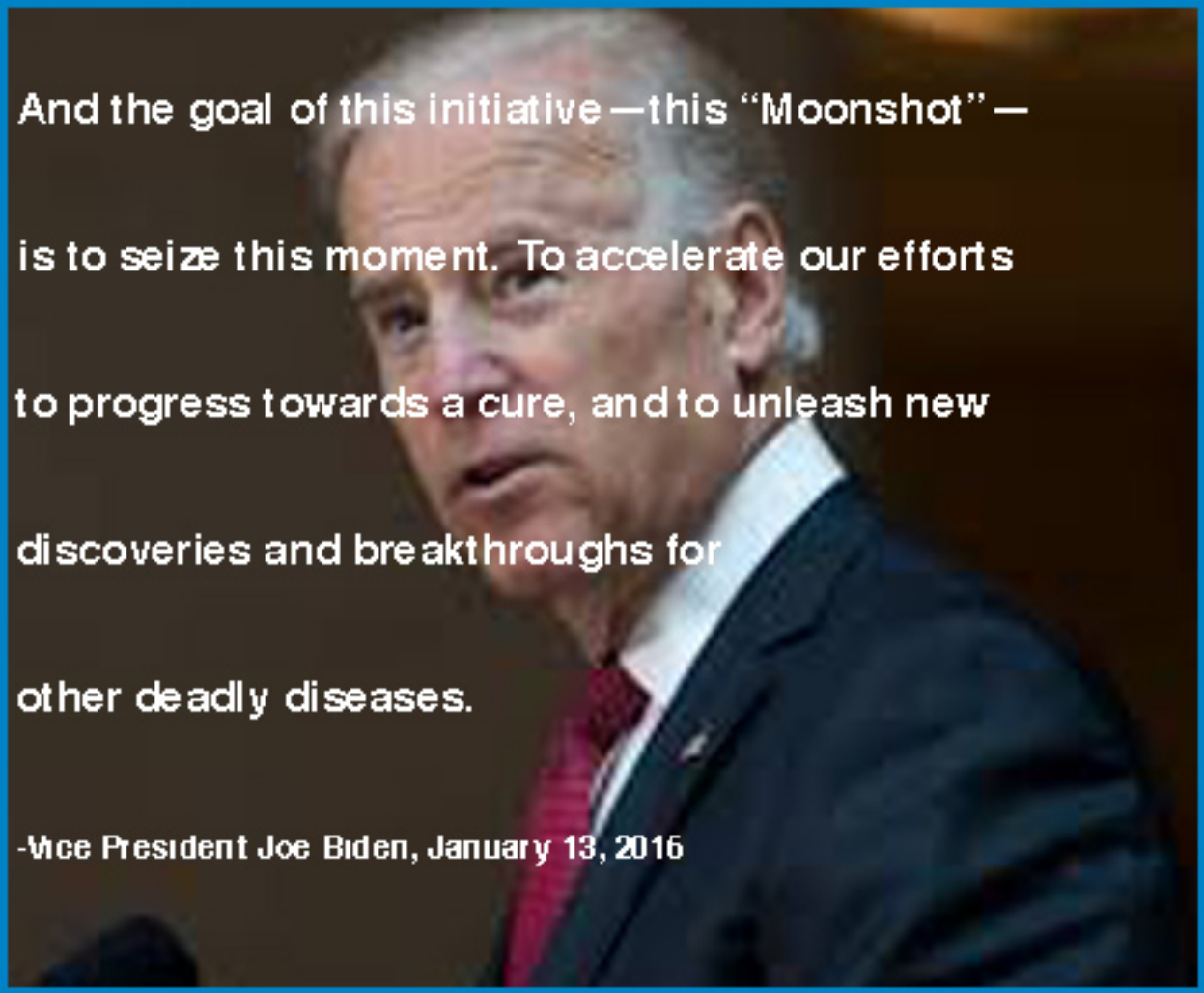
"There is a lot of opportunity and a lot of need in the neuroscience community to benefit from the tools and the organization of the labs to do this kind of big project," Moniz told reporters in November, days before issuing his charge to SEAB.

Dimitri Kusnezov, chief scientist for DOE's National Nuclear Security Administration, is involved in discussions with NIH. "The question we're asking ourselves is, Are there real wins in pushing diagnostics—for example, in a multimode analysis—or is the community geared to move forward at the same pace anyway?" he says. "Can we accelerate things in a significant way or not? We don't have the answer yet."

Biomedical research has long benefited from DOE assets. Life-sciences researchers represent the single largest sector of users (about 40%) at the DOE national laboratories' x-ray light sources, half of whom are supported by NIH. And initial genome-sequencing work at Los Alamos National Laboratory begat the NIH-led Human Genome Project.

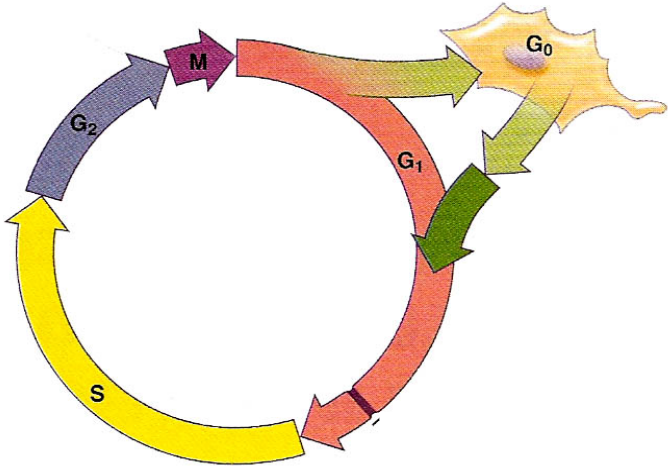
The nanoscale-science research centers operated by the national labs and other groups have been developing sensors that can read nanoparticles. "It's conceivable that nanoparticles with certain characteristics can be embedded in a living system like a brain," says Steve Binkley, associate director for advanced scientific computing research in DOE's Office of Science. "And one could then also conceive of reading the signals coming out of them. The holy grail is to get real-time mapping of signals that exist in neurons as a function of time to certain stimuli," he says. Such mapping has been done with mice, but scientists used invasive probes not suitable for research on humans.

Imaging is another DOE strength that will be useful to BRAIN, Binkley says. The labs have expertise using UV, x rays, IR, coherent light sources, and lasers for imaging. "It's often not obvious at the outset how one puts all those things together to image a certain type of thing.


And the goal of this initiative—this "Moonshot"—
is to seize this moment. To accelerate our efforts
to progress towards a cure, and to unleash new
discoveries and breakthroughs for
other deadly diseases.
-Vice President Joe Biden, January 13, 2016

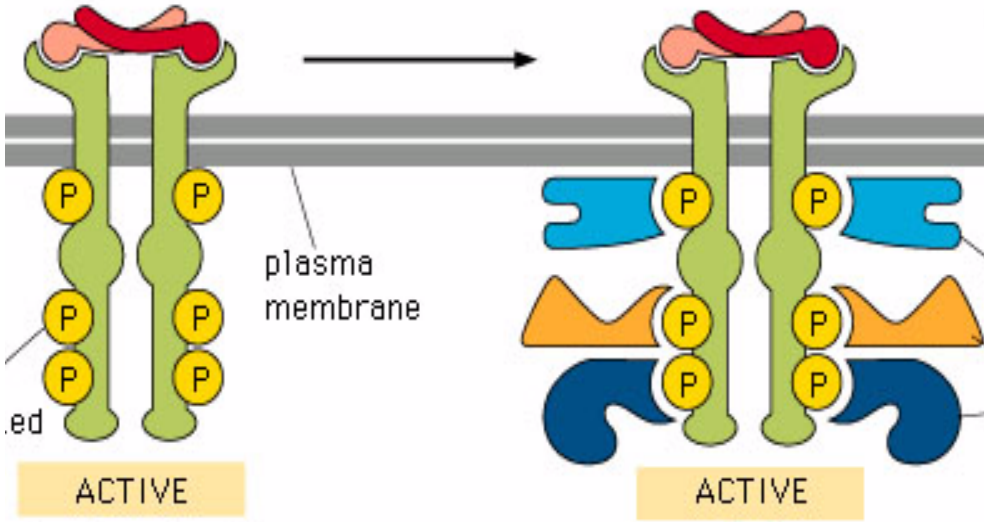
The Cell Cycle

- Most adult cells, **without growth stimulus**, will go into the G_0 phase of the cell cycle
- However, when a growth factor binds to its receptor on the cell membrane, a cascade starts and the cell prepares to enter G_1



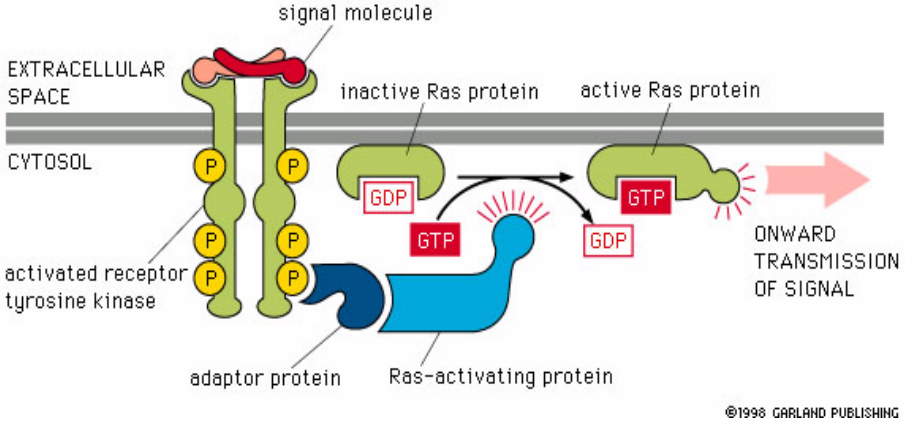
Growth stimulus

- Growth factors
  - Epidermal Growth Factor (EGF)
  - Platelet-Derived Growth Factor (PDGF)
- Binds to Receptors Protein Tyrosine Kinase (RPTK)



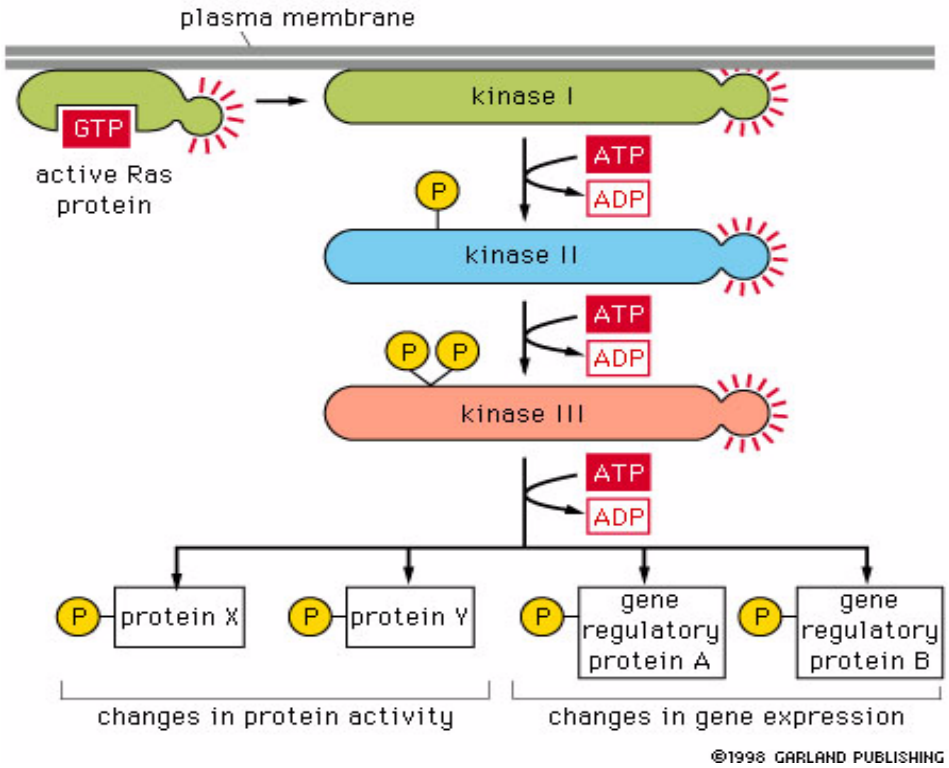
Preparing the cascade

- Grb2 (adaptor protein) binds to phosphorylated tyrosine
  - Recruits SoS (Ras activating protein)
- SoS exchanges GDP for GTP
  - **Activates Ras**
- Ras must be membrane bound to be active

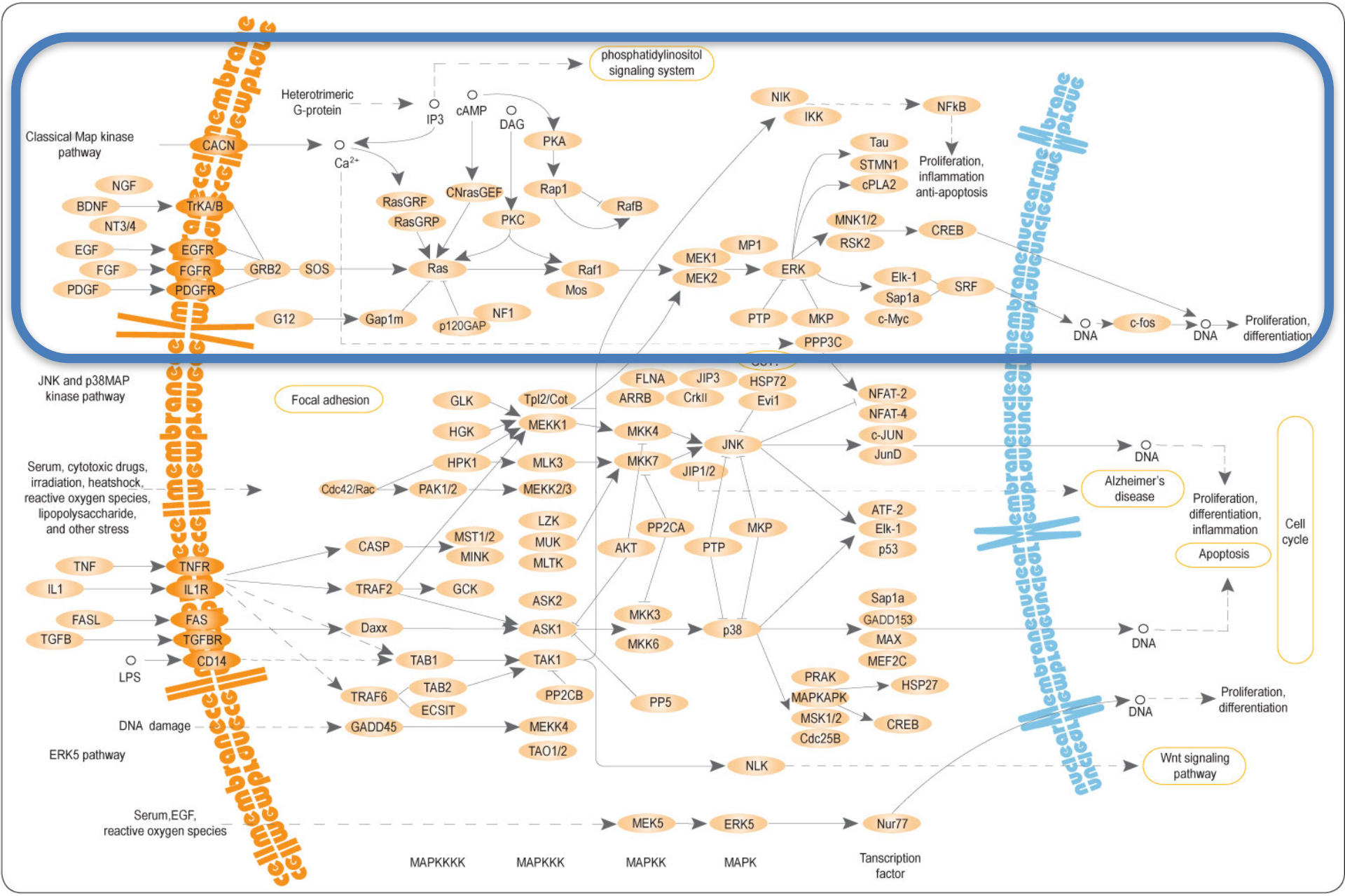


The ERK Cascade

- RAS
  - Raf
    - MEK
      - ERK

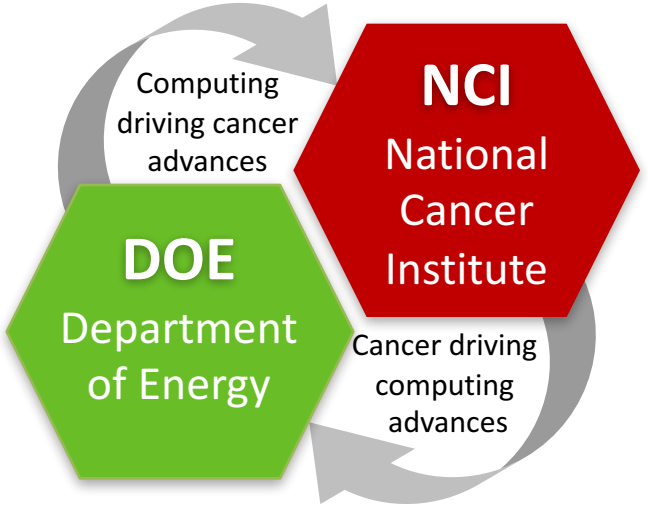


- Causes gene expression changes via proteins such as c-Myc


phosphatidylinositol signaling system
Heterotrimeric G-protein
IP3
cAMP
DAG
Classical Map kinase pathway
CACN
Ca2+
PKA
NGF
BDNF
NT3/4
TrkA/B
RasGRF
RasGRP
CNrasGEF
Rap1
RafB
PKC
EGF
FGF
PDGF
EGFR
FGFR
PDGFR
GRB2
SOS
Ras
Raf1
Mos
G12
Gap1m
p120GAP
NF1
NIK
IKK
NFkB
Tau
STMN1
cPLA2
Proliferation, inflammation anti-apoptosis
MNK1/2
RSK2
CREB
MEK1
MEK2
MP1
ERK
Elk-1
Sap1a
SRF
c-Myc
PTP
MKP
PPP3C
DNA
c-fos
Proliferation, differentiation
JNK and p38MAP kinase pathway
Focal adhesion
FLNA
JIP3
HSP72
ARRB
CrkII
Evi1
NFAT-2
NFAT-4
c-JUN
JunD
GLK
Tpl2/Cot
MEKK1
HGK
MKK4
JNK
HPK1
MLK3
MKK7
JIP1/2
Serum, cytotoxic drugs, irradiation, heatshock, reactive oxygen species, lipopolysaccharide, and other stress
Cdc42/Rac
PAK1/2
MEKK2/3
Alzheimer's disease
Proliferation, differentiation, inflammation
Cell cycle
ATF-2
Elk-1
p53
LZK
MUK
MLTK
PP2CA
MKP
AKT
PTP
Apoptosis
CASP
MST1/2
MINK
TNF
IL1
FASL
TGFB
LPS
TNFR
IL1R
FAS
TGFBR
CD14
TRAF2
GCK
ASK2
Daxx
ASK1
MKK3
MKK6
p38
Sap1a
GADD153
MAX
MEF2C
TAB1
TAK1
TRAF6
TAB2
ECSIT
PP2CB
PP5
PRAK
MAPKAPK
MSK1/2
Cdc25B
HSP27
CREB
DNA damage
GADD45
MEKK4
TAO1/2
ERK5 pathway
NLK
Wnt signaling pathway
Serum,EGF, reactive oxygen species
MEK5
ERK5
Nur77
MAPKKKK
MAPKKK
MAPKK
MAPK
Tanscription factor

Joint Design of Advanced Computing Solutions for Cancer

DOE-NCI partnership to advance cancer research and high performance computing in the U.S.



December 11, 2015

Presented to:
Secretary Moniz and Director Lowy

U.S. DEPARTMENT OF ENERGY | NIH NATIONAL CANCER INSTITUTE

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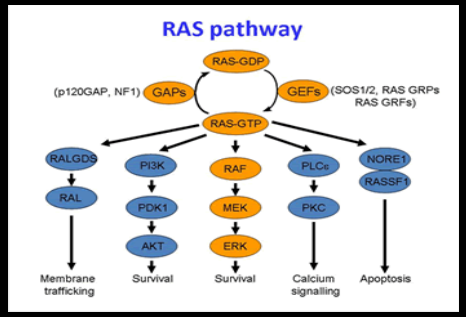
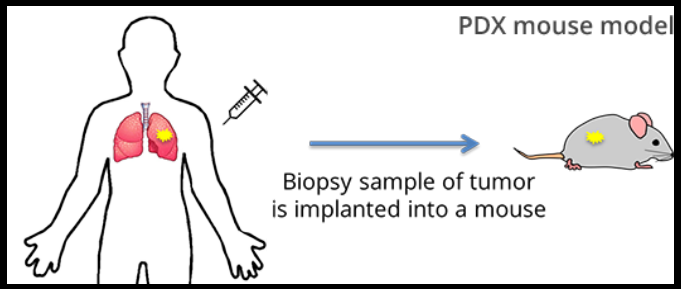
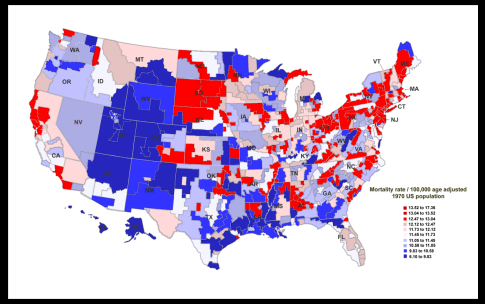
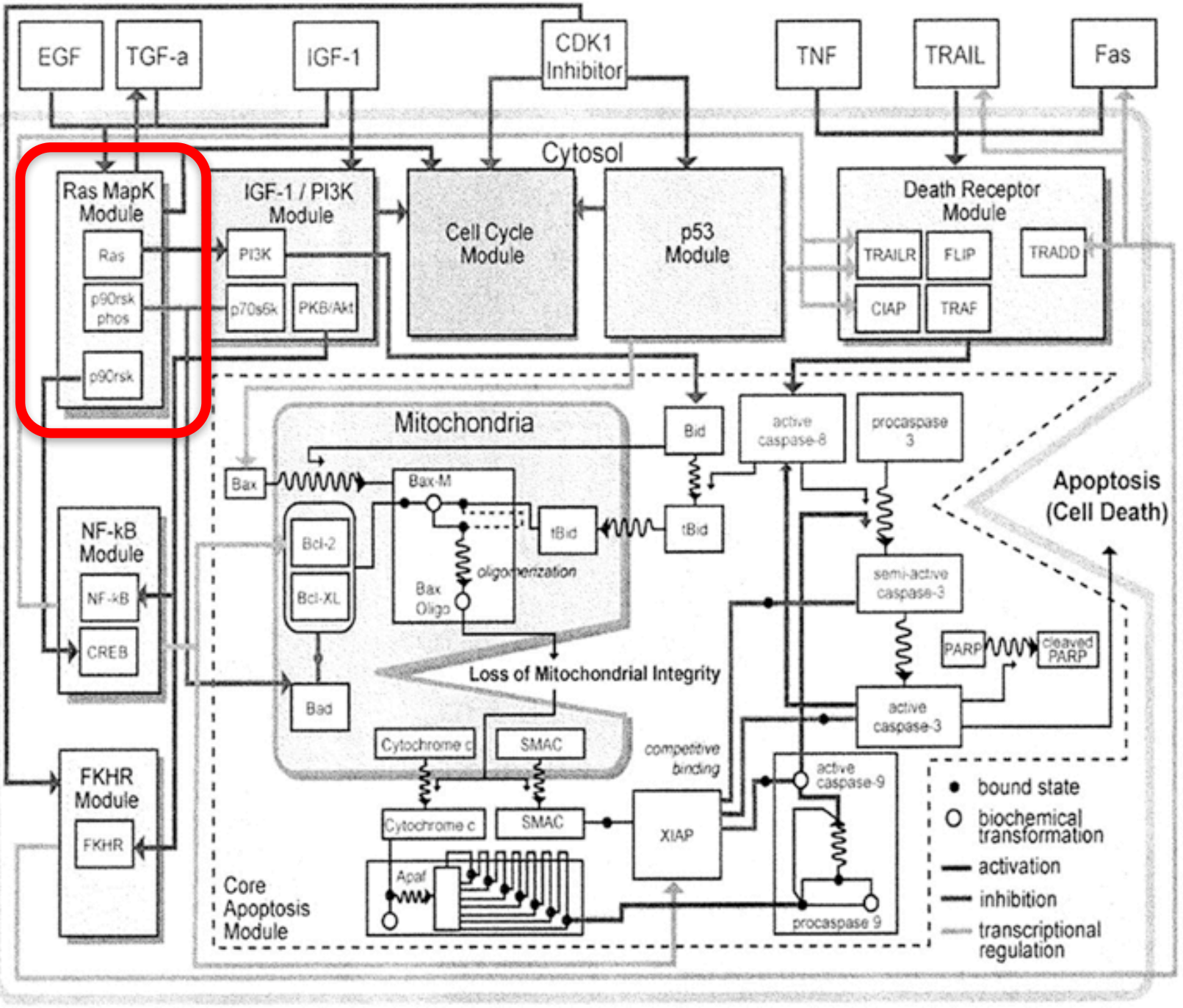
The NCI-DOE partnership will extend the frontiers of precision oncology (Three Pilots)

- **Cancer Biology**
  - **Molecular Scale Modeling of RAS Pathways**
  - Unsupervised Learning and Mechanistic models
  - Mechanism understanding and Drug Targets
- **Pre-clinical Models**
  - **Cellular Scale PDX and Cell Lines**
  - ML, Experimental Design, Hybrid Models
  - Prediction of Drug Response
- **Cancer Surveillance**
  - **Population Scale Analysis**
  - Natural Languge and Machine Learning
  - Agent Based Modeling of Cancer PateintTrajectories

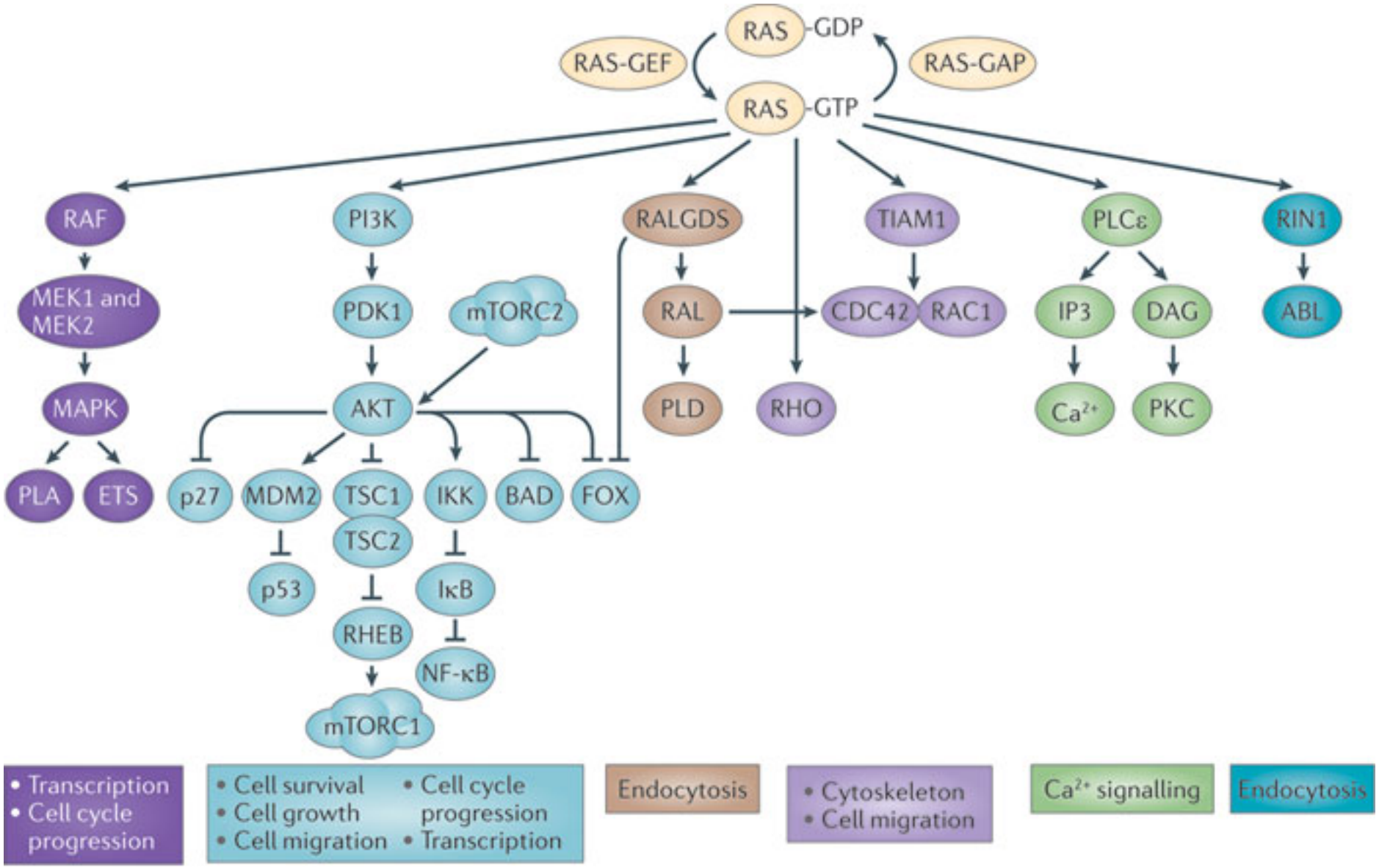






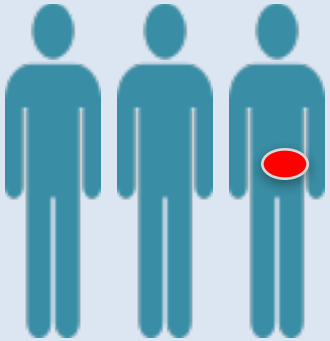

EGF
TGF-a
IGF-1
CDK1 Inhibitor
TNF
TRAIL
Fas
Cytosol
Ras MapK Module
Ras
p90rsk phos
p90rsk
IGF-1 / PI3K Module
PI3K
p70s6k
PKB/Akt
Cell Cycle Module
p53 Module
Death Receptor Module
TRAILR
FLIP
TRADD
CIAP
TRAF
Mitochondria
Bid
active caspase-8
procaspase 3
Bax
Bax-M
tBid
tBid
Bcl-2
Bcl-XL
oligomerization
Bax Oligo
Apoptosis (Cell Death)
NF-kB Module
NF-kB
CREB
semi-active caspase-3
PARP
cleaved PARP
Loss of Mitochondrial Integrity
Bad
active caspase-3
Cytochrome c
SMAC
competitive binding
active caspase-9
FKHR Module
FKHR
Cytochrome c
SMAC
XIAP
Apaf
procaspase 9
Core Apoptosis Module
bound state
biochemical transformation
activation
inhibition
transcriptional regulation

RAS Protein Interaction Network

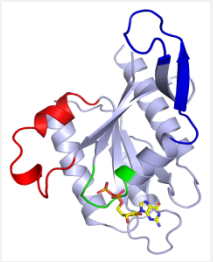


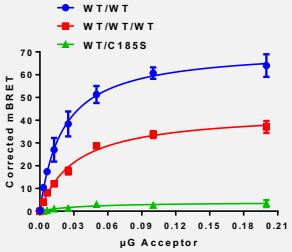
Developing new therapeutic approaches to target RAS-driven cancer

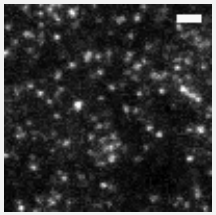
30% of cancers have mutated RAS
~1M deaths/year



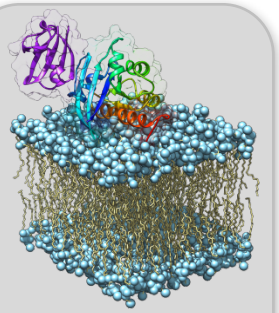
Current therapies ineffective against RAS-driven cancer



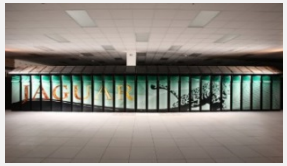




Molecular Dynamics
Simulation
Modeling

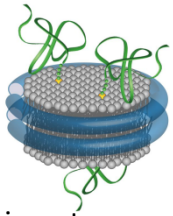


RAS biology
ID targets
New inhibitors

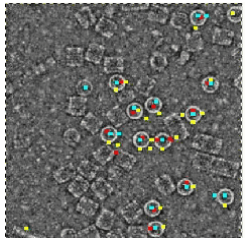


Pilot 2: RAS proteins in membranes

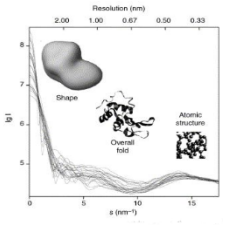
RAS activation experiments at NCI/FNL



Experiments on nanodisc



CryoEM imaging



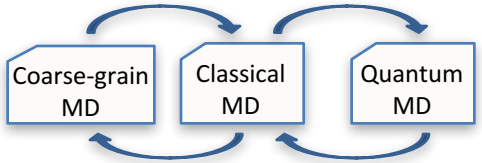
X-ray/neutron scattering

Multi-modal experimental data, image reconstruction, analytics

Protein structure databases

New adaptive sampling molecular dynamics simulation codes

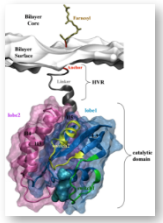
Adaptive time stepping



Adaptive spatial resolution

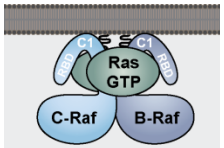
High-fidelity subgrid modeling

Predictive simulation and analysis of RAS activation



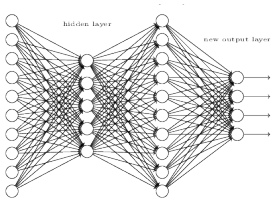
Granular RAS membrane interaction simulations

Atomic resolution sim of RAS-RAF interaction

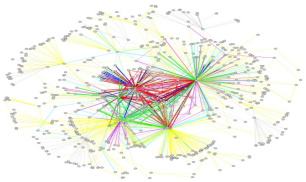


Inhibitor target discovery

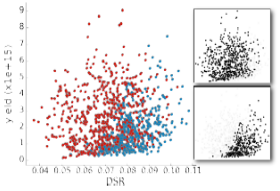
Machine learning guided dynamic validation



Unsupervised deep feature learning

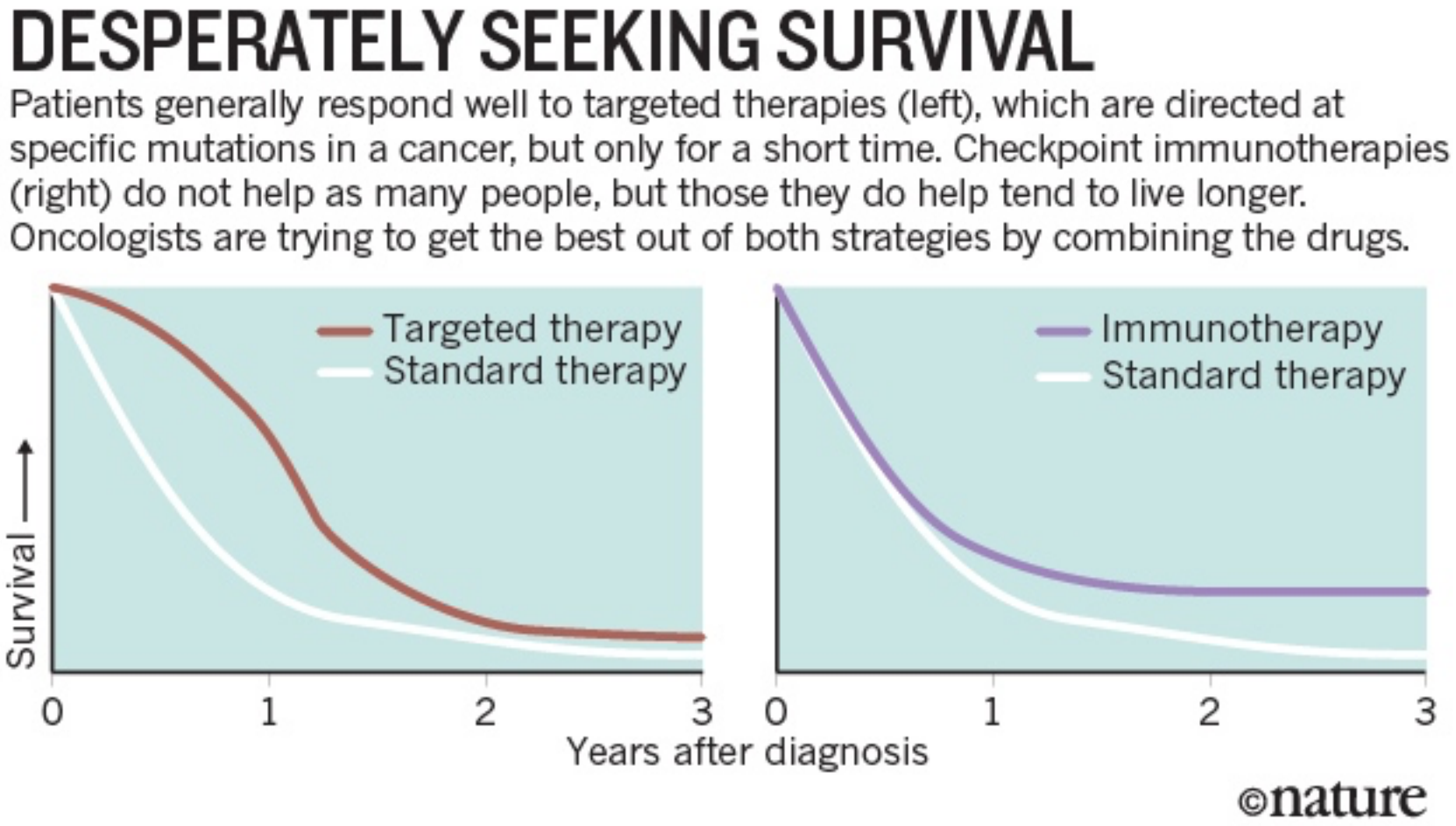


Mechanistic network models



Uncertainty quantification

>50% of Patients do not respond to chemotherapy for some tumors



Extremely high genetic diversity in a single tumor points to prevalence of non-Darwinian cell evolution

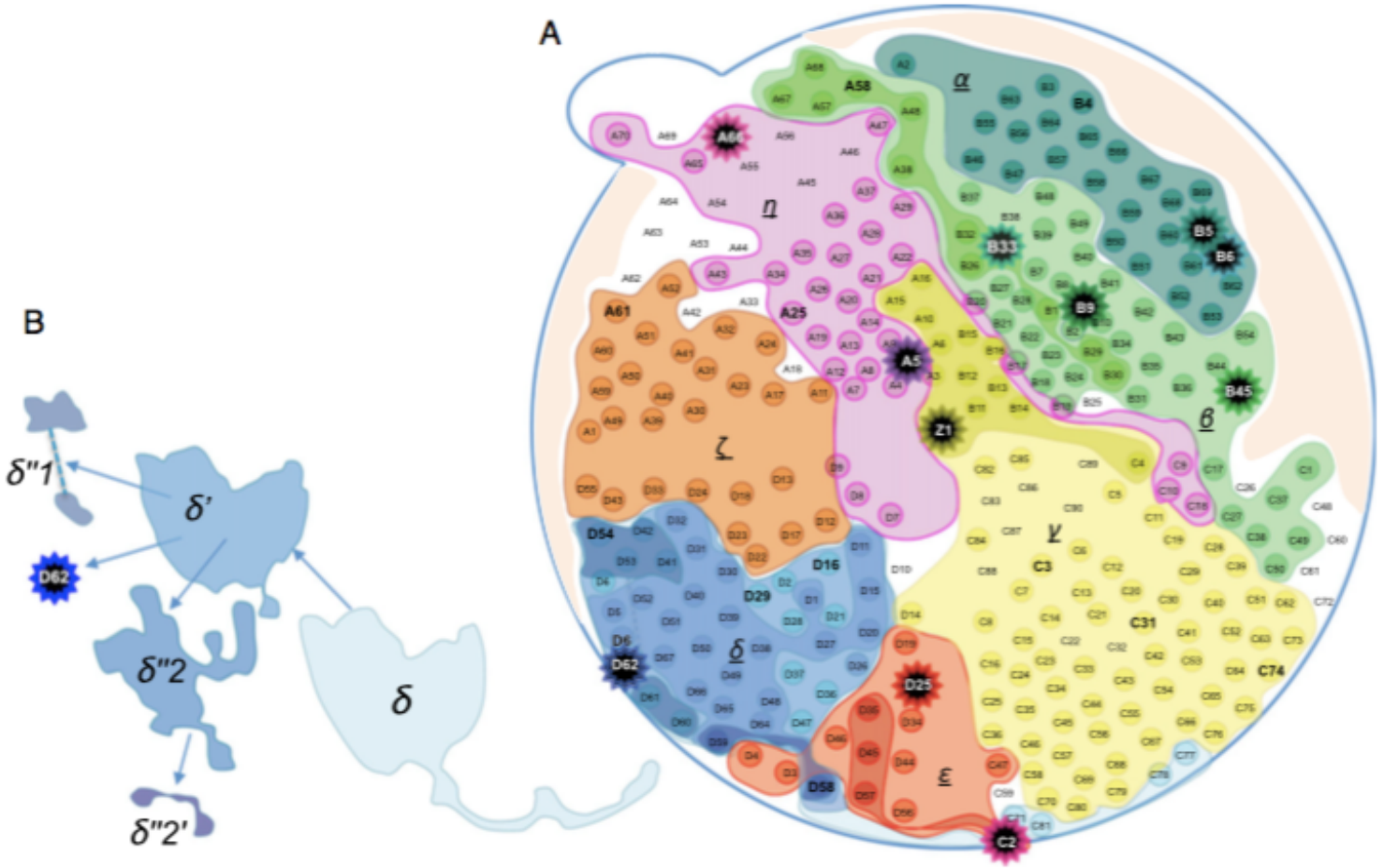


Fig. 2. Map of the mutation clones of HCC-15. A mutation clone is the aggregate of all samples carrying that mutation (main text). Hence, subclones (with increasingly darker hues) are nested within their parent clones. (*A*) Each star symbol indicates a singleton clone, represented by one sample. The clonal boundaries are delineated by the genotypes of all 286 samples. Many samples straddle two clones (including A3, B17, B19, B20, C78, D6, D9, and Z1). In this "sectoring" pattern of growth, δ′ grew outward from δ and, subsequently, δ′′s (−1, −2) grew outward from δ′. Note that tumors grew in three-dimensional (3D) space but the observations made were on a two-dimensional (2D) plane. This was apparent in the "northeast" direction, along which both the α and β clones were extending from the interior toward the periphery. It appears that α grew above or below β in their expansion toward the periphery. (*B*) The δ lineage clones are pulled out to display the overlaying pattern of mutation clones. The clonal map was also used to compute the mutation frequency spectrum, ξ_i, which is the number of sites where the frequency of the mutation was between $(i-1)/23$ and $i/23$ from the 286 samples. We kept the number of frequency bins at 23 because the mutations discovered remained based on the initial 23 samples. The spectrum, as given in the text, is $[\xi_i = 26, 7, 1, 1, 0, 0, \ldots]$ for $i = 1$–22 (*Materials and Methods*, section 9 and Dataset S8).

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Estimated Cell Lineages

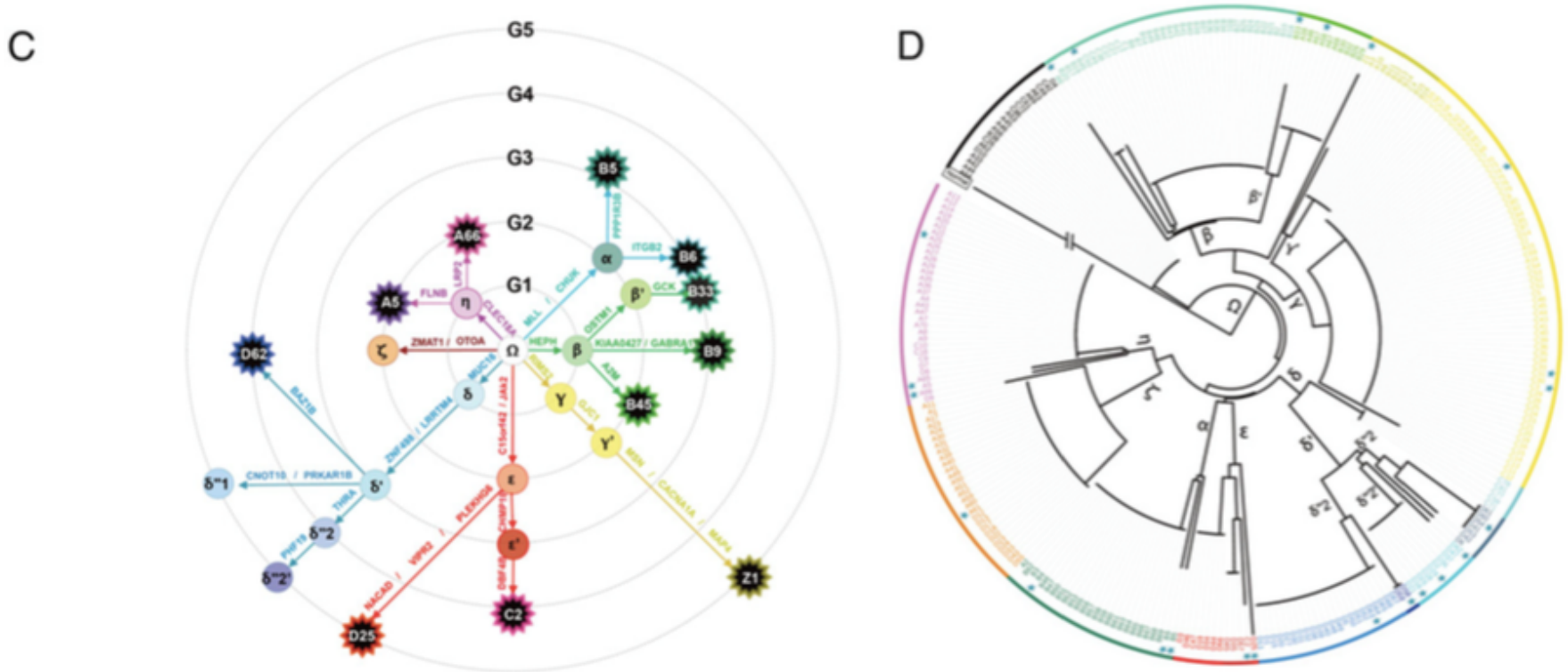

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Fig. 1. Sampling scheme and clonal genealogy of HCC-15. (*A*) Samples were taken from a 1-mm-thick slice cut through the middle of a HCC tumor, 3.5 cm in diameter. Of the 286 samples, 23 were subjected to whole-exome sequencing (red numbers) and the rest (black numbers) were used in genotyping for mutations discovered in sequencing (*Materials and Methods*, sections 1–5). The numbers correspond with those of Fig. 2. Across the sequenced samples, the average read depth was 74.4× (Dataset S1). On average, these samples contained 85% cancerous cells estimated by ABSOLUTE (52). This level of purity is consistent with previous reports regarding hepatic tumor samples (12), especially when the sample volumes are small (~20,000 cells). Pathology reports, when available for the matched HCC samples, generally agreed with the purity estimates. (*B*) All 35 polymorphic nonsynonymous mutations in the sequenced samples are shown in the heat map, which depicts the observed frequencies (from 0 in white to 1 in yellow) with mutation names at the top of the map. Each row presents the mutations in a sequenced sample. *Far Right* shows six fixed mutations that are potential drivers. *Left* shows the genealogy of the 24 samples. Only two clones, indicated by blue bars, are represented by more than one sample. (*C*) The genealogy of clones arranged to reflect their spatial relationships. The ancestral clone, Ω, is in the middle and the descendant clones radiate outward. These clones are arranged on six rings with each outer ring having one more nonsynonymous mutation (indicated) than its interior neighbor. Each star symbol represents a singleton clone. (*D*) The expanded genealogy that includes all 286 samples. The blue stars designate the sequenced samples.

Significance

When the data were analyzed by modern population genetic theory, we estimated more than 100 million coding region mutations in this unexceptional tumor.

The extreme genetic diversity implies evolution under the non-Darwinian mode.

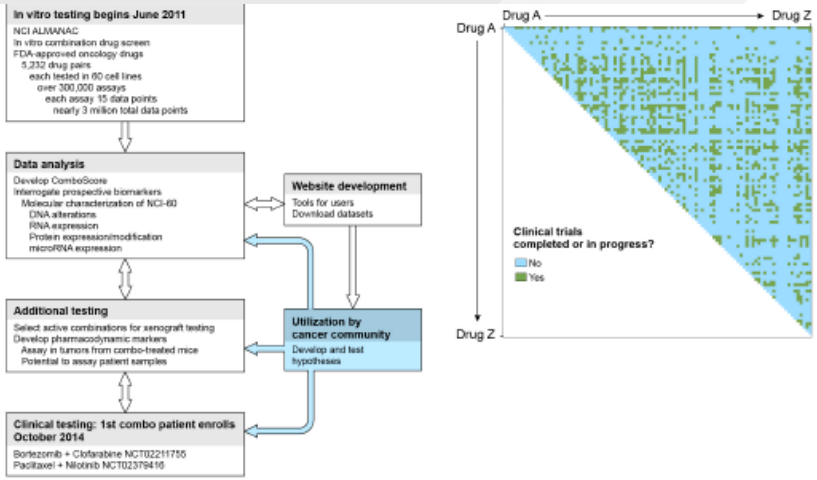
In contrast, under the prevailing view of Darwinian selection, the genetic diversity would be orders of magnitude lower.

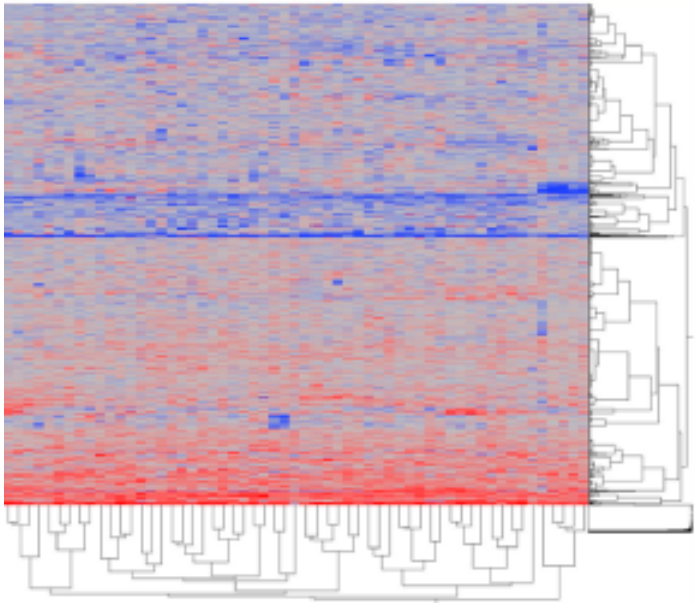
Because genetic diversity accrues rapidly, a high probability of drug resistance should be heeded, even in the treatment of microscopic tumors.

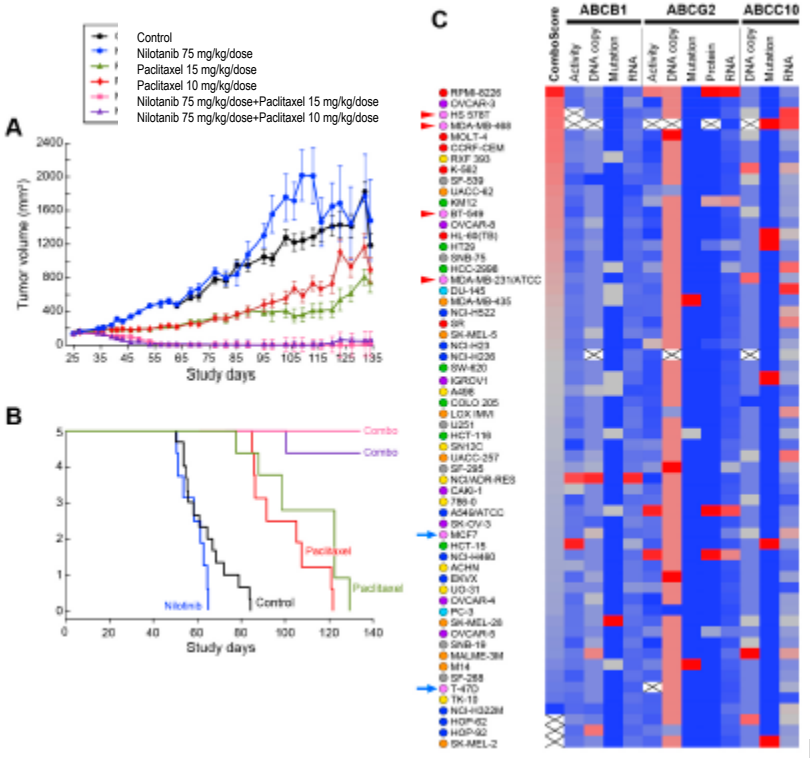
The NCI ALMANAC: Testing All Pairwise Combinations of Approved Cancer Drugs

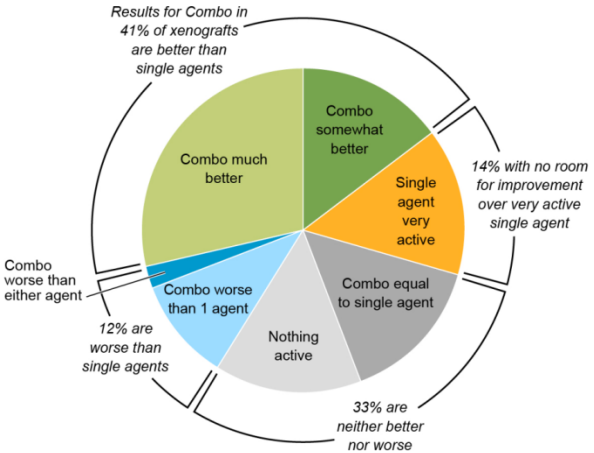
- The NCI ALMANAC (A Large Matrix of AntiNeoplastic Agent Combinations)
- Currently just over 100 small molecule oncology drugs are FDA-approved.
- Test all possible pairwise combinations: ~5000 drug pairs
- Test each drug pair in each of the cell lines in the NCI-60 panel:
  - ~300,000 experiments
  - ~4.3 million wells
- Screen run at Frederick National Labs & 2 contract locations

NCI-60 Combination Data





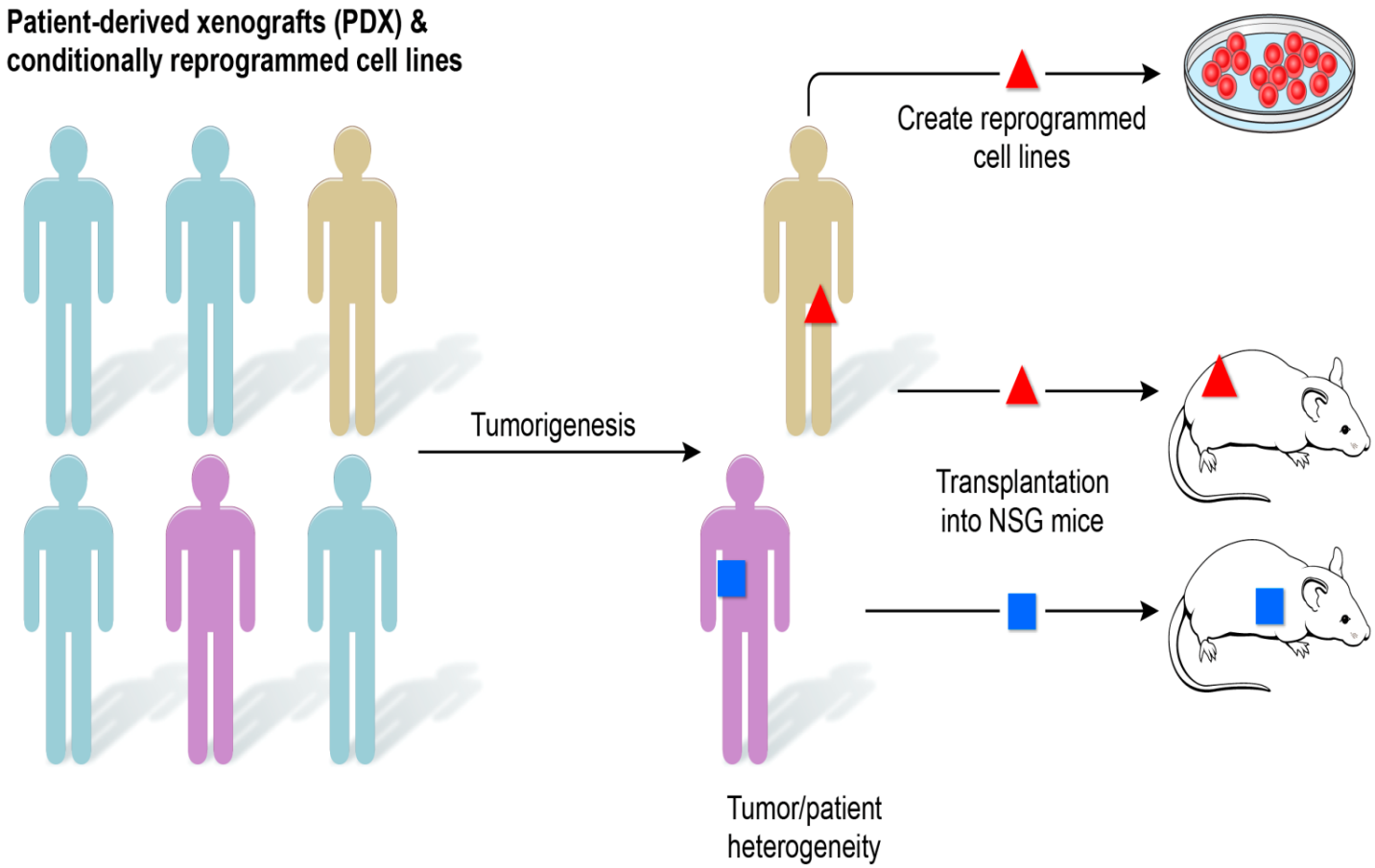




In addition, 92 xenograft experiments have been completed with at least 80% of control mice reaching 1 doubling "event" for 41 drug pairs. These drug pairs all had a good ComboScore in the corresponding cell line.

Manuscript In Preparation

Patient Derived Xenograft Models



Molecularly characterize, treat/screen mice bearing transplants & cells with relevant drugs.

"Pre-clinical clinical trials"

Nature Rev. Clin. Oncol. 11: 649-662, 2014.

Pilot 1: Predictive Models for Pre-Clinical Screening

Terabytes **Cell Line Compound Screens**

Terabytes **Cell Line Molecular Assays**

Terabytes **Compound Databases**

Petabytes **PDX Features (DNA, RNA, Images)**

Terabytes **PDX Compound Screens**

Petabytes **Protein-Protein Interactions**

Terabytes **Cancer Pathway Databases**

Petabytes **Cancer Genome Atlas**

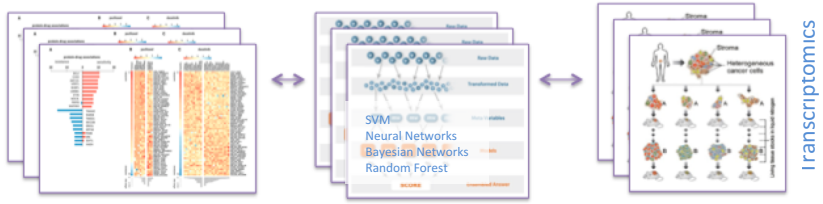
Petabytes **Cancer Data Commons**

Petabytes **Gene Expression Omnibus**

Machine Learning Based Predictive Models

Cell Line Based Screens | Machine Learning Methods | PDX Based Screens

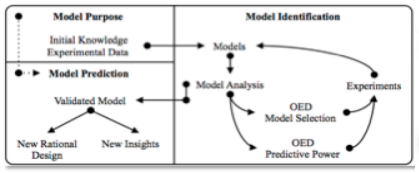
Transcriptomics
Proteomics
Variation



Transcriptomics
Imaging
Small RNAs

Feature Engineering, Cross Validation, Scalable Compute on CORAL

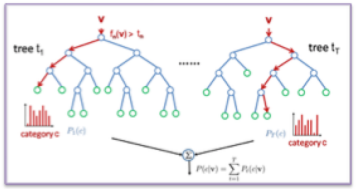
Uncertainty and Optimal Experiment Design

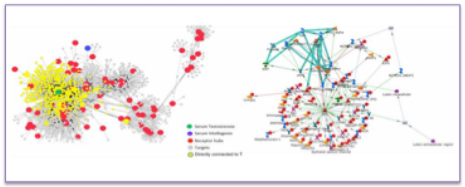


UQ Analysis, Model Selection, Model Improvement, Proposed Experiments

Hypotheses Formation and Mixed Modeling

Feature Importance Mining | Biological Interaction Network Modeling

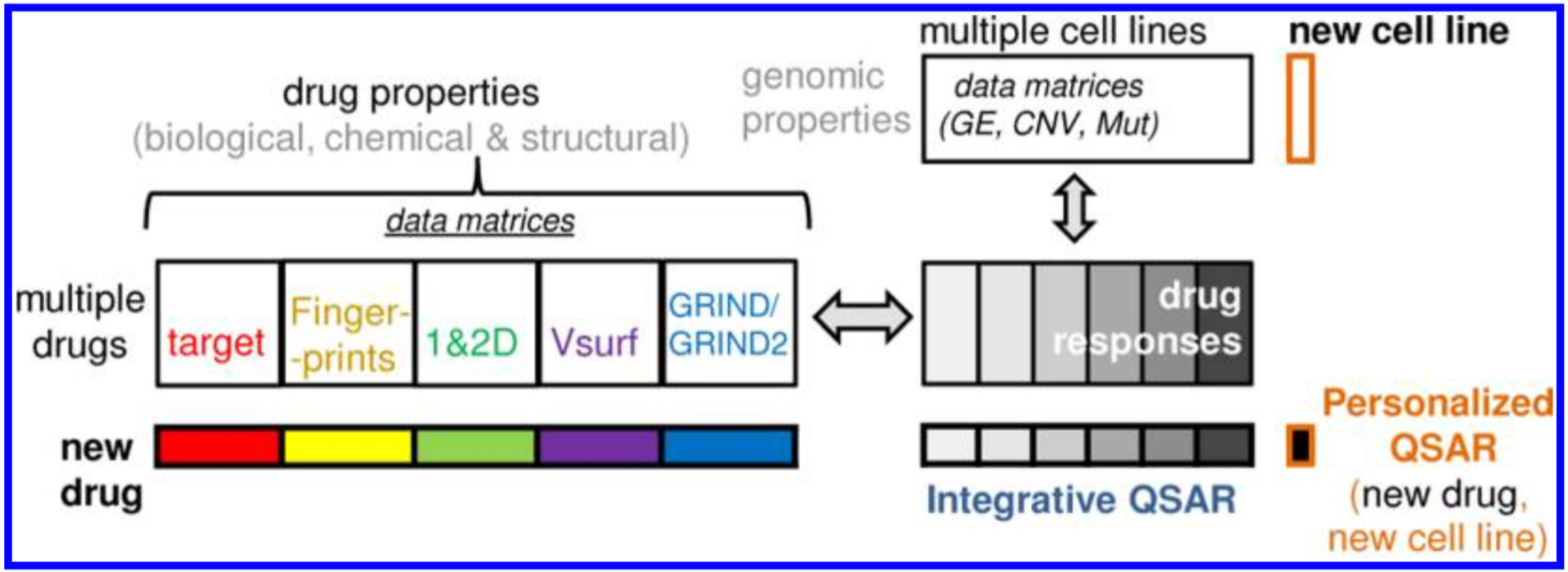




Integration of Mechanistic, Statistical and Inferential Modeling

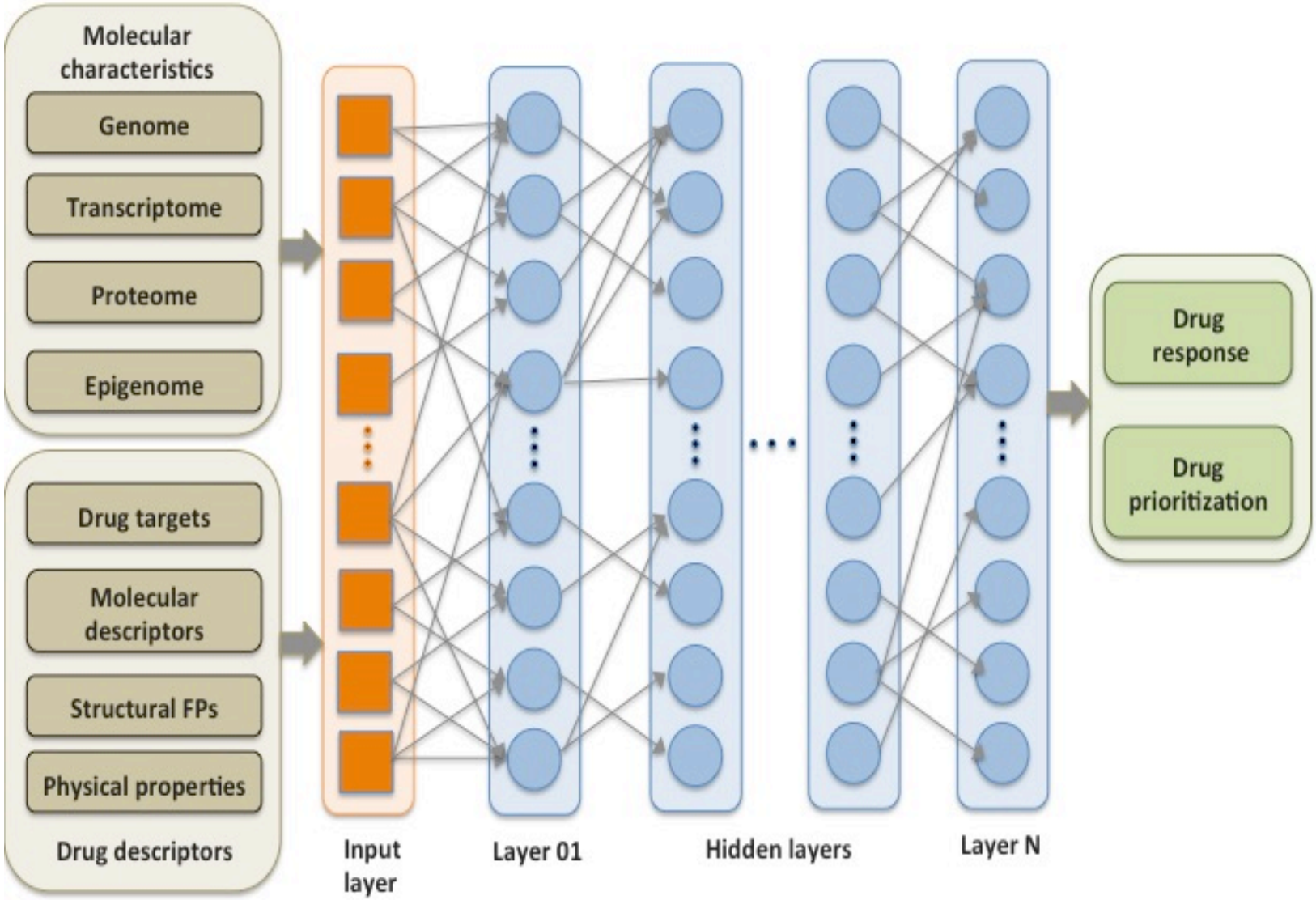
Deep Learning Formulation

$O(10^7)$ instances x $O(10^7)$ features



Drugs + Cell Lines ⇒ DNN ⇒ IC50

- Virtual screening new drugs on existing cell lines and PDX models
- Prediction of drug IC50 on new tumor/cell lines


Molecular characteristics
Genome
Transcriptome
Proteome
Epigenome
Drug targets
Molecular descriptors
Structural FPs
Physical properties
Drug descriptors
Input layer
Layer 01
Hidden layers
Layer N
Drug response
Drug prioritization

Hybrid Models in Cancer

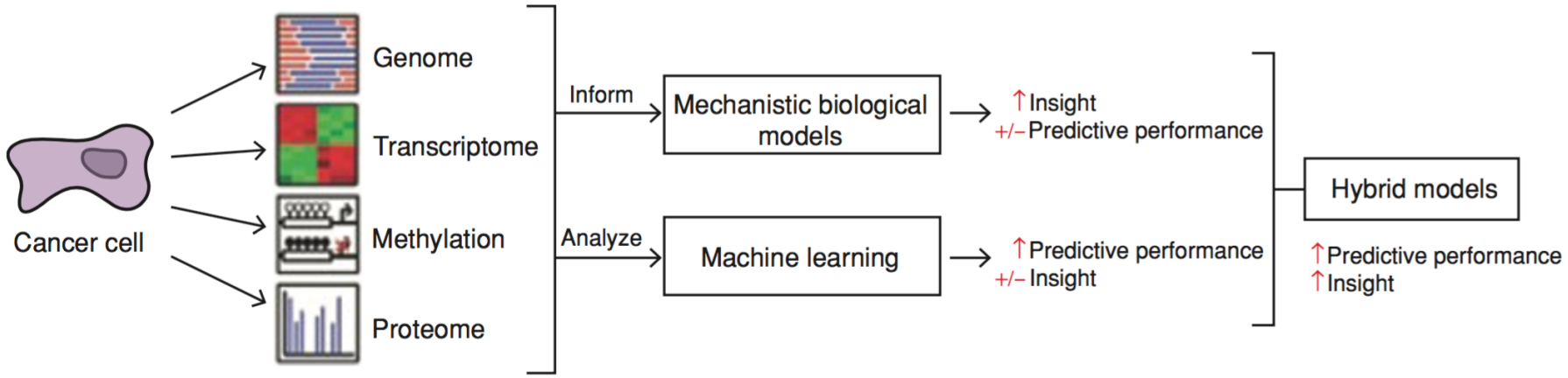


Figure 1. In two DREAM challenges, high throughput data characterizing cancer cells are used to build predictive models. Mechanistic models provide insight into the underlying biology, but do not take full advantage of the information within the data to achieve high performance. Machine learning methods are associative and extract maximum predictive value from the data, but do not always provide insight about mechanism. The future may bring hybrid models that combine the best of both approaches.

Predicting Cancer Drug Response: Advancing the DREAM

Russ B. Altman

Summary: The DREAM challenge is a community effort to assess current capabilities in systems biology. Two recent challenges focus on cancer cell drug sensitivity and drug synergism, and highlight strengths and weaknesses of current approaches. *Cancer Discov; 5(3); 237–8. ©2015 AACR.*

Cancer Registries
Surveillance, Epidemology and End Results

Figure 1. Trends in Average Survival from Cancer Diagnosis in the United States and Ten European Countries, 1983-99

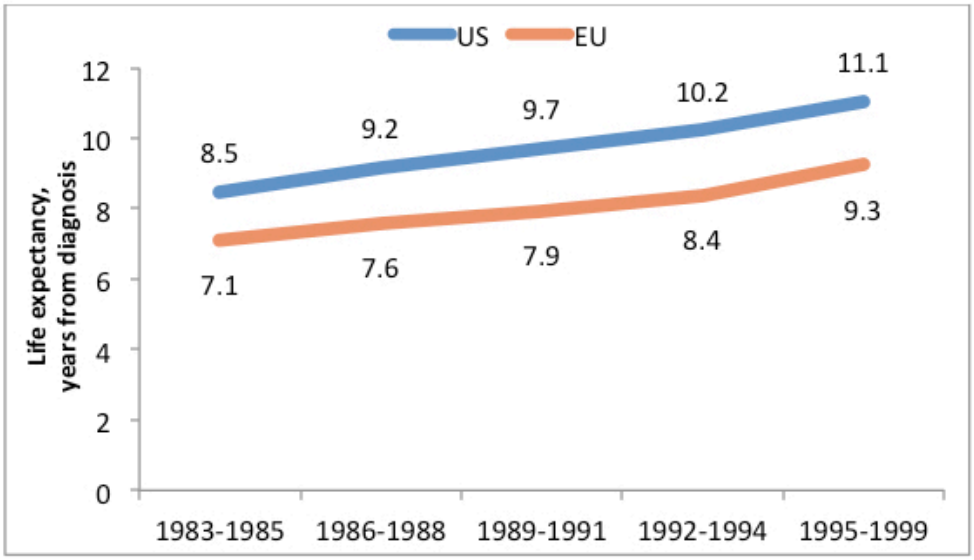
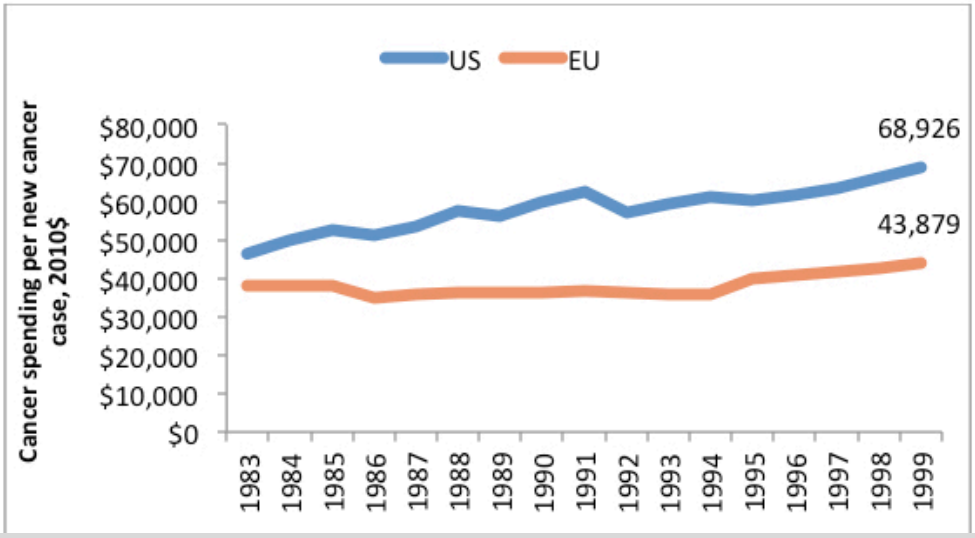


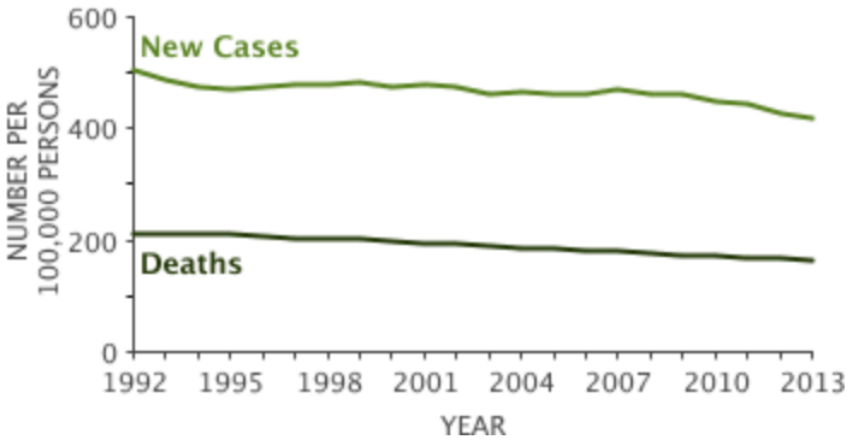
Figure 2. Trends in Average Cancer Spending In the United States and Ten European Countries, 1983-99



SEERs Database All Cancer Summary

At a Glance

Estimated New Cases in 2016	1,685,210
% of All New Cancer Cases	100.0%
Estimated Deaths in 2016	595,690
% of All Cancer Deaths	100.0%



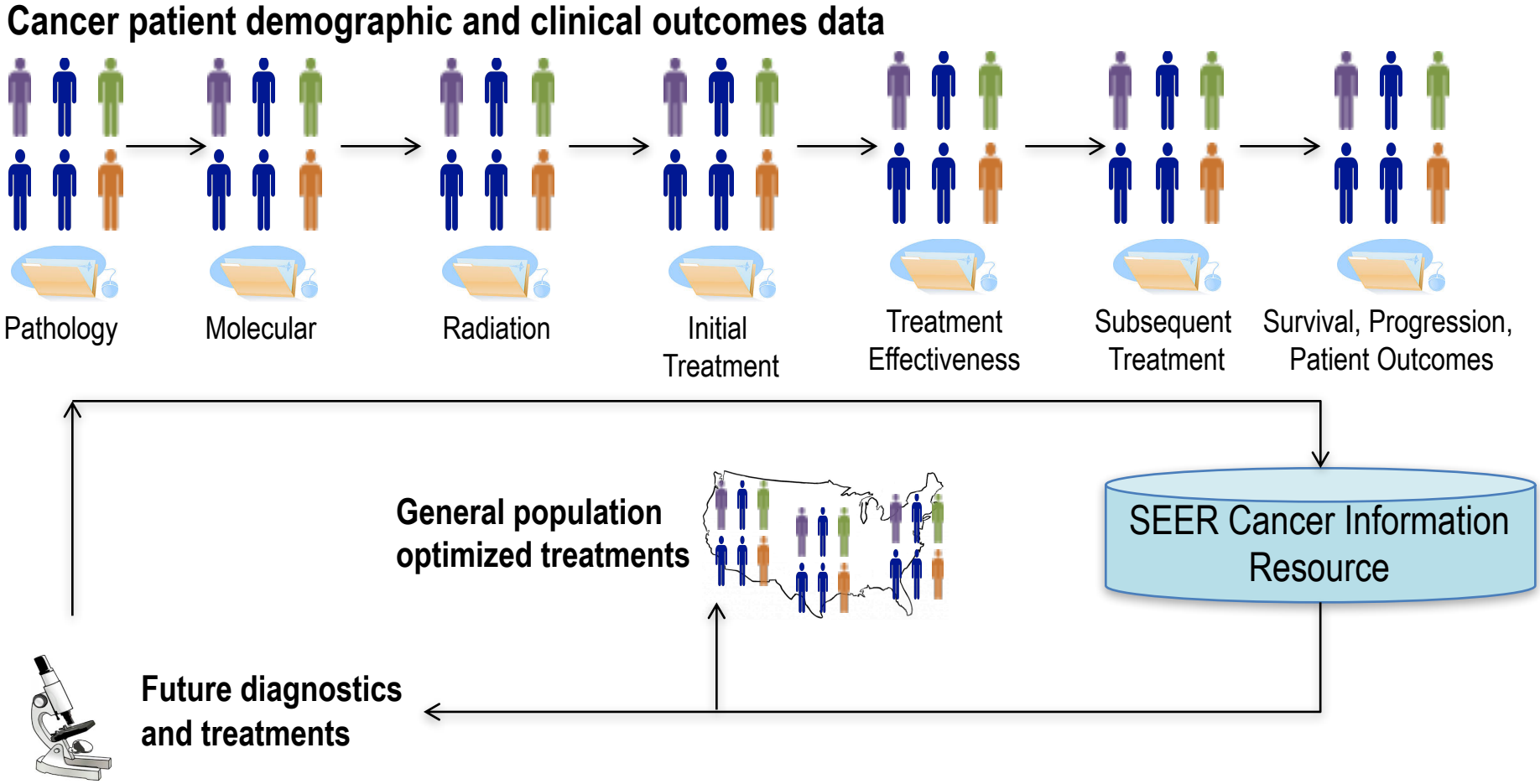
Percent Surviving 5 Years
66.9%
2006–2012

Number of New Cases and Deaths per 100,000: The number of new cases of cancer of any site was 448.7 per 100,000 men and women per year. The number of deaths was 168.5 per 100,000 men and women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

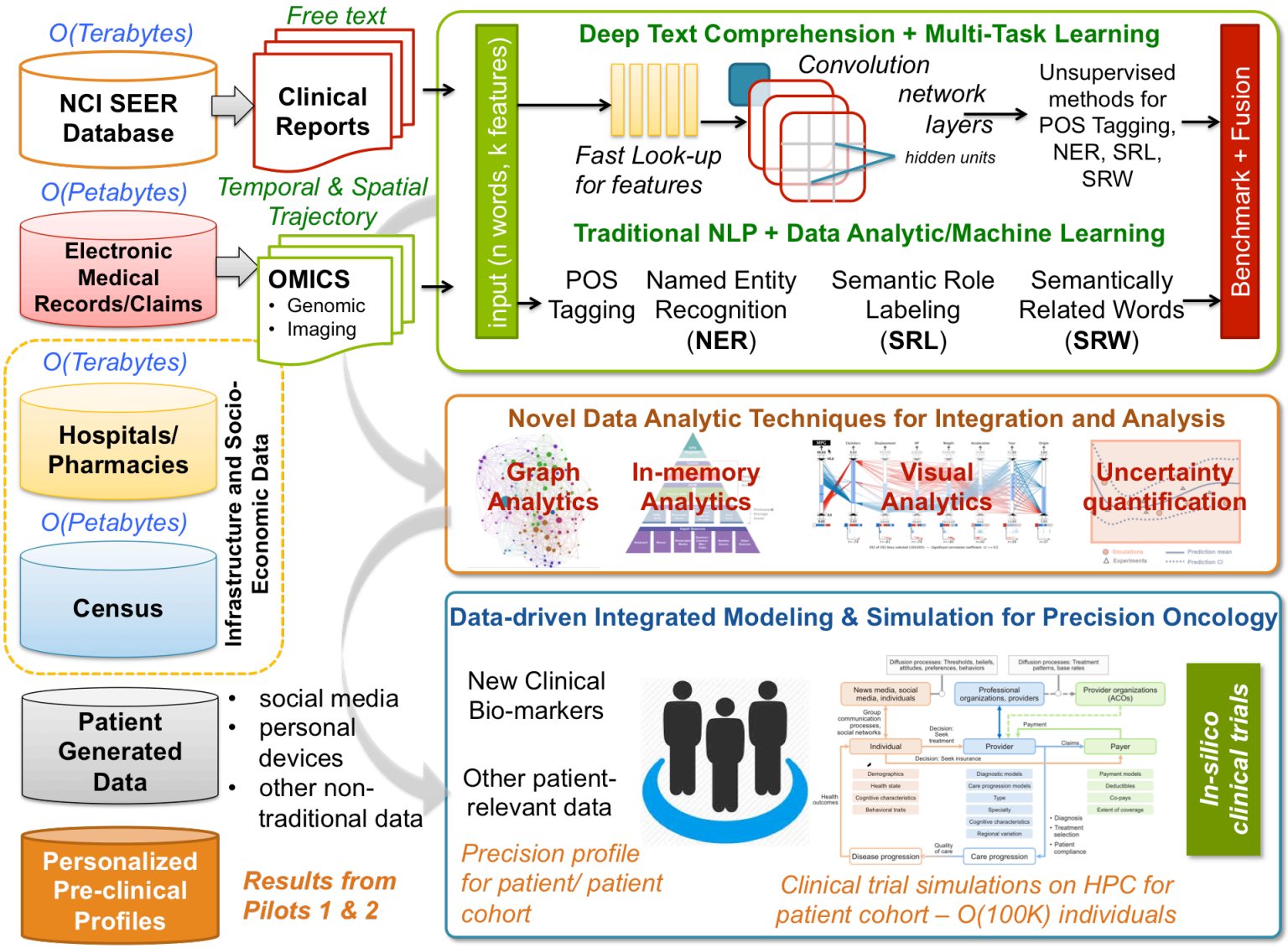
Lifetime Risk of Developing Cancer: Approximately 39.6 percent of men and women will be diagnosed with cancer of any site at some point during their lifetime, based on 2010–2012 data.

Prevalence of This Cancer: In 2013, there were an estimated 14,140,254 people living with cancer of any site in the United States.

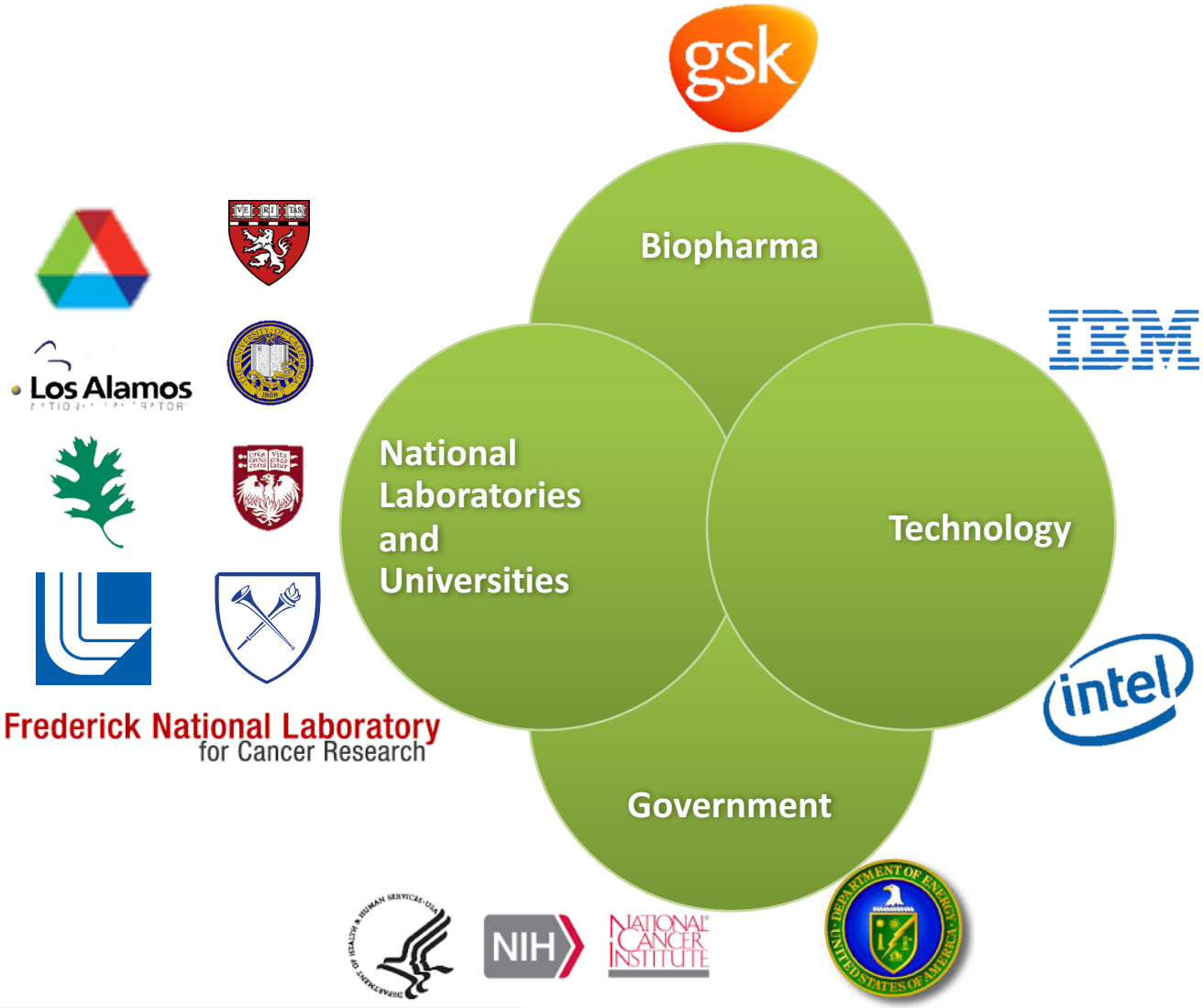
Cancer Patient Surveillance and Information Integration



Pilot 3: Population Information Integration, Analysis and Modeling



Emerging NSCi Public Private Partnership for Computing Precision Medicine



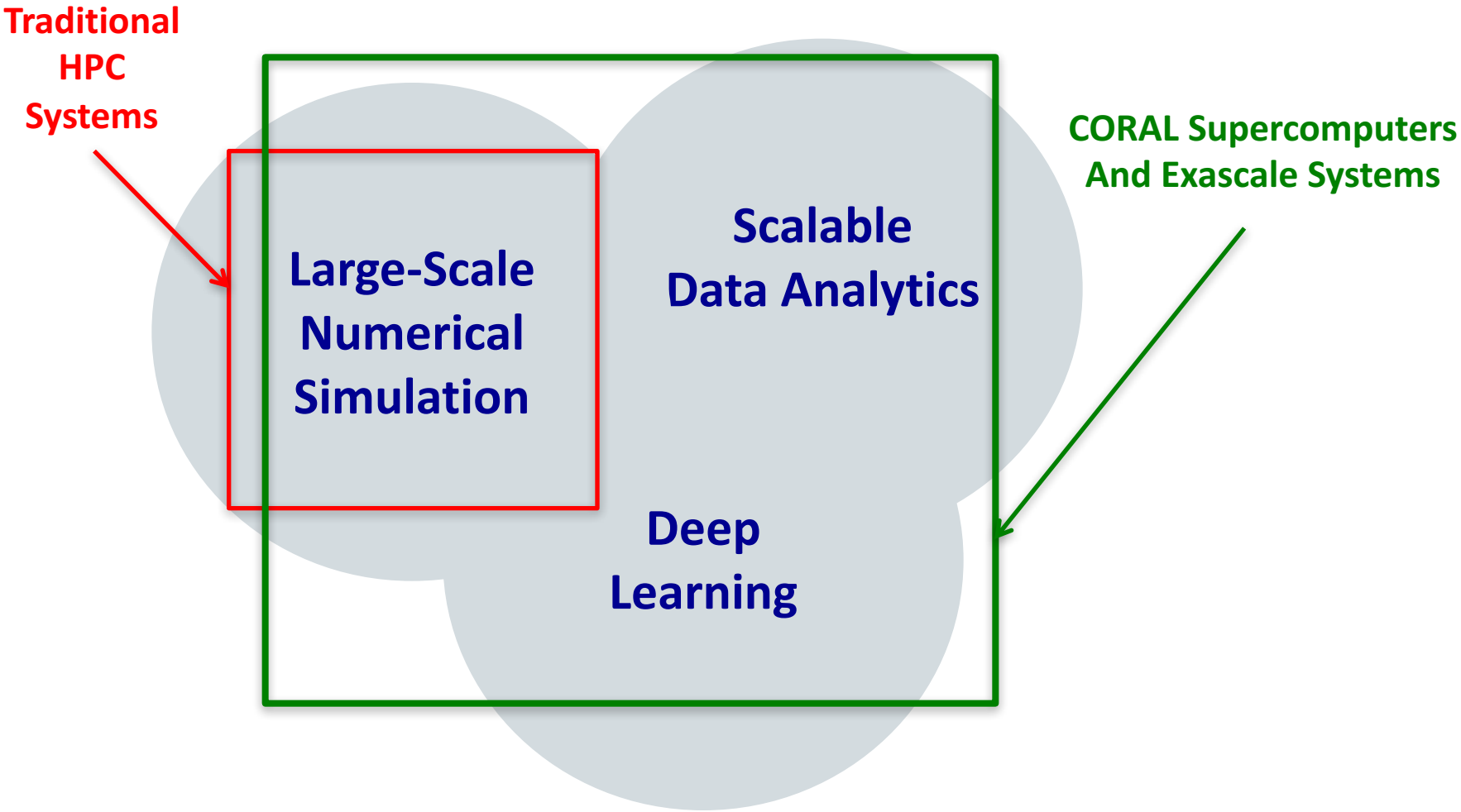
National Laboratories and Universities
ANL
ORNL
LLNL
LANL
FNLCR
Harvard University
University of Chicago

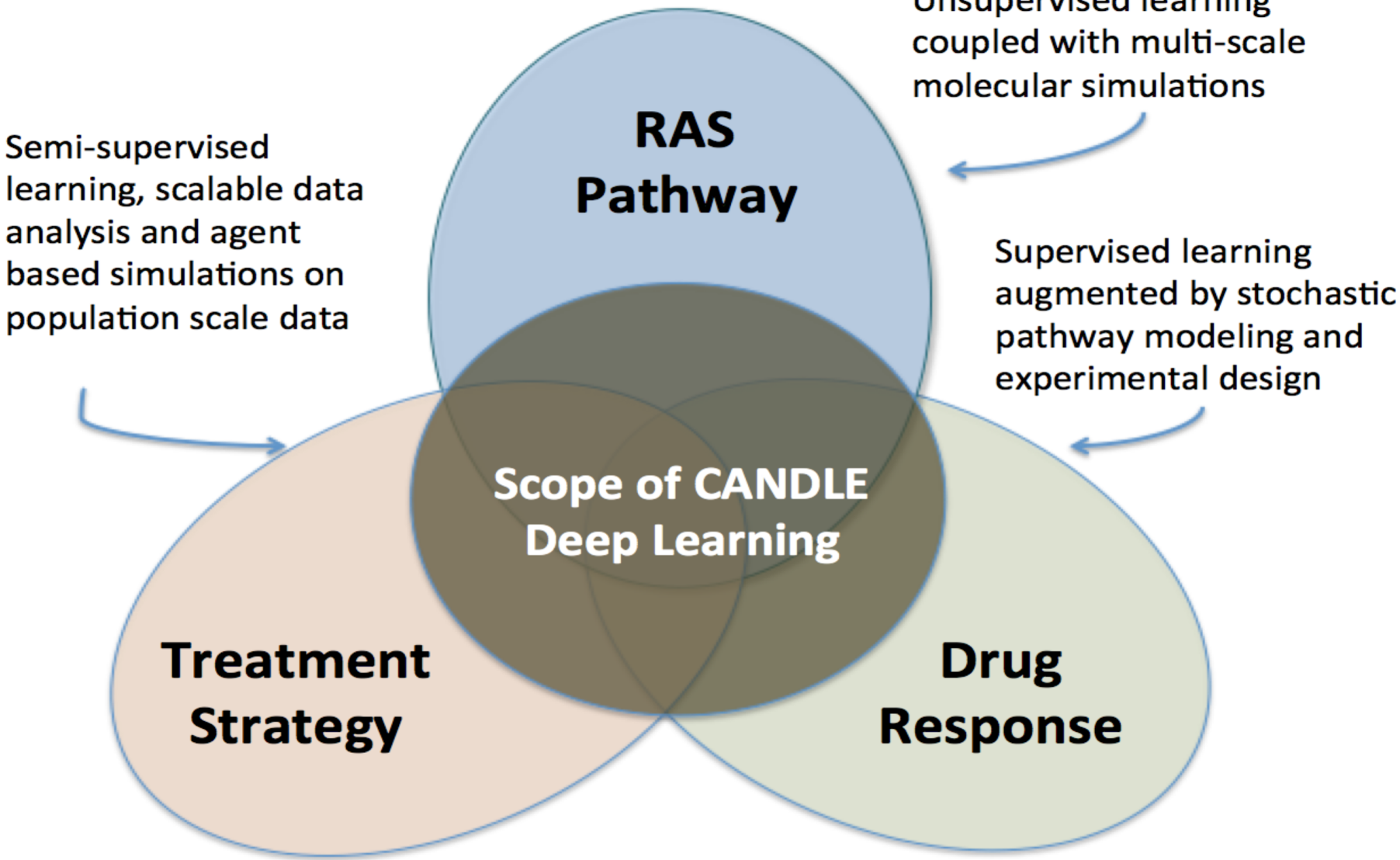
Government
Department of Energy
National Cancer Institute

Biopharma
Glaxo Smith-Kline

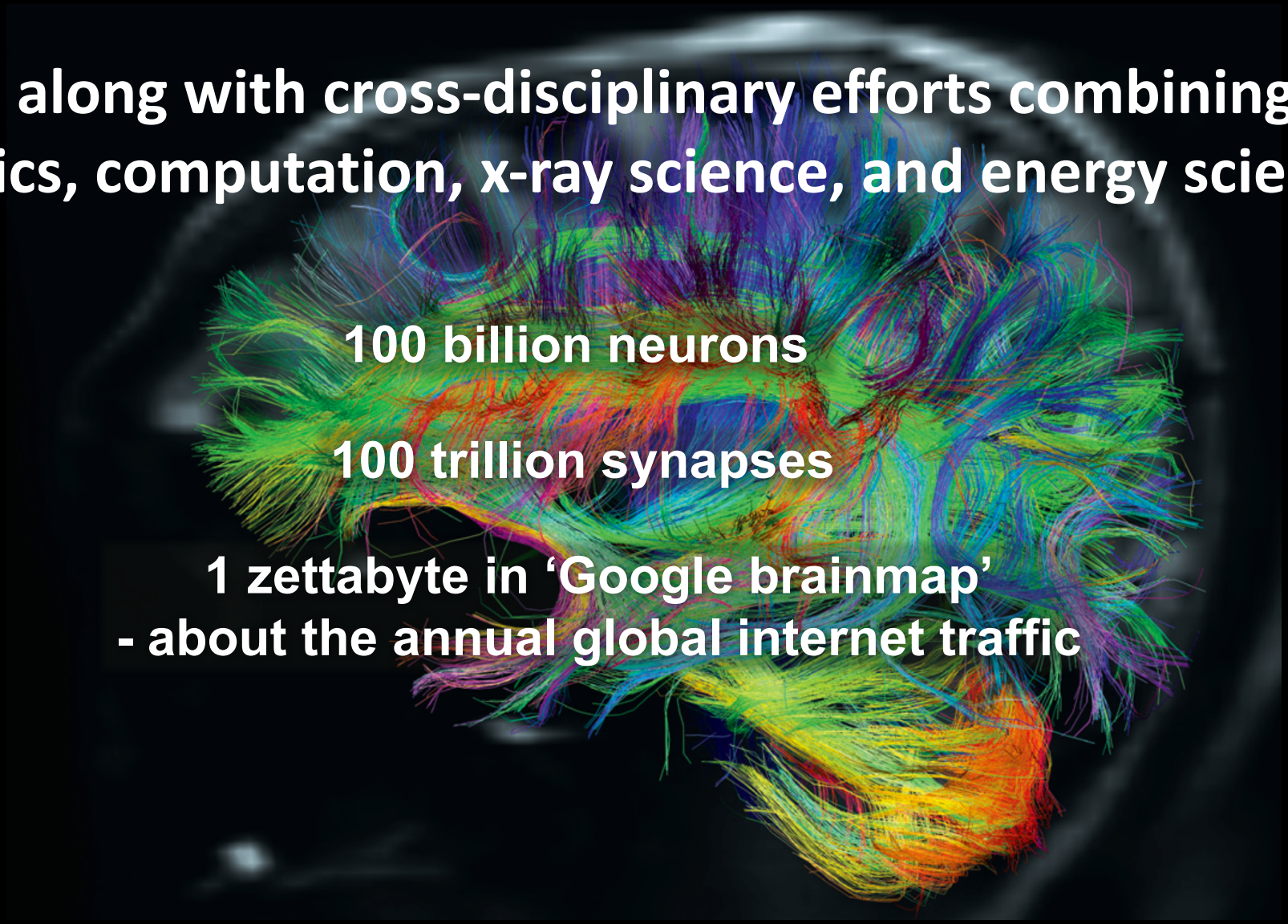
Technology
Intel
IBM

Integration of Simulation, Data Analytics and Machine Learning




Unsupervised learning coupled with multi-scale molecular simulations
RAS Pathway
Semi-supervised learning, scalable data analysis and agent based simulations on population scale data
Supervised learning augmented by stochastic pathway modeling and experimental design
Scope of CANDLE Deep Learning
Treatment Strategy
Drug Response

The challenge of understanding the brain requires extraordinary advances in neuroscience…



… along with cross-disciplinary efforts combining physics, computation, x-ray science, and energy science

100 billion neurons

100 trillion synapses

1 zettabyte in ‘Google brainmap’
- about the annual global internet traffic

U.S. President Barack Obama walks off stage after announcing his administration's BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative at the White House in Washington, April 2, 2013.

the WHITE HOUSE

BRAIN INITIATIVE

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES

The Big Picture Goal

- The challenge is to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities.
- We should pursue this goal simultaneously in humans and in simpler nervous systems in which we can learn important lessons far more quickly. But our ultimate goal is to understand our own brains.

DENTATE GYRUS

POSSIBLE LONG-TERM OUTCOMES

The BRAIN Initiative has the potential to do for neuroscience what the Human Genome Project did for genomics by supporting the development and application of innovative technologies that can create a dynamic understanding of brain function. It aims to help researchers uncover the mysteries of brain disorders, such as Alzheimer's and Parkinson's diseases, depression, Post-Traumatic Stress Disorder (PTSD), and traumatic brain injury (TBI).

The Human Genome Project demonstrates the potential impact that ambitious research programs like the BRAIN initiative can have.

From 1988-2003, the Federal Government invested $3.8 billion in the Human Genome Project, which has since generated an economic output of $796 billion —a return of $141 for every $1 invested.

Goals of the BRAIN 2025

- Discovering diversity: cell types
- Maps at multiple scales: connectome
- Brain in action: dynamic activity
- Demonstrating causality: link to behavior
- Identifying fundamental principles
- Advancing human neuroscience
- BRAIN to brain: integration and translation

Overall Planning Document
(15 academic authors, NIH, NSF, DARPA, FDA)

- Vision and Philosophy
- Priority Research Areas
- Implementation goals, deliverables, timelines and Costs
- 6 workshops
- ~100 Participants

- computer scientists?
- Mathematicians?

146 pages

CS mentioned 5 times

Math mentioned 4 times

Proposed BRAIN Initiative 12 Year Budget

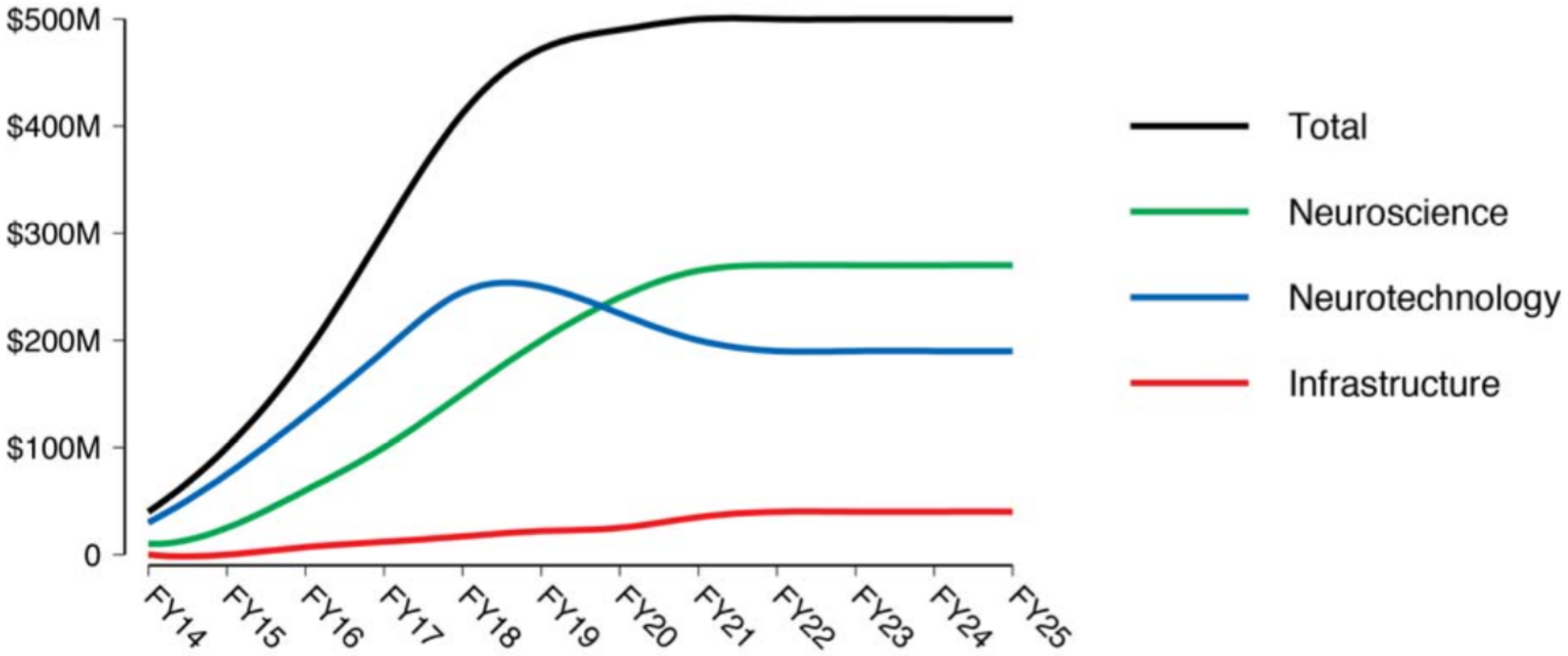
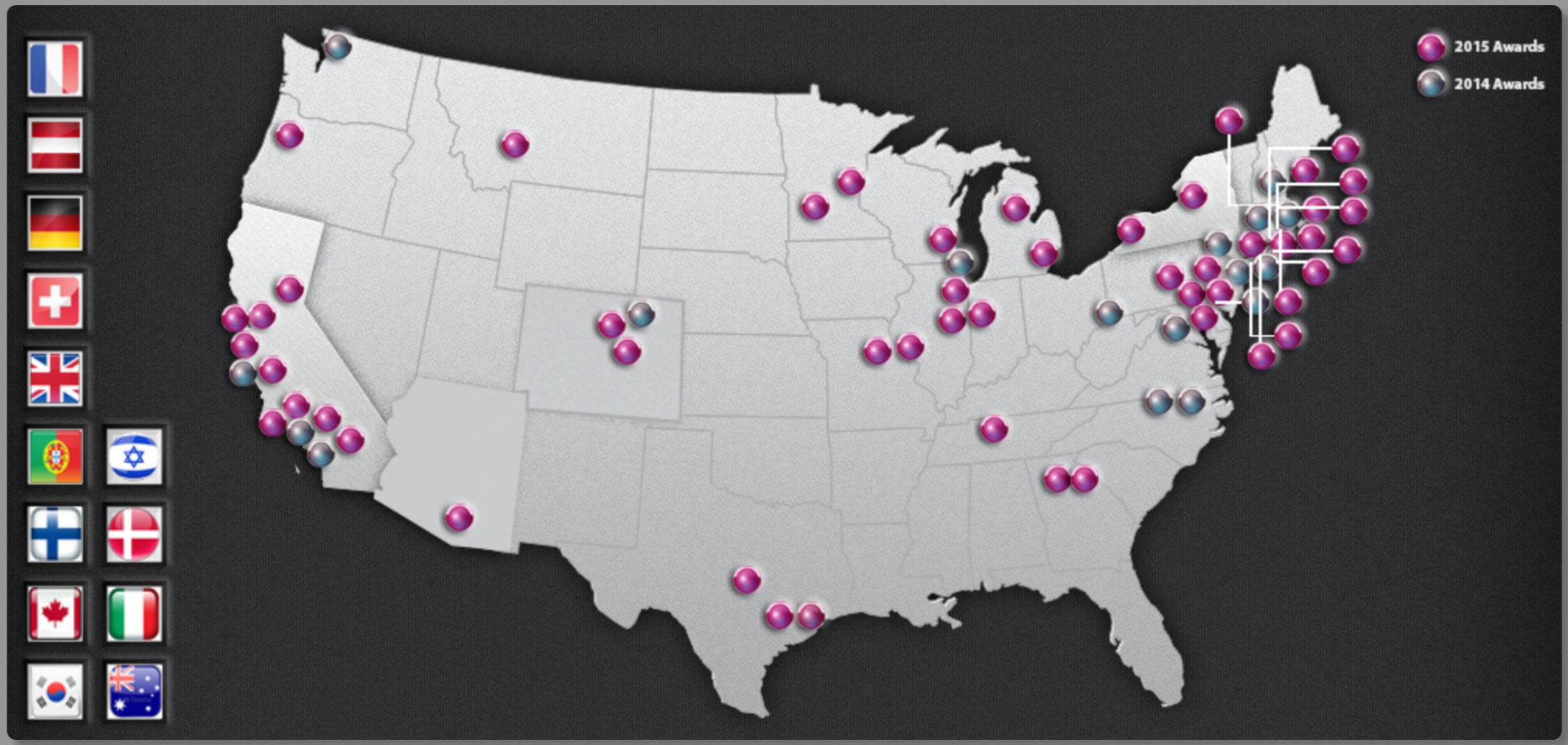


Figure caption. Proposed 12-year budget for the BRAIN Initiative. Collaborative technology development is emphasized through FY2019, while discovery-driven science receives priority beginning in FY2020. 'Infrastructure' is for facilities and capabilities that will benefit researchers across the entire nation, with emphasis on data sharing resources, training in the use of new technologies and quantitative methods, and possible regional instrumentation centers during the last half of the BRAIN Initiative.

BRAIN initiative Awards



FY2016 Investments

FY2015 ~$200M

- NIH $135M
- DARPA $95M
- NSF $72M
- IARPA $XM
- FDA $YM

DOE has a proposed FY17 role for BES, BER and ASCR

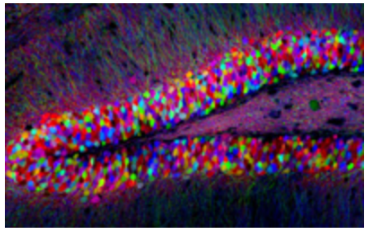
Darpa Program Elements

- Electrical Prescriptions (ElectRX)
- Hand Proprioception and Touch Interfaces (HAPTIX)
- Neural Engineering Systems Design (NESD)
- Neuro Function, Activity, Structure and Technology (Neuro-FAST)
- Reliable Neural-Interface Technology (RE-NET)
- Restoring Active Memory (RAM)
- Restoring Active Memory (RAM Replay)
- Revolutionizing Prosthetics
- Systems-Based Neurotechnology for Emergying Therapies (SUBNETS)
- Targeted Neuroplasticity Training (TNT)

BRAIN Thematic Areas:

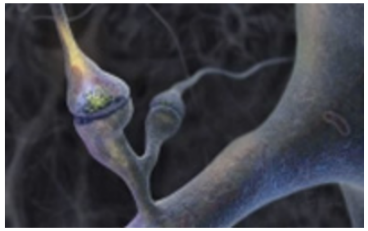
Multi-scale Integration of the Dynamic Activity and Structure of the Brain

To elucidate and link dynamics of the brain and neural circuits with brain function, including its real-time physiological, behavioral and cognitive outputs



Neurotechnology and Research Infrastructure

To create tools to image, sense, record and affect real-time brain function and complex behavior, and develop theories and systems to collect, visualize, analyze, model , store, and distribute BRAIN data



Quantitative Theory and Modeling of Brain Function

To reveal emergent properties of the brain and provide predictive theoretical frameworks to guide future research

Brain-Inspired Concepts and Designs

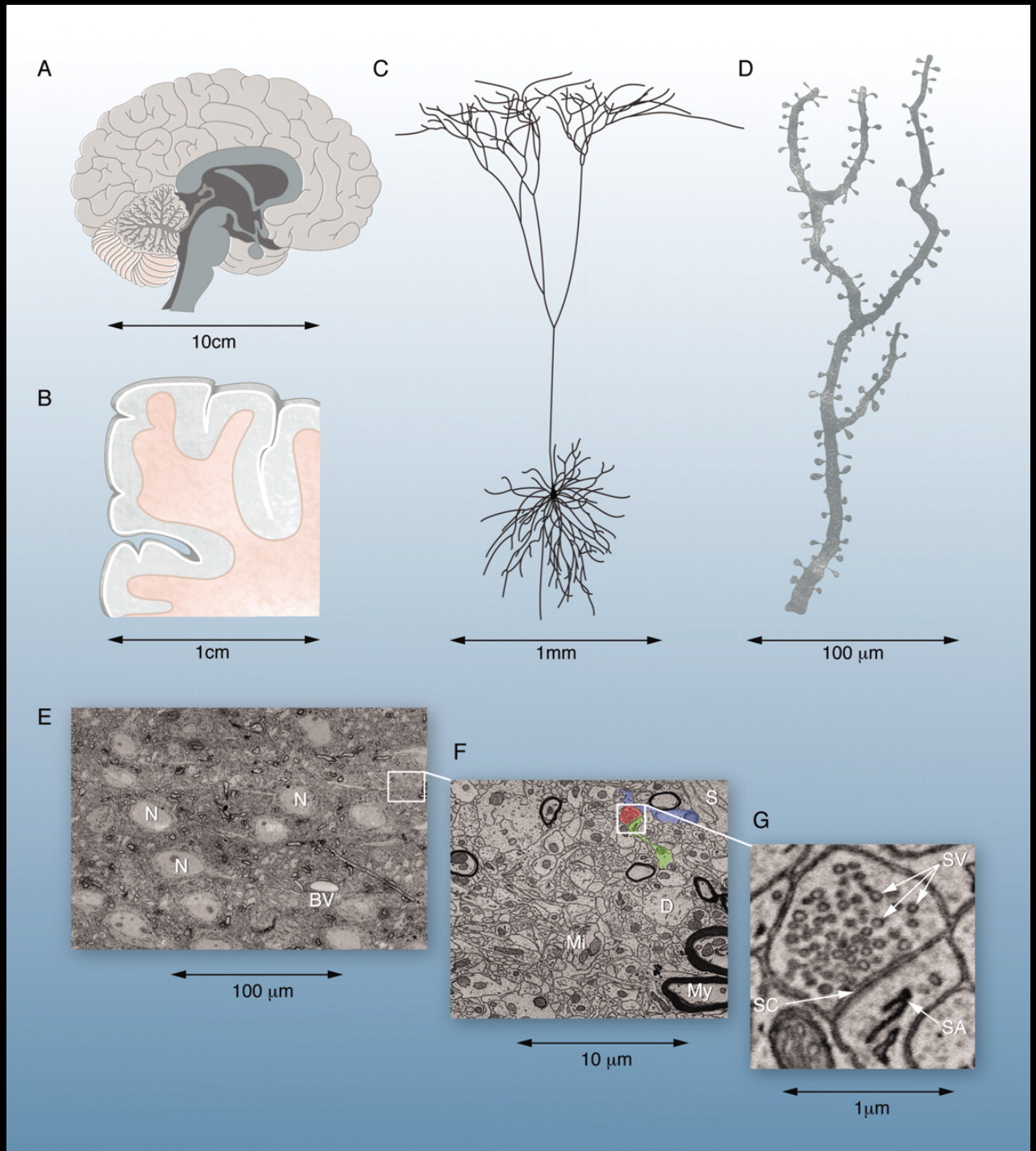
To strategically capitalize on insights gained from BRAIN to inspire novel conceptual paradigms and innovative technologies and designs that will benefit society

BRAIN Workforce Development

To educate a BRAIN workforce and create new career opportunities for BRAIN discovery and innovation

NSF Program Scope

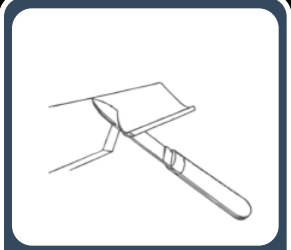
Scales in the brain



Lichtman and Denk 2011

Connectomics Workflow

Tissue Preparation



Sectioning & Wafer Prep

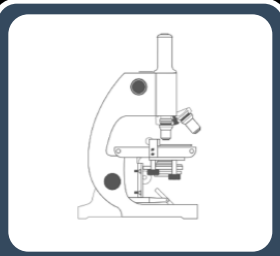
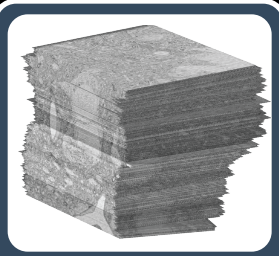
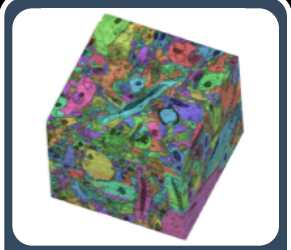


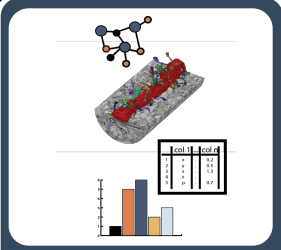
Image Acquisition



Registration



Segmentation & Synapse Detection



Visualization & Analysis

Automated Tape Collection of Slices

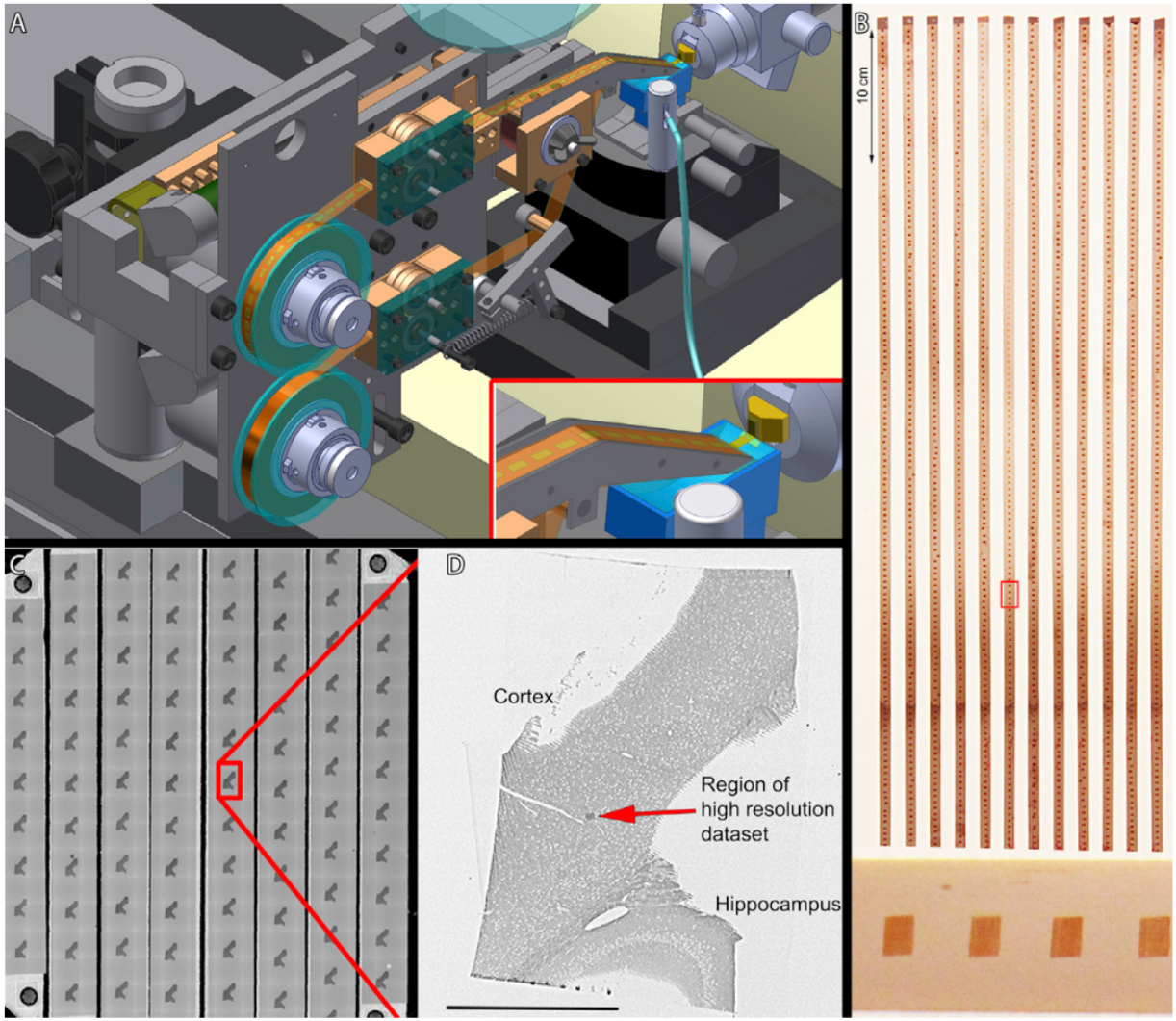


Figure 1. Automatic Tape Collection of Ultrathin Brain Sections

(A) Diagram of the automated tape-collecting ultramicrotome (ATUM). The bottom reel of the ATUM contains a plastic tape that is fed into the knife boat of a diamond knife mounted on a commercial ultramicrotome. The tape is collected on a take up reel (top). (Red inset) Close-up view of the tape conveyor positioned in the knife boat. The diamond knife boat (dark blue) is filled with water (light blue). The diamond knife (green rectangle) is at the opposite end of the knife boat from the taping mechanism. It cuts serial ultrathin sections from tissue embedded in a plastic block. The sections then float on the surface of the water in the knife boat until they adhere to the moving tape (see Movie S1).

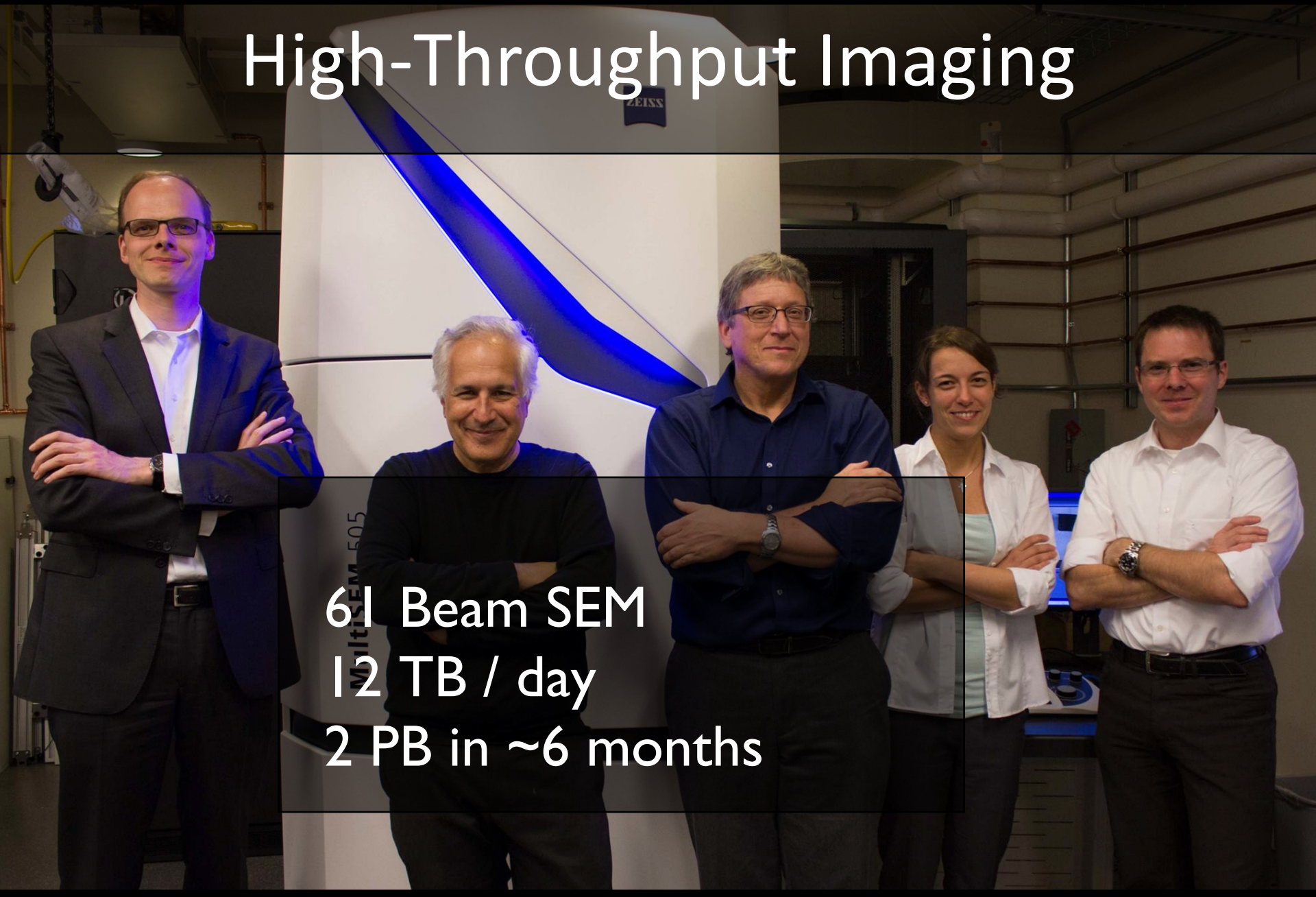
(B) ~10 m of Kapton tape with ~2,000 sections collected. Four of the 29-nm sections (red rectangle) are shown at a higher magnification at the bottom of the panel.

(C) The reel of tape is then cut into individual strips and mounted on silicon wafers for poststaining and/or carbon coating. A low-power scanning electron microscopy image of part of a wafer containing 85 brain sections is shown. One of the sections (red rectangle) is shown at a higher magnification in the next panel.

(D) One 29-nm section containing neocortex and hippocampus. The region that was studied at high resolution is the dark-looking box (red arrow). Scale bar, 1 mm.

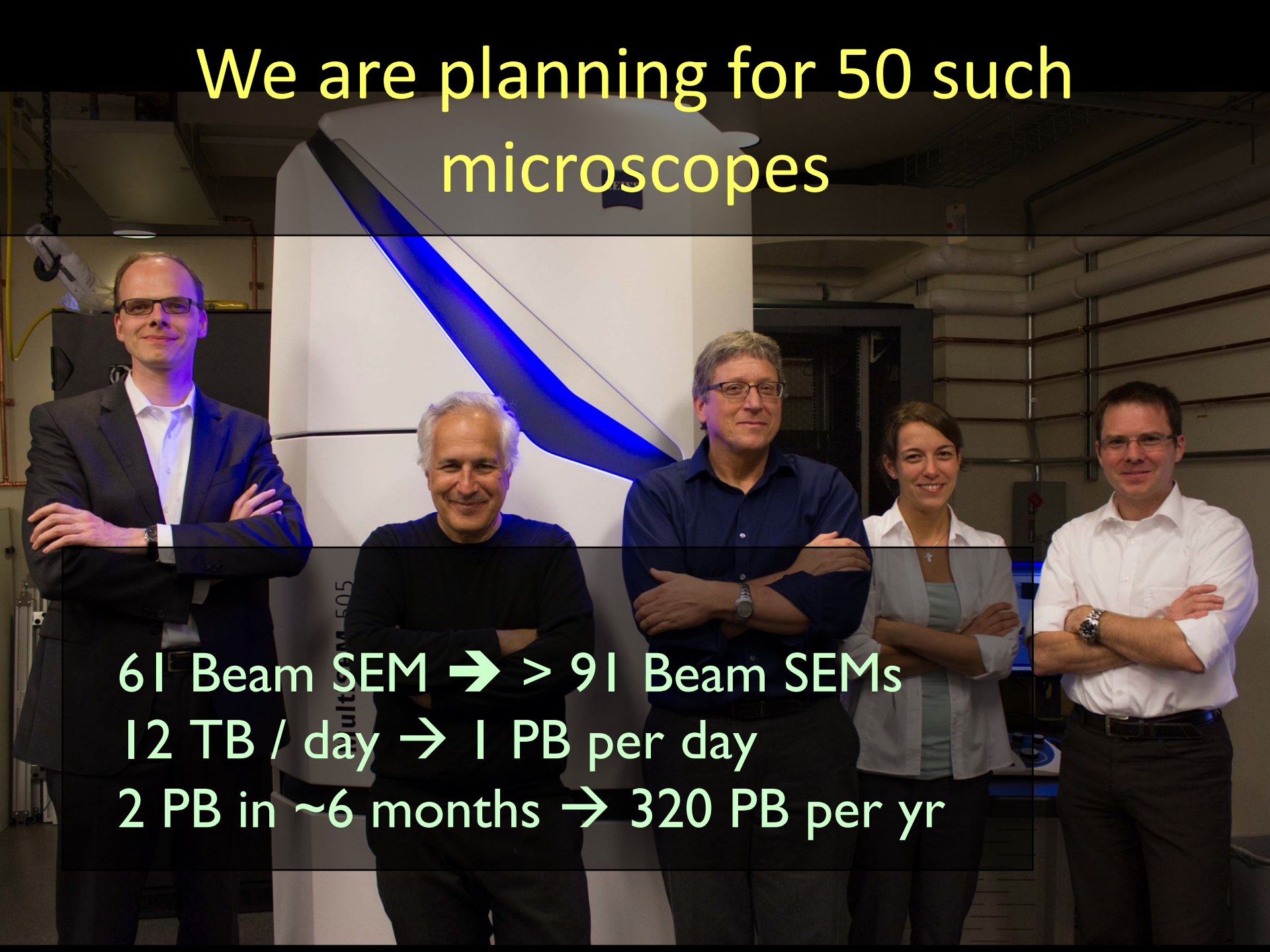
See also Movie S1.

High-Throughput Imaging

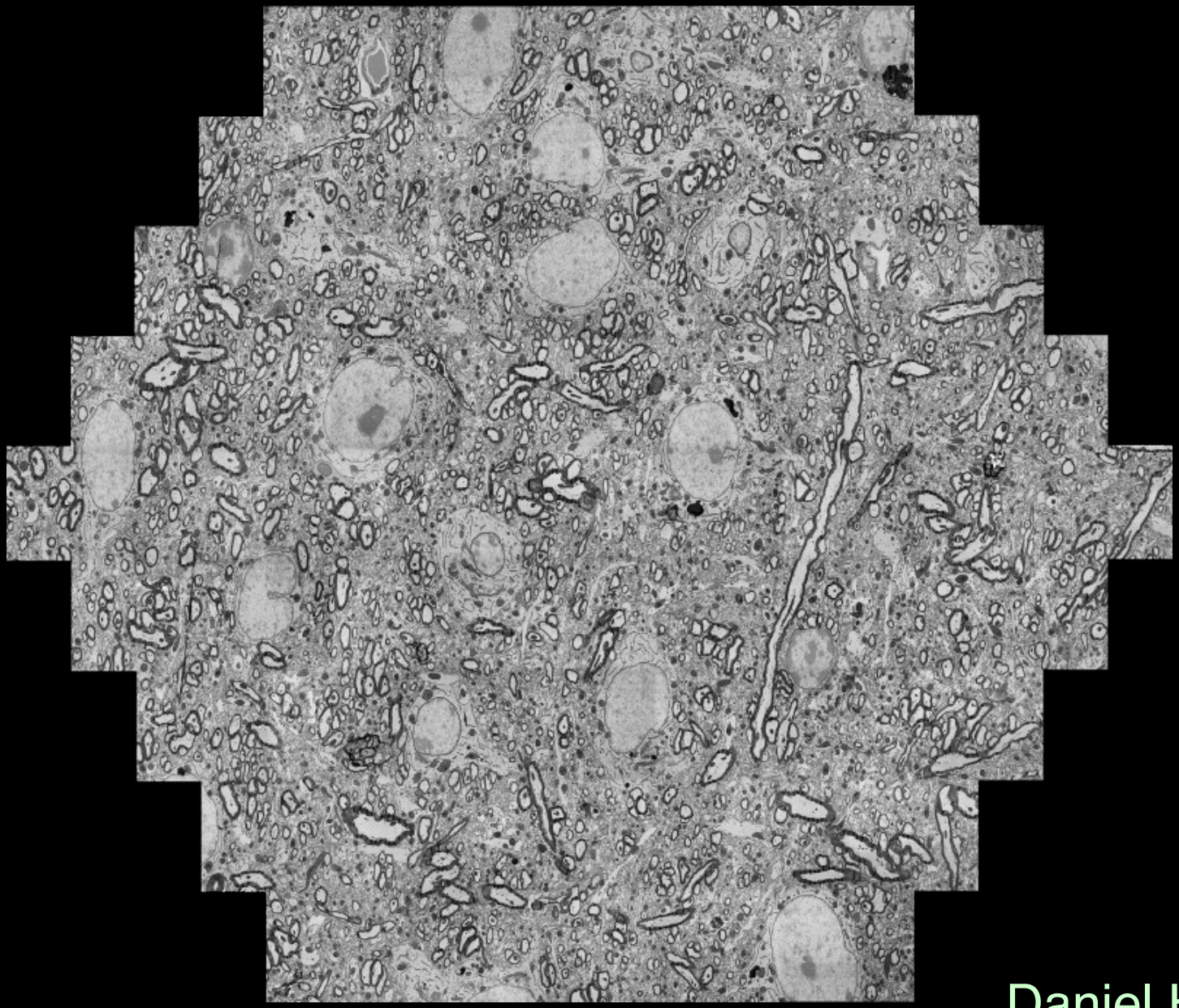


61 Beam SEM
12 TB / day
2 PB in ~6 months

We are planning for 50 such microscopes

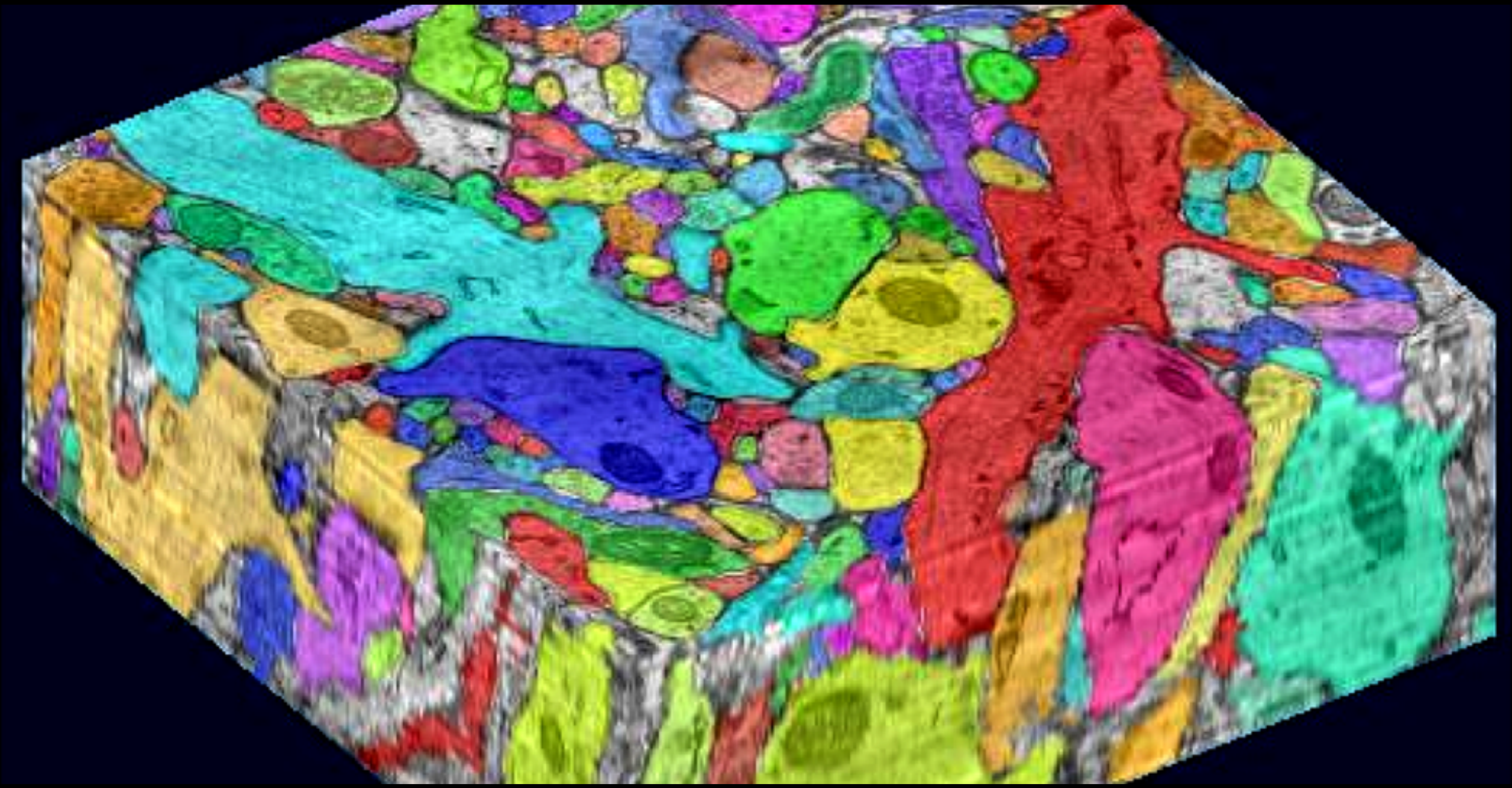


61 Beam SEM → > 91 Beam SEMs
12 TB / day → 1 PB per day
2 PB in ~6 months → 320 PB per yr



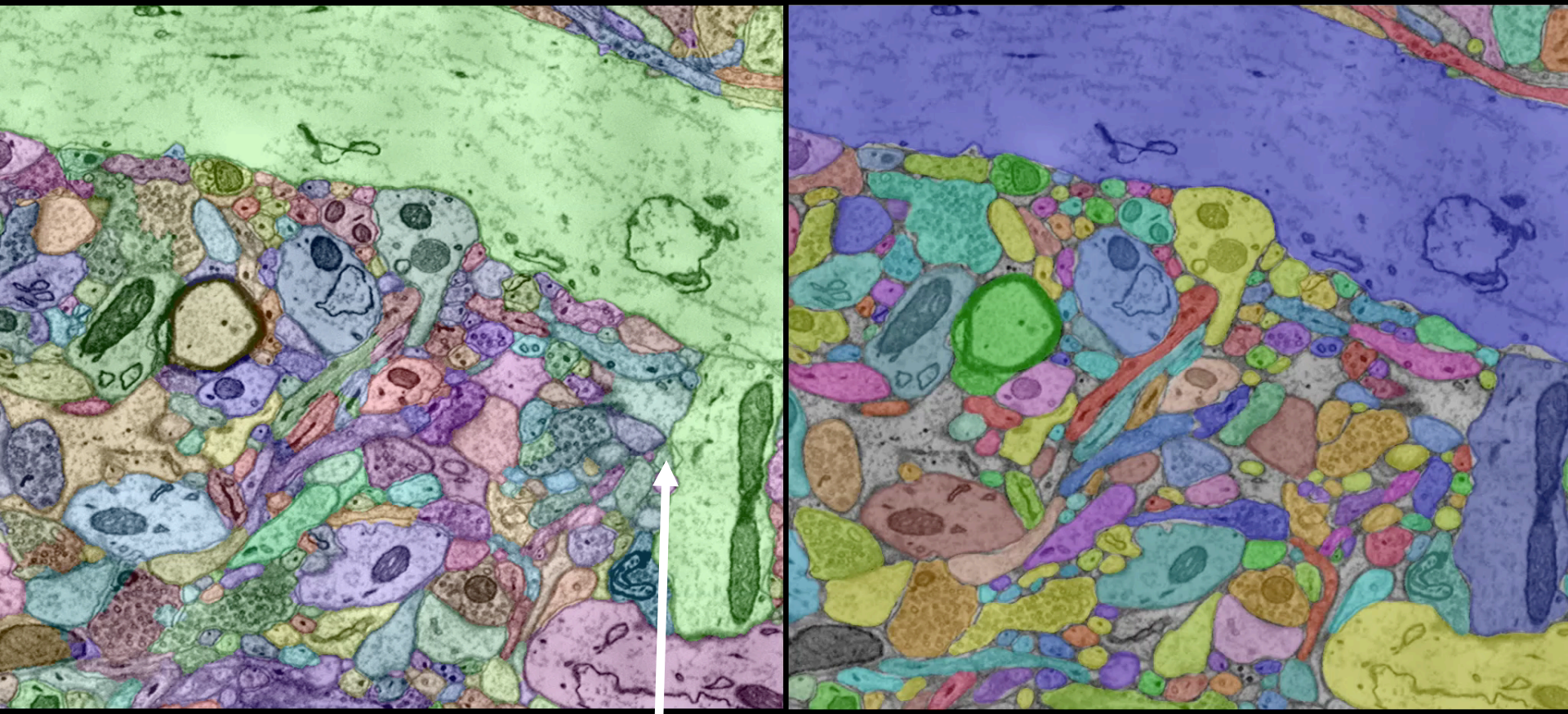
Daniel Haehn

Stack Many Slices (each ~30nm thick)



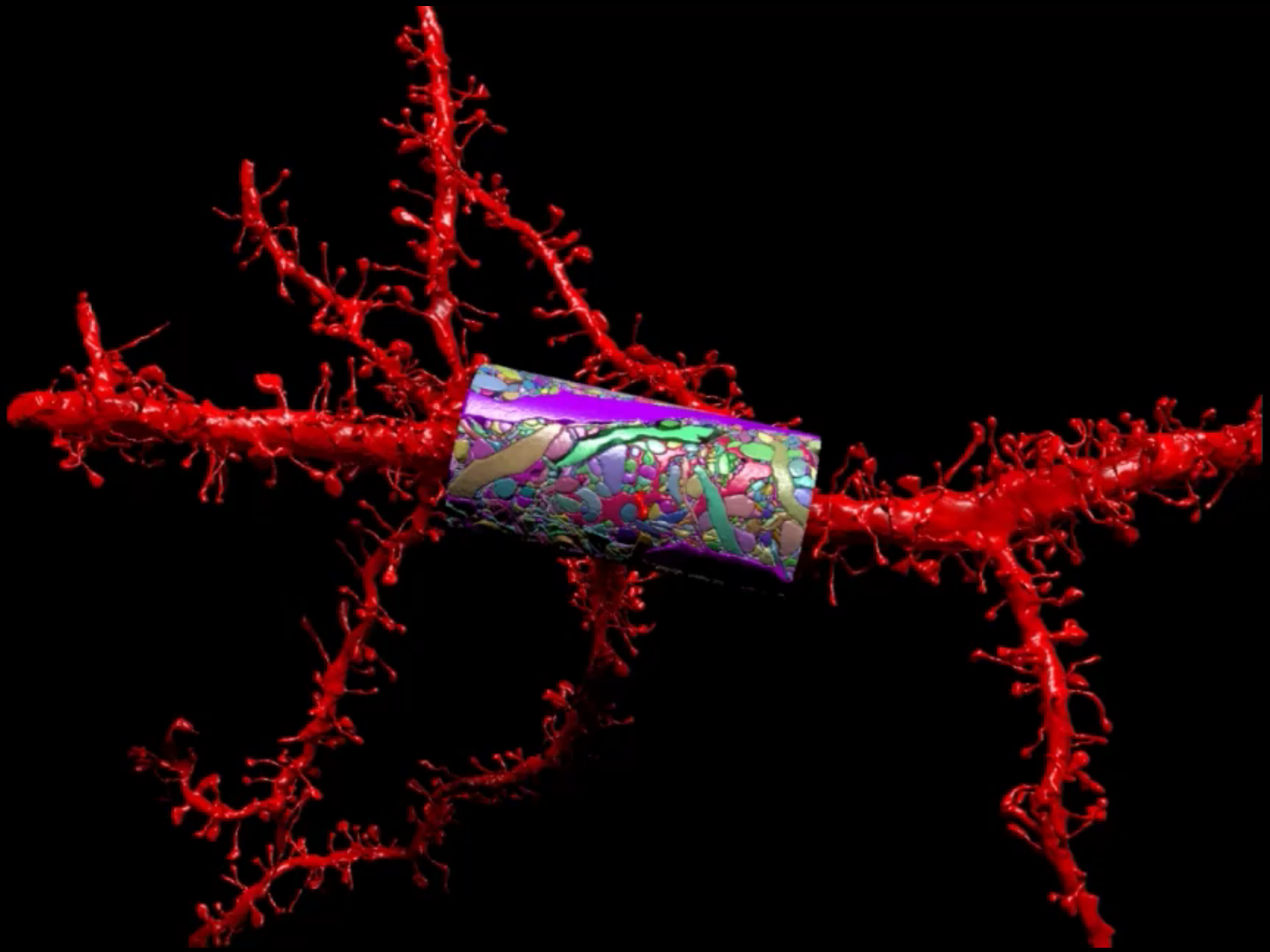
13.7 million cell profiles in 1,850 slices

Fully automatic (RhoANA) Hand segmentation (VAST)

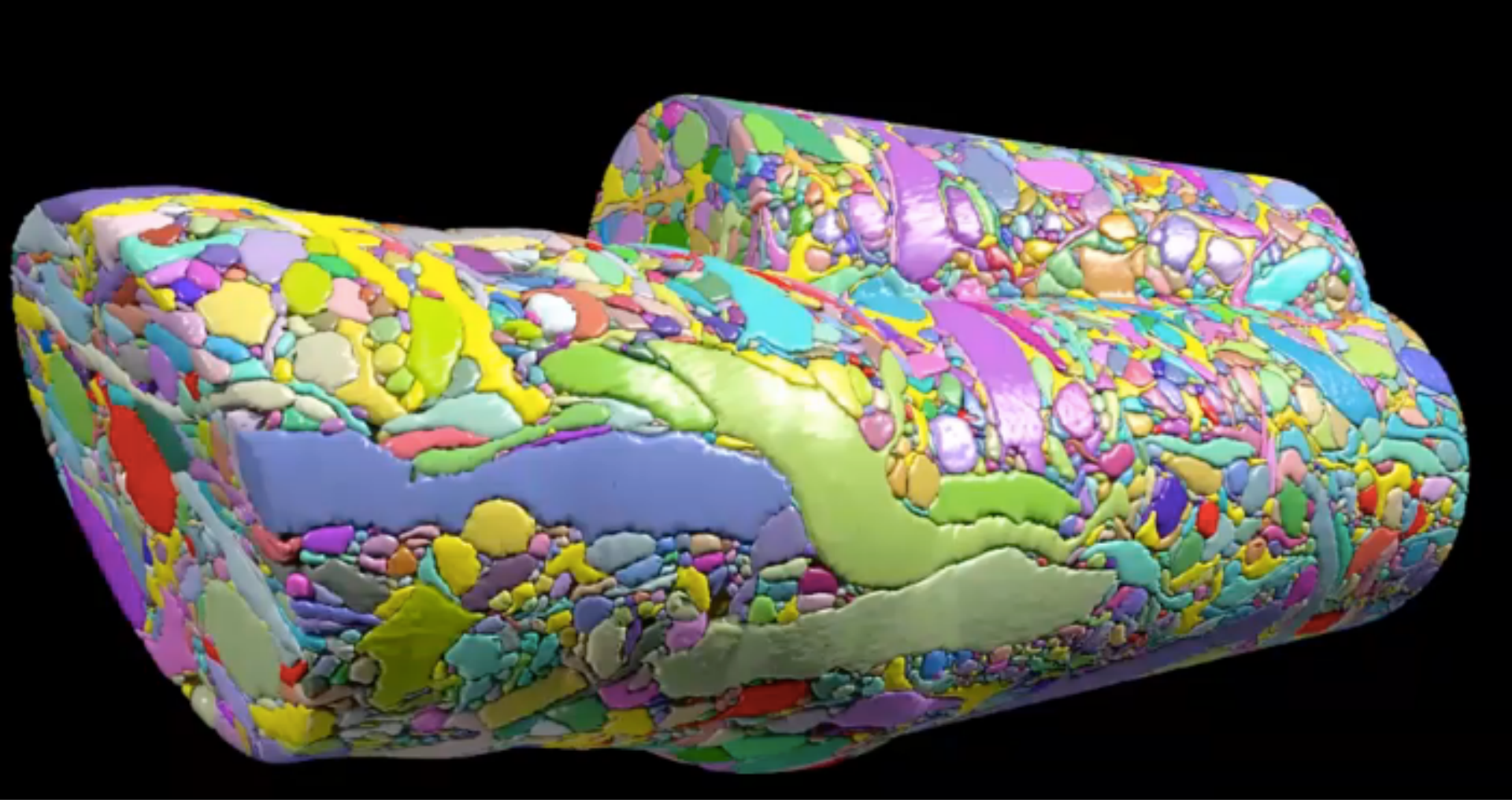


Kasthuri et al., Cell 2015
Knowles-Barley et al.

Progress on the (micro) Connectome

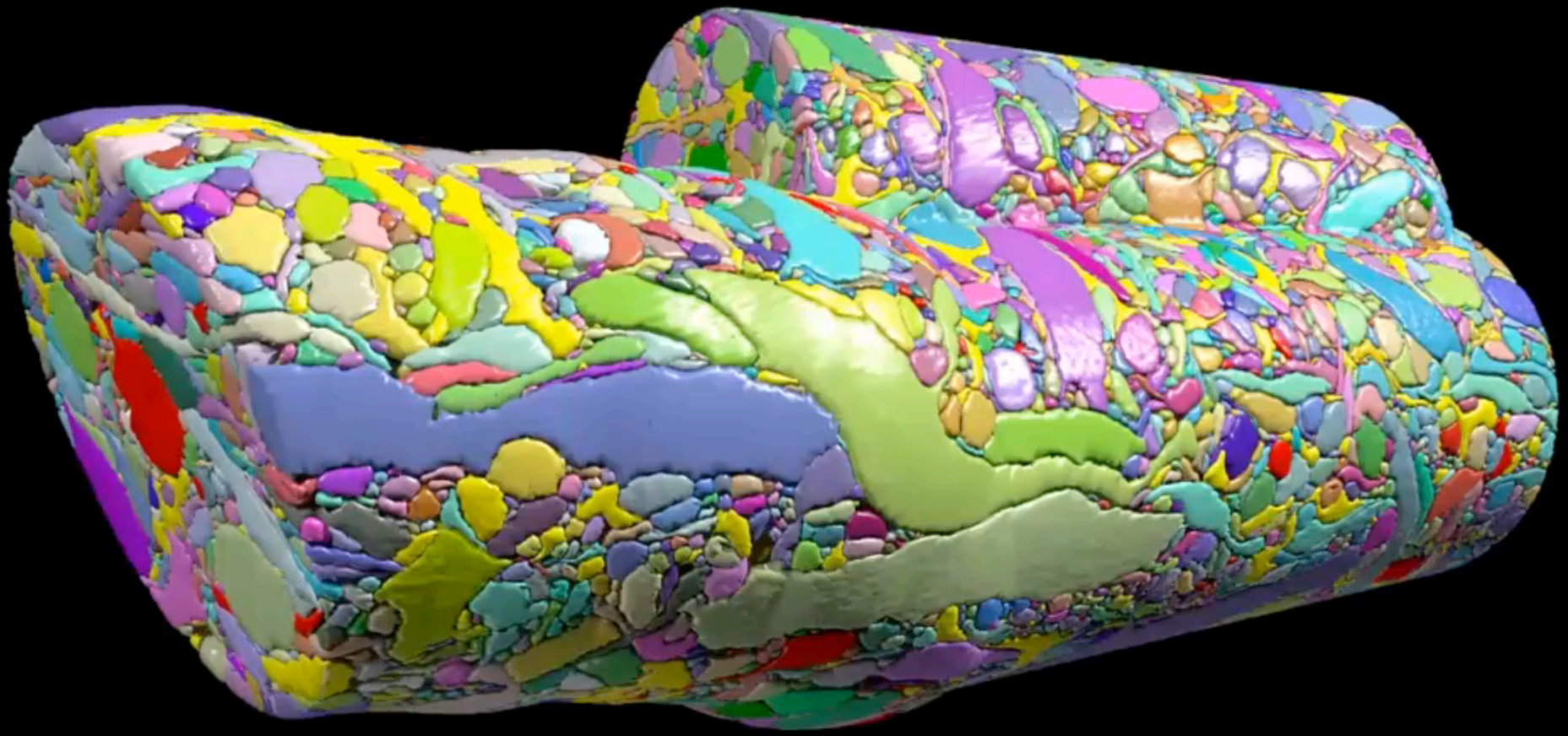


Bobby Kasthuri, et. al. Argonne, UChicago and Harvard



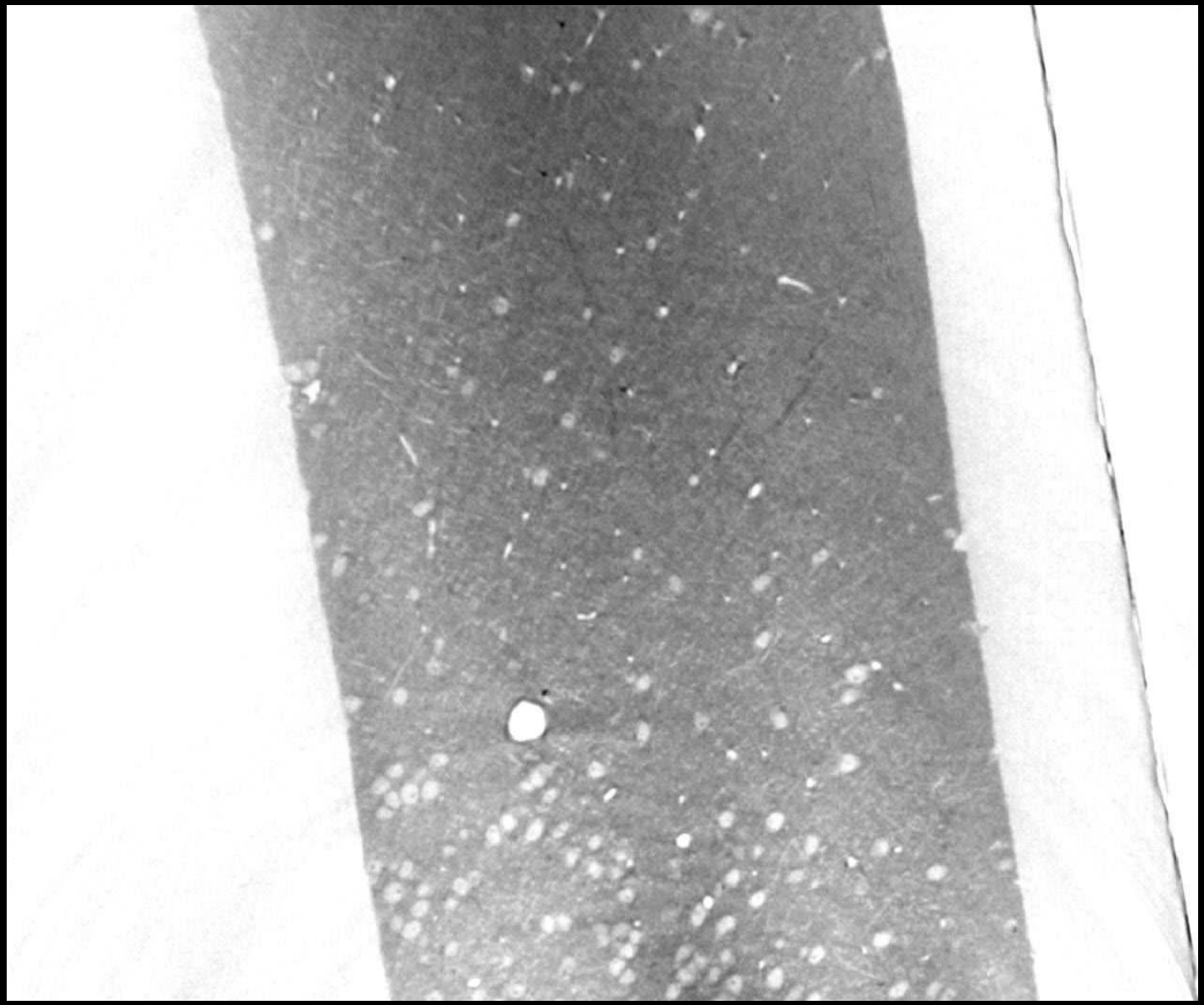
2 person-years
1500 μm^3
1/666,666th of 1 mm^3

Kasthuri et al., Cell 2015



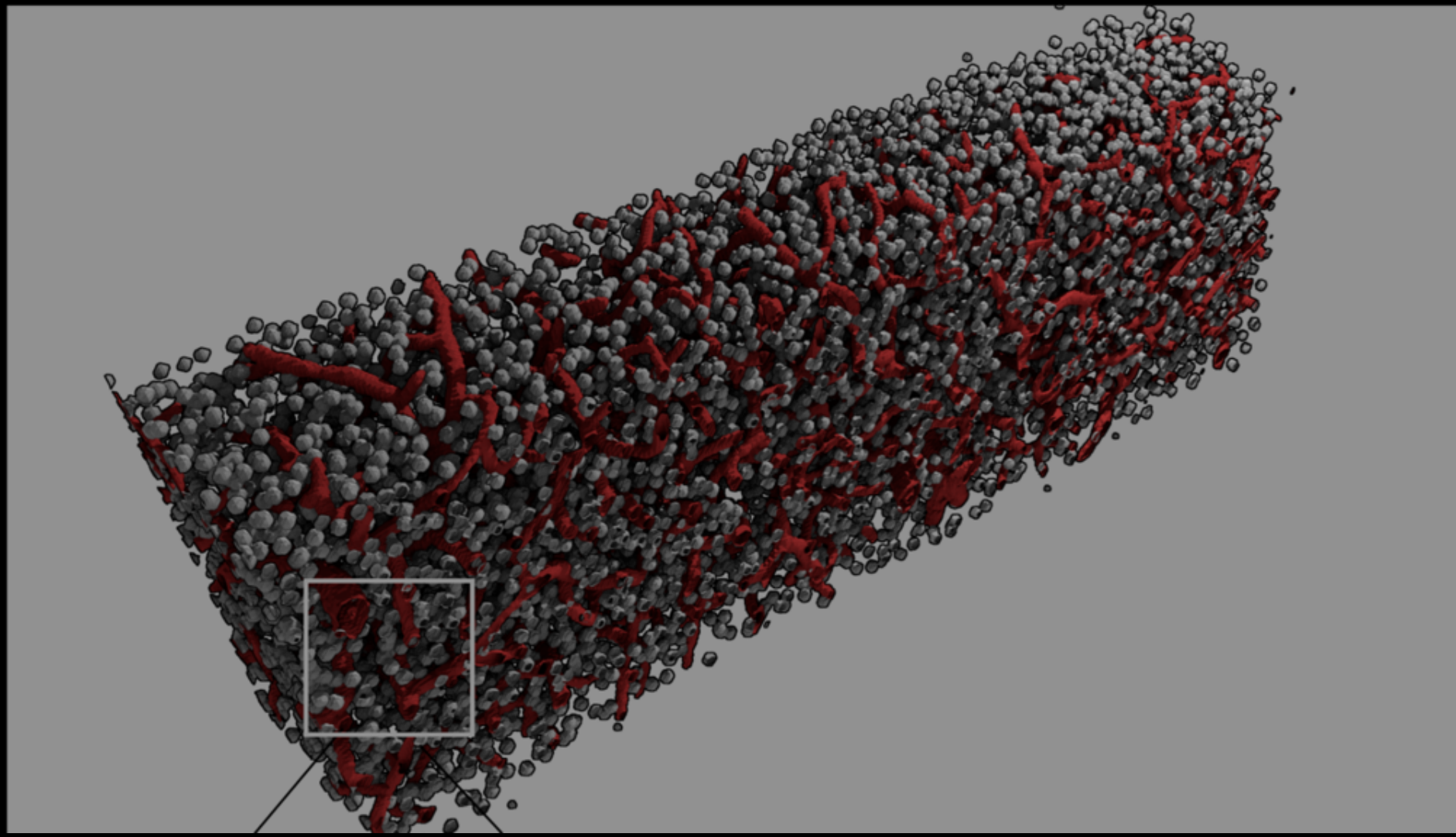
Kasthuri et al., Cell 2015

APS and X-Rays for Connectome

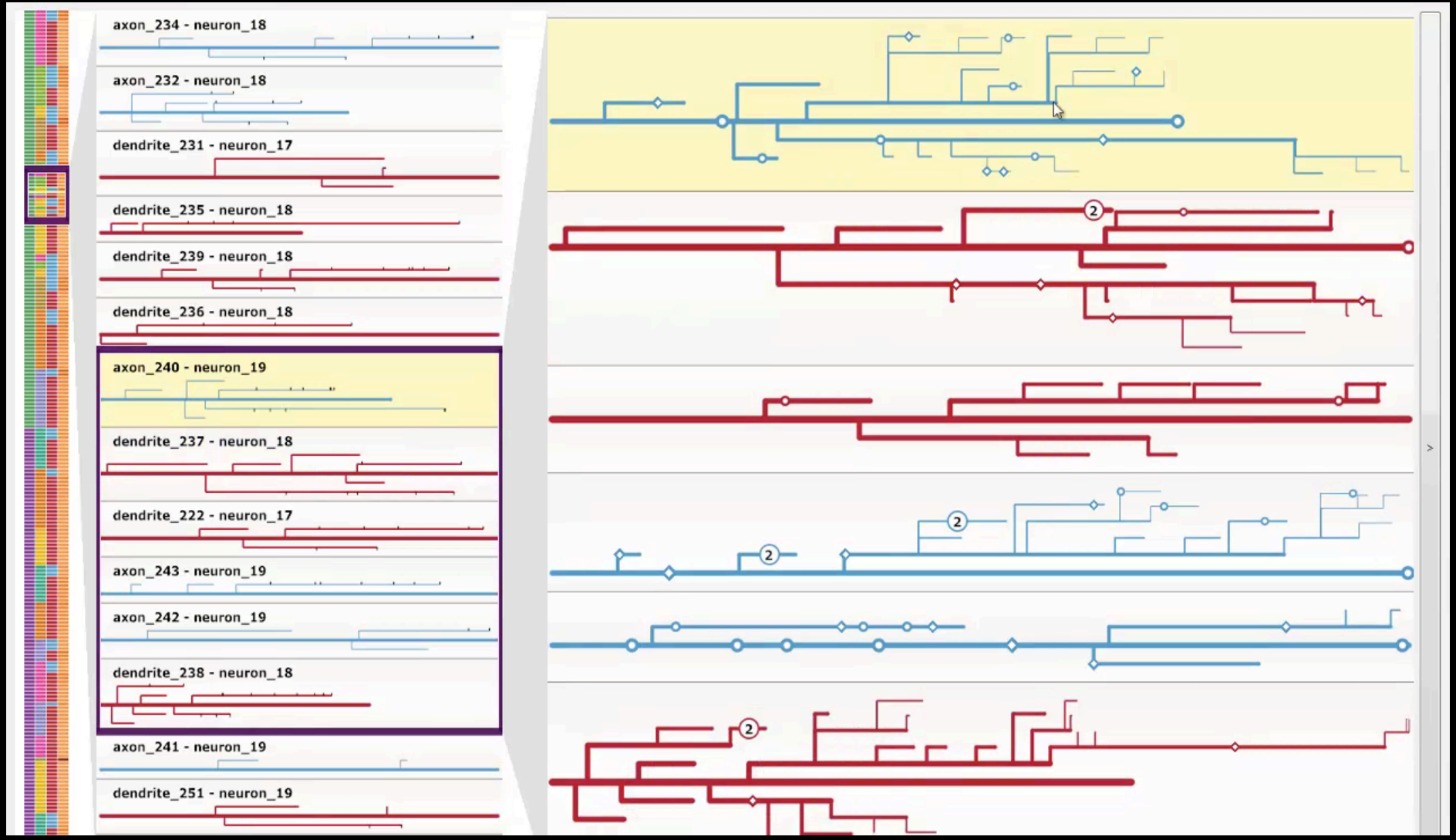


Kasthuri et. al. Argonne

In-situ Reconstruction via X-ray Tomography



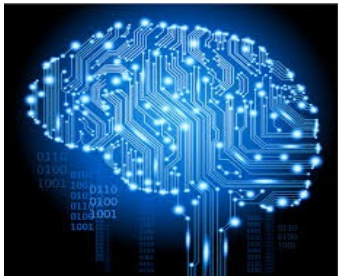
NeuroLines – Neuronal Connectivity Analysis



Al-Awami et al., TVCG 2014

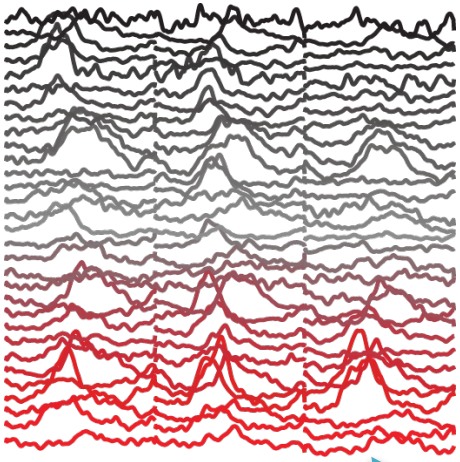
DOE Contributions to BRAIN

ASCR can play a unique role in BRAIN computing through advances in applied mathematics and computer science together with HPC facilities.



Function

dynamic data

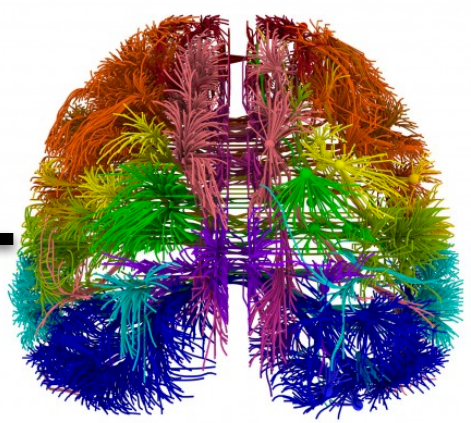


Theory & Models

abstractions

Structure

static data



Generation and analysis of raw data

Linking structure to function is a ‘grand challenge’ in general biology and materials

Acknowledgements

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