SEAB TASK FORCE REPORT

ON BIOMEDICAL SCIENCES

September 22, 2016

Steven Koonin & Harold Varmus
Co-chairs

CHARGE TO SEAB FROM SECRETARY MONIZ

(November 21, 2015)

"…form a new Task Force to identify:

- New areas for research by DOE investigators that could… significantly advance the pace of progress in biomedical sciences.

- New mechanisms for conducting research in coordination with scientists from government laboratories (both DOE and the NIH), universities, academic medical centers and industry…."

By September 2016, the Task Force should produce a report…
available to the public, Congress, & the current and next Administration.

TASK FORCE MEMBERS

Steven Koonin* (co-chair), NYU
Harold Varmus* (co-chair), Cornell Med
Drew Endy, Stanford
Stuart Feldman, Schmidt Fund
Paula Hammond*, MIT
David Haussler, UCSC
Markus Meister, CalTech
David Piwnica-Worms, MD Anderson
Martha Schlicher*, Malinckrodt

WORKSHOPS

NYU Center for Urban Science, March 10-11, 2016
LBNL, Berkeley CA, July 18-19, 2016

PREMISES

- Biomedical sciences are vital to the nation
- Biomedical research depends on many disciplines
- Scientific responsibilities and agencies are imperfectly aligned
- Relevant technologies could be developed more efficiently
- Despite cultural differences, DOE and NIH are well suited to form partnerships

CULTURES OF THE TWO AGENCIES AND A BRIEF HISTORY OF INTERACTIONS

DOE

- Mission-driven activities
- Technology: primary mission
- Physical sciences
- Large team science (National Labs, Hubs, User Facilities, ARPA-E)
- Service to other agencies

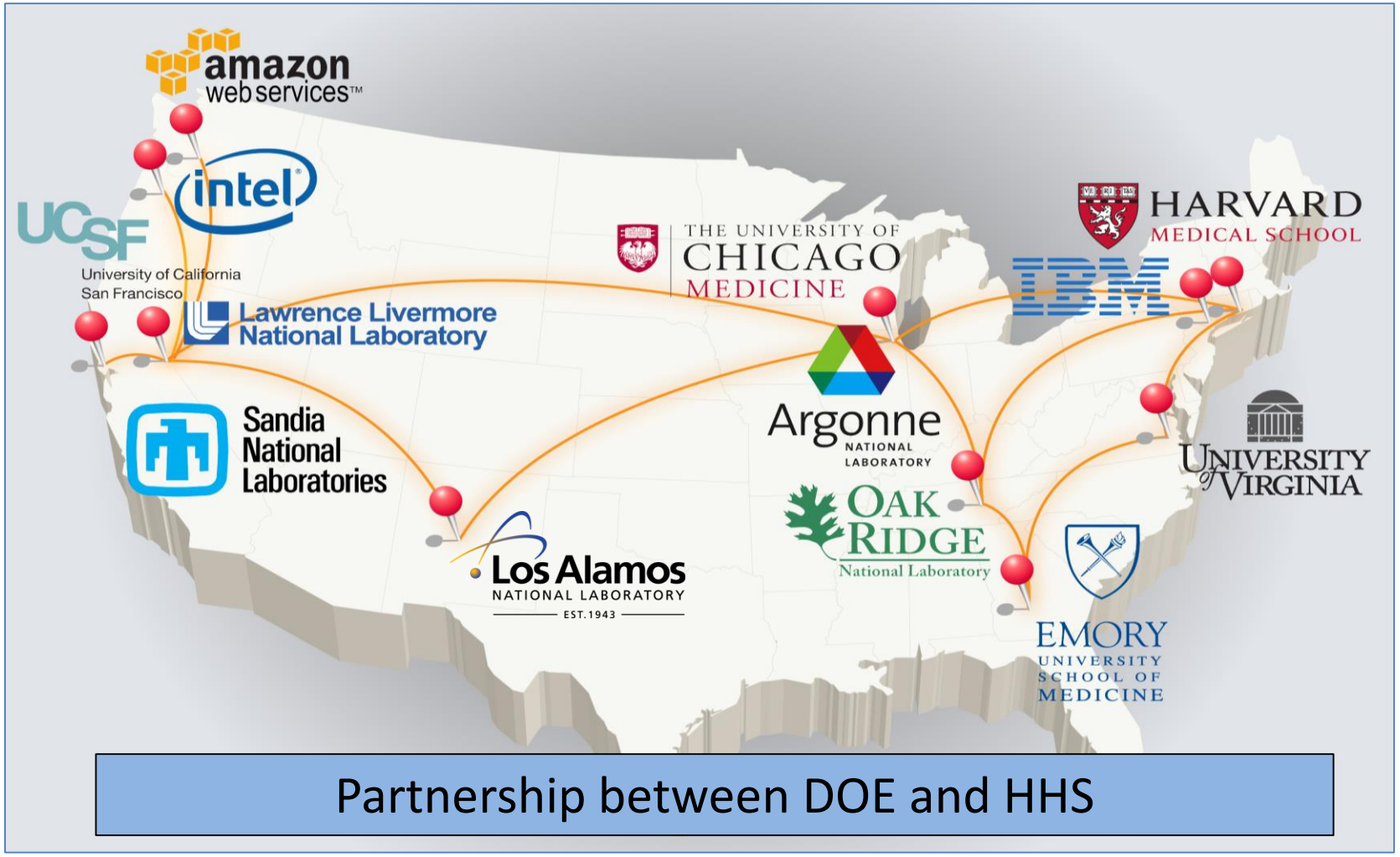
NIH

- Largely investigator-initiated, public health goals
- Technology: secondary
- Biology and medicine, plus other disciplines
- Individual labs, small teams
- Extramural:Intramural = 10:1
- Large training component

COLLABORATIVE HISTORY:

- Human Genome Project
- DOE beam lines for structural biology
- Contributions to BRAIN, Precision Medicine…
- Other co-funded projects and plans

Initiative to build a national partnership in high performance computing and life sciences



CENTRAL MESSAGE

"With increasing recognition of the utility of DOE-supported technologies in biomedical research and the announcements of national goals for biomedicine, this is an appropriate time to propose the kinds of mechanisms that would make synergistic interactions between the agencies more frequent, less complicated, and more productive."

CENTRAL GOALS

Expand the utility of DOE capabilities,
enhance the range and speed of NIH discoveries,
broaden perspectives in both agencies,
help to meet nation's scientific goals….

WHERE US GOVERNMENT GOALS FOR MEDICAL SCIENCE CONNECT WITH DOE CAPABILITIES

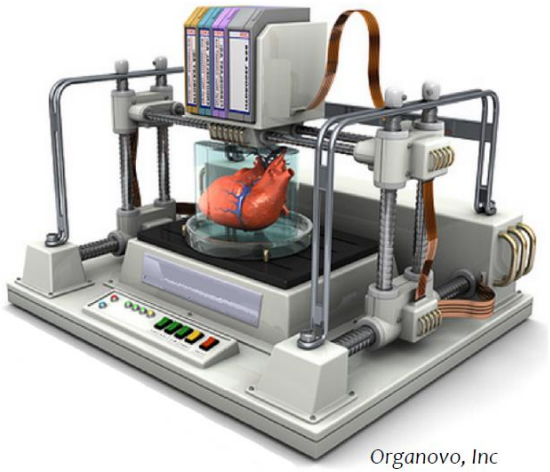
Administration's Biomedical Initiatives:

- BRAIN
- Precision Medicine
- Cancer Moonshot
- Alzheimer's Disease
- Microbial drug resistance

Wide Expanse of Modern Research in Biology and Medicine:

- Data analysis and management; simulations, etc.
- Measurements: instruments, sensors, fabrication…
- Images (large and small scale)
- Materials for study, drug delivery, etc
- High throughput methods (genomics, etc)
- Radiobiology and biothreats
- Health care delivery practices

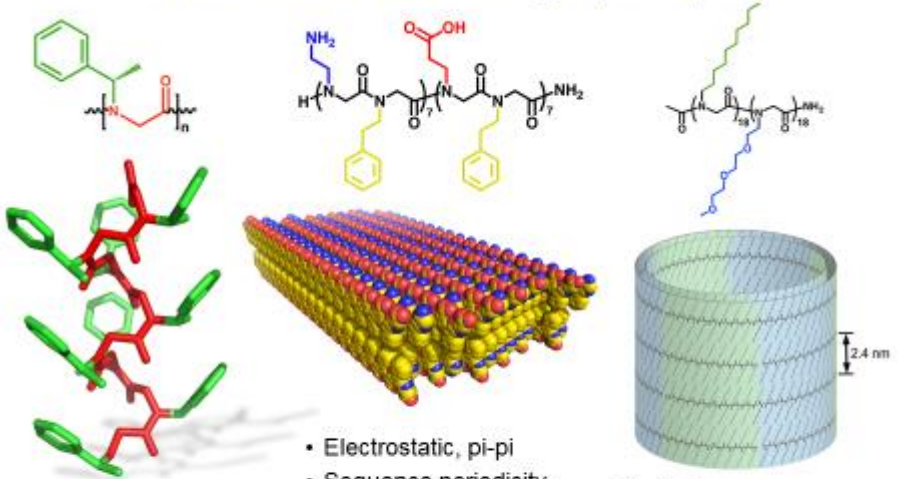
Materials science



Organovo, Inc

- Generate realistic tissue models with 3D geometry
- Scalable to larger tissue constructs
- Reproducible & automated technology
- Precision positioning of cells

Nanoarchitecture design principles



- Steric congestion
- Sidechain chirality

Helix

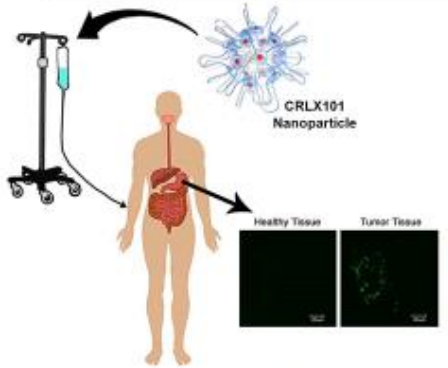
- Electrostatic, pi-pi
- Sequence periodicity
- Sigma strand
- Tiling

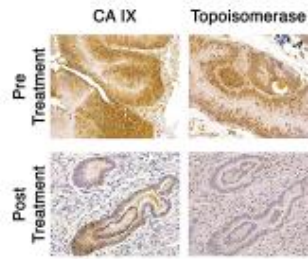
Sheet

- Size & shape congruence
- Chemically dissimilar blocks
- Tiling

Tube

Properly Designed Nanoparticles Can Function as Designed in Humans





Therapeutic Inhibits Intended Targets in Tumors of Humans

CRLX101 nanoparticles localize in human tumors and not in adjacent, nonneoplastic tissue after intravenous dosing

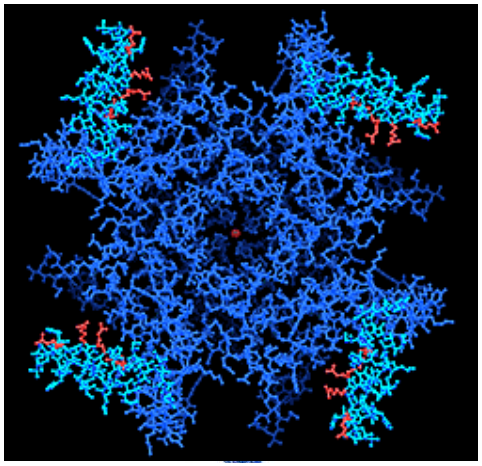
Andrew J. Clark[a], Devin T. Wiley[a], Jonathan E. Zuckerman[a,b], Paul Webster[c], Joseph Chao[d], James Lin[e], Yun Yen[f,1], and Mark E. Davis[a,1]

[a]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125; [b]Department of Pathology and Laboratory Medicine, University of California, Los Angeles, CA 90095; [c]Oak Crest Institute of Science, Pasadena, CA 91103; [d]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA 91010; [e]Division of Gastroenterology, City of Hope Comprehensive Cancer Center, Duarte, CA 91010; and [f]Graduate Institute for Cancer Biology and Drug Discovery, Taipei Medical University, Taipei 11031, Taiwan

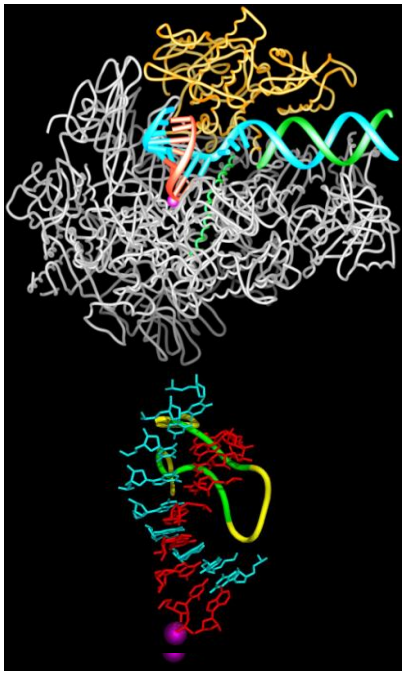
3850-3854 | PNAS | April 5, 2016 | vol. 113 | no. 14

Impact of Synchrotron Structural Biology - Enabling Nobel Prize Winning Research

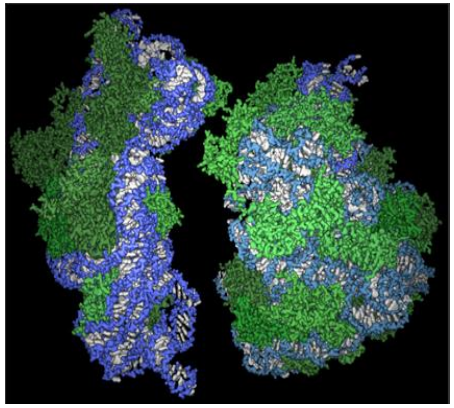
Membrane Channels, Polymerase, Ribosome, GPCRs



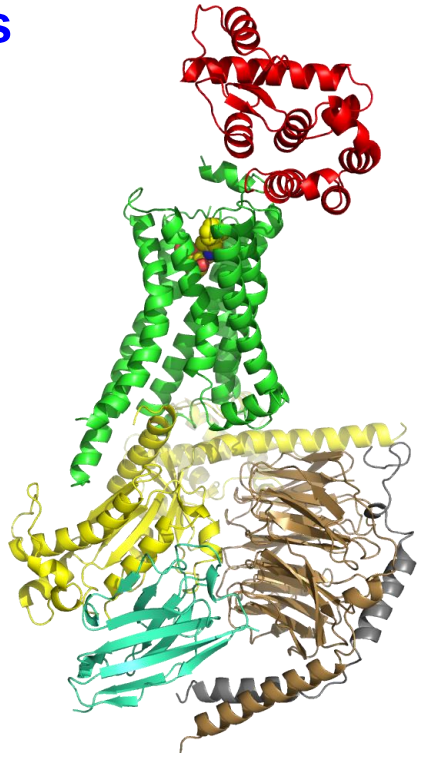
Roderick MacKinnon and Peter Agre – 2003 – K+ channel (KcsA)



Roger Kornberg – 2006 - RNA Polymerase II



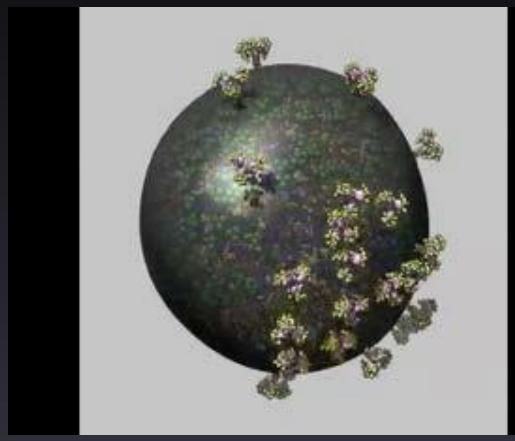
Venki Ramakrishnan, Thomas Steitz and Ada Yonath – 2009 - Ribosome

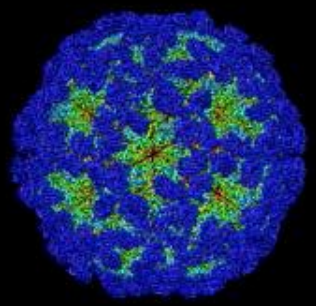


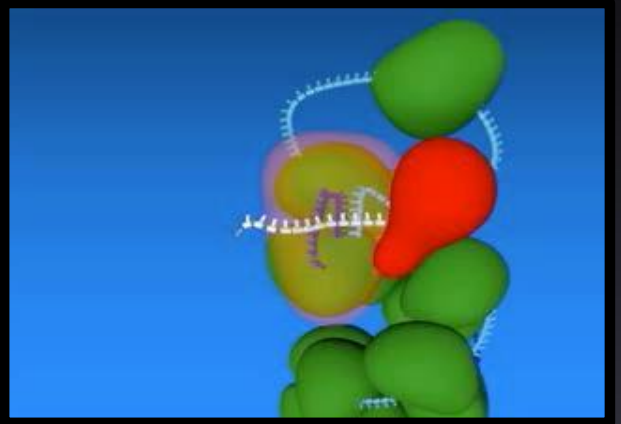
Brian Kobilka and Robert Lefkowitz – 2012 – β_2AR- beta adrenergic receptor

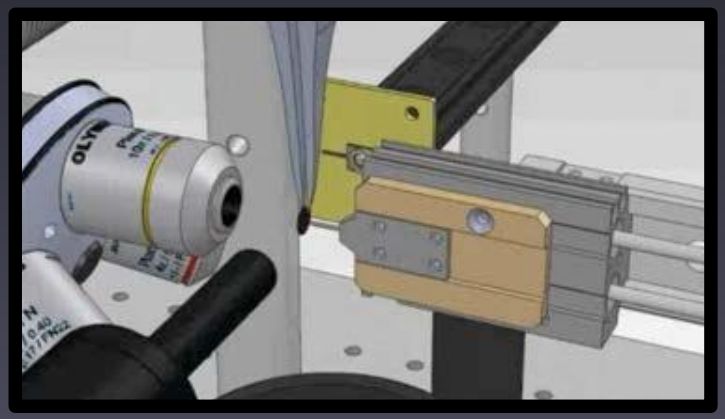
Most challenging class of problems (often requiring significant effort and time) but yielding remarkable 'atomic level/chemical' insights into some of the most important processes in biology)

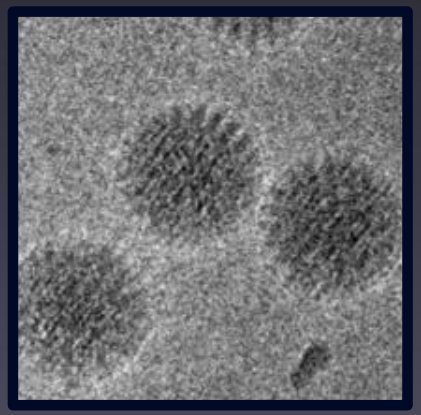
Using EM to Understand the Dynamics of Molecular Machines

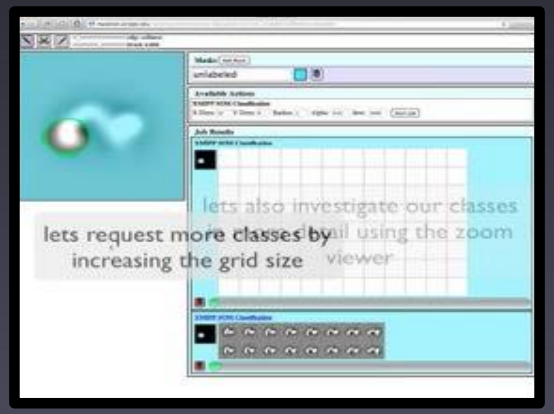












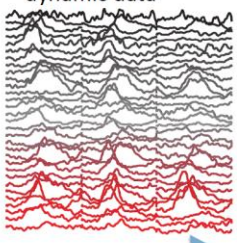
NEW YORK STRUCTURAL BIOLOGY CENTER
Simons Electron Microscopy Center

Computational and data sciences

Possible DOE computing role in BRAIN

DOE 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

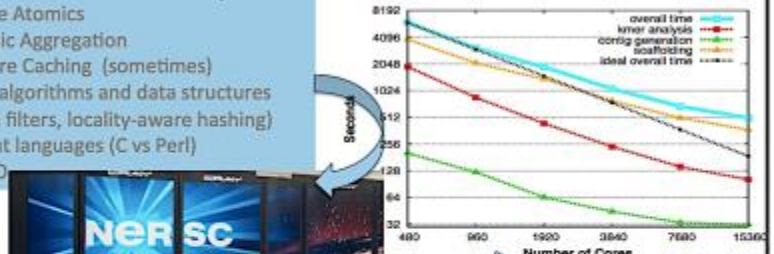
Linking structure to function is a 'grand challenge' in general biology and materials

"HiP-mer" high performance assembler

JGI

Computer Science HPC Expertise

- Remote Atomics
- Dynamic Aggregation
- Software Caching (sometimes)
- Clever algorithms and data structures (bloom filters, locality-aware hashing)
- Efficient languages (C vs Perl)
- Fast I/O

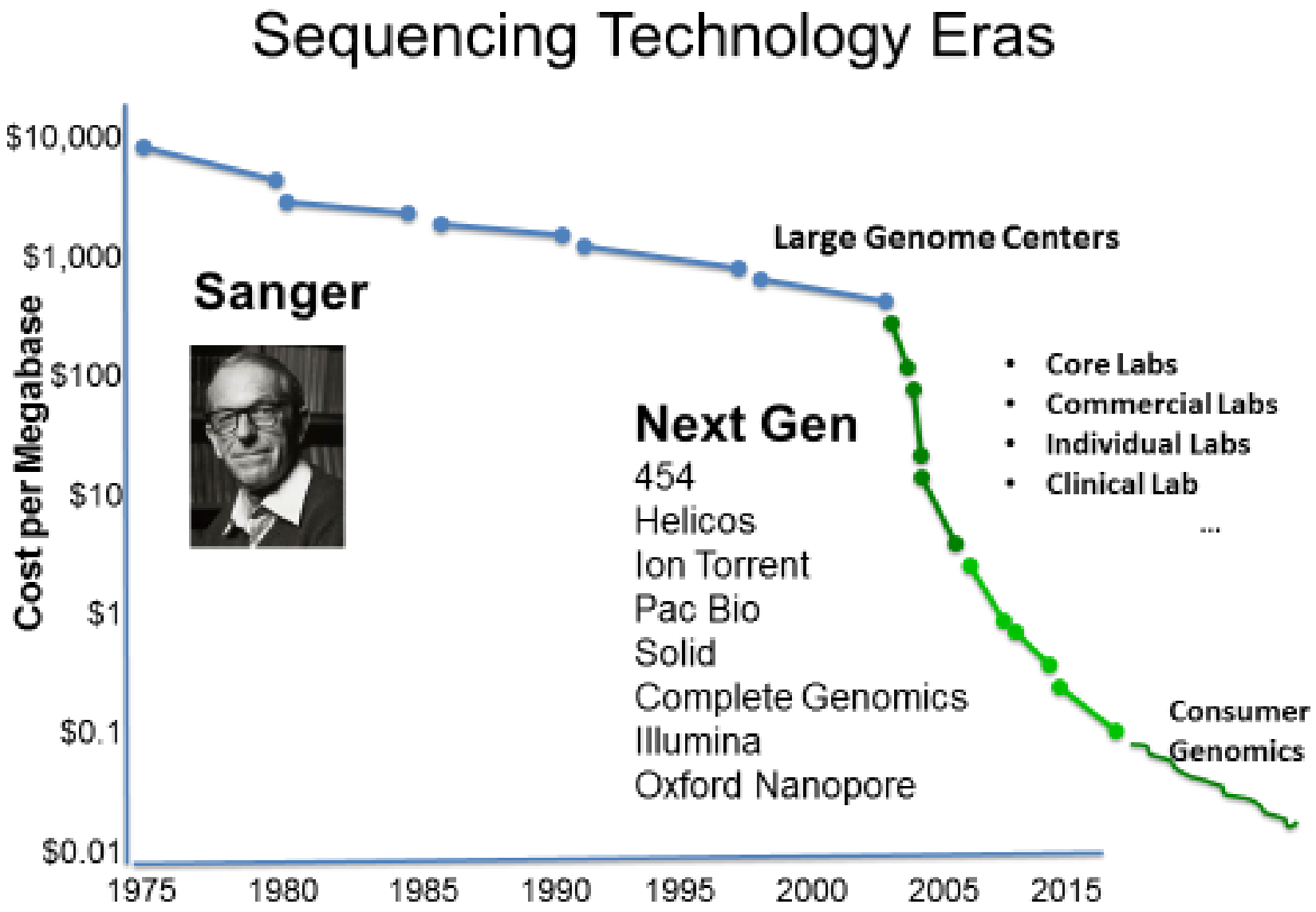


HPC systems with high speed interconnect networks

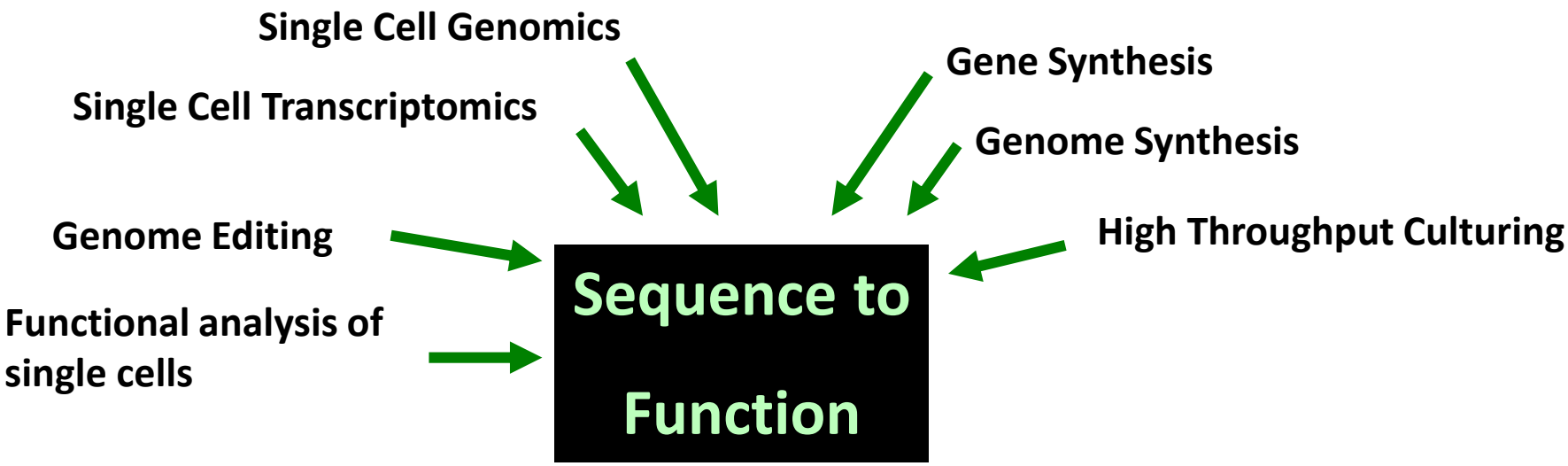
Grad student + software engineers needed to get to production

De novo Human genome assembly in 8 minutes! (15,000 cores)
Enables assembly of wheat (6x size of human!) in 40 minutes

DNA science

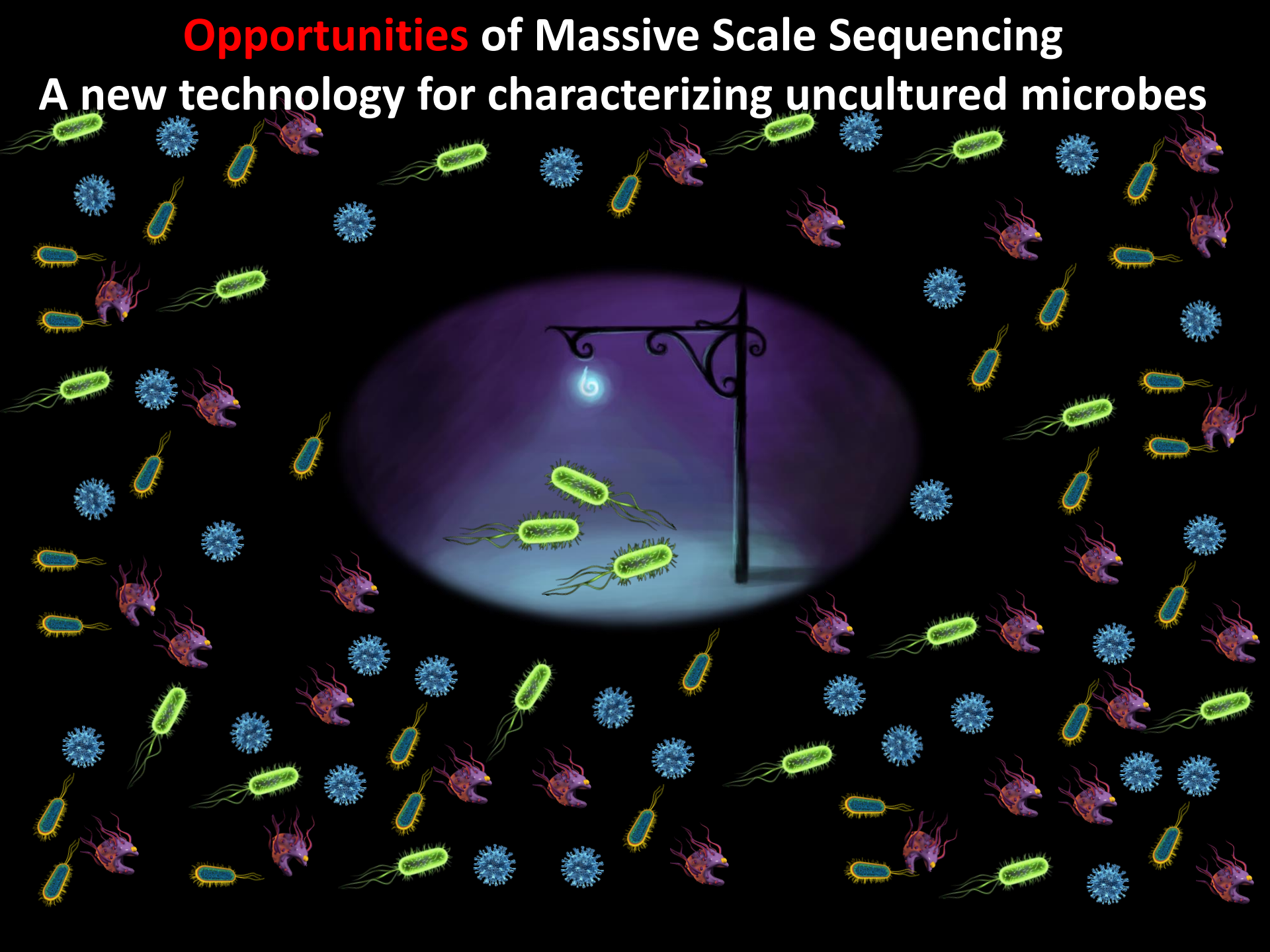

Sequencing Technology Eras
$10,000
$1,000
$100
$10
$1
$0.1
$0.01
Cost per Megabase
1975
1980
1985
1990
1995
2000
2005
2015
Sanger
Large Genome Centers
Next Gen
454
Helicos
Ion Torrent
Pac Bio
Solid
Complete Genomics
Illumina
Oxford Nanopore
• Core Labs
• Commercial Labs
• Individual Labs
• Clinical Lab
...
Consumer Genomics

Genomic Sequence to Function: Capabilities

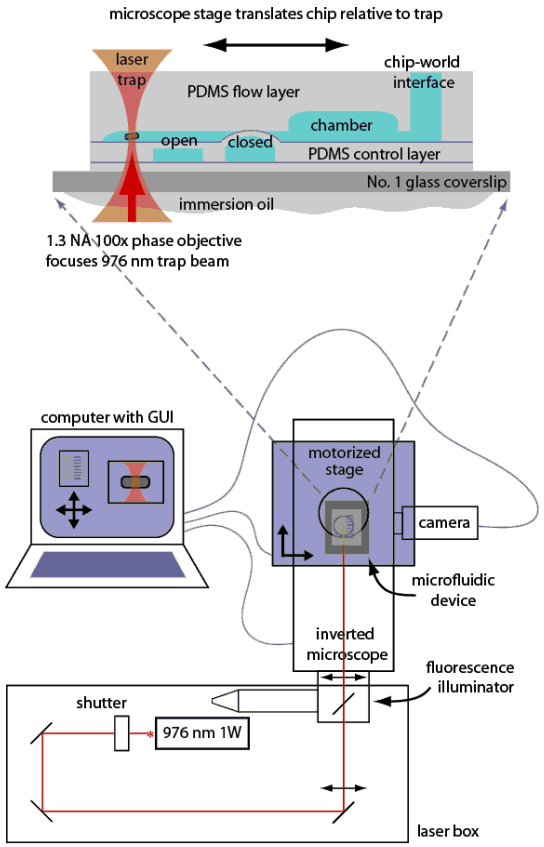


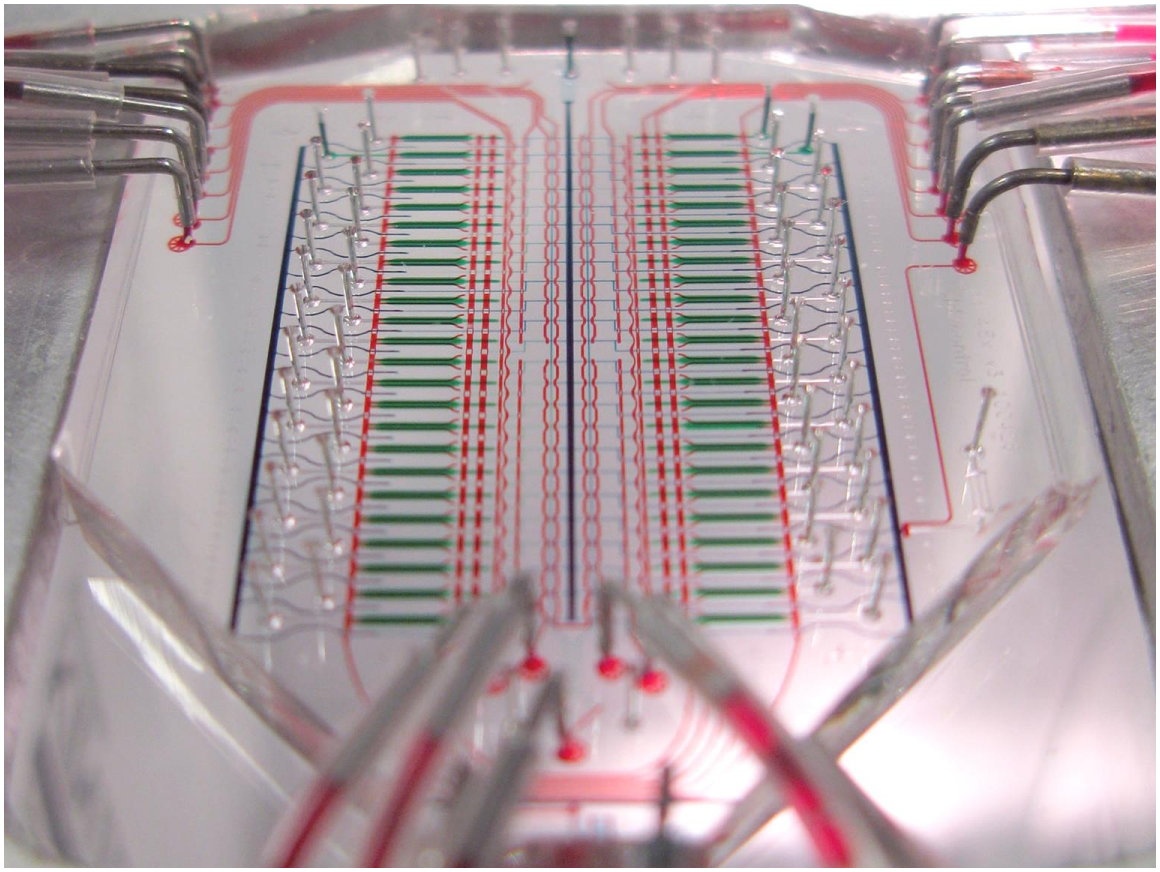
Opportunities of Massive Scale Sequencing

A new technology for characterizing uncultured microbes



micro-optofluidic cell sorter & MDA amplifier



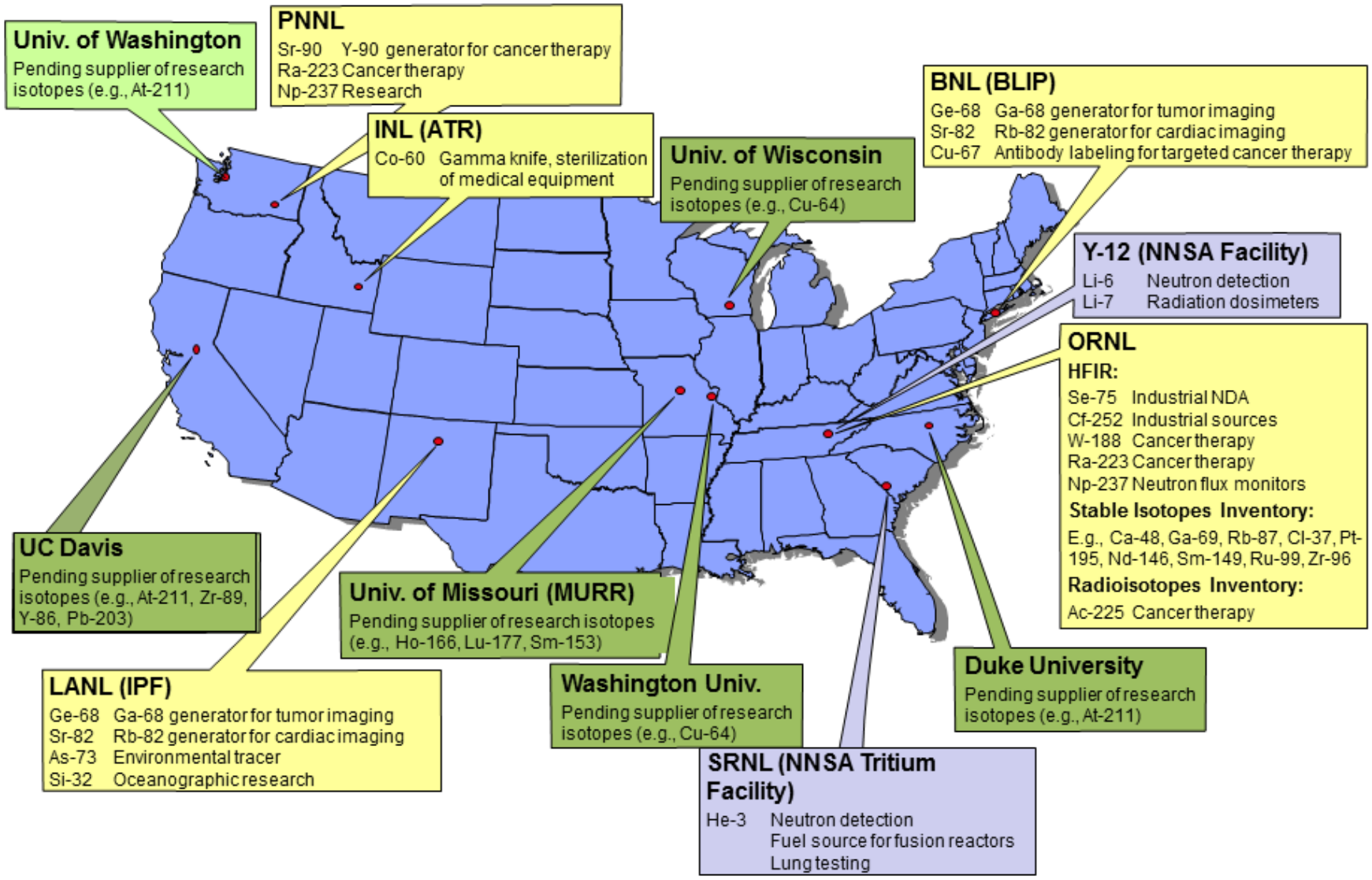


- reduces contamination (samples, reagents, environment)
- automates reaction set-up with low reagent consumption
- 1 µL sample OK
- aggregated/sticky sample OK

- compatible with optical microscopes
- cell concentrations 10^3 /mL – 10^8 /mL OK
- tiny & large cells OK
- low MDA bias
  (Quake & Lasken et al, PLoS Genet 2007)

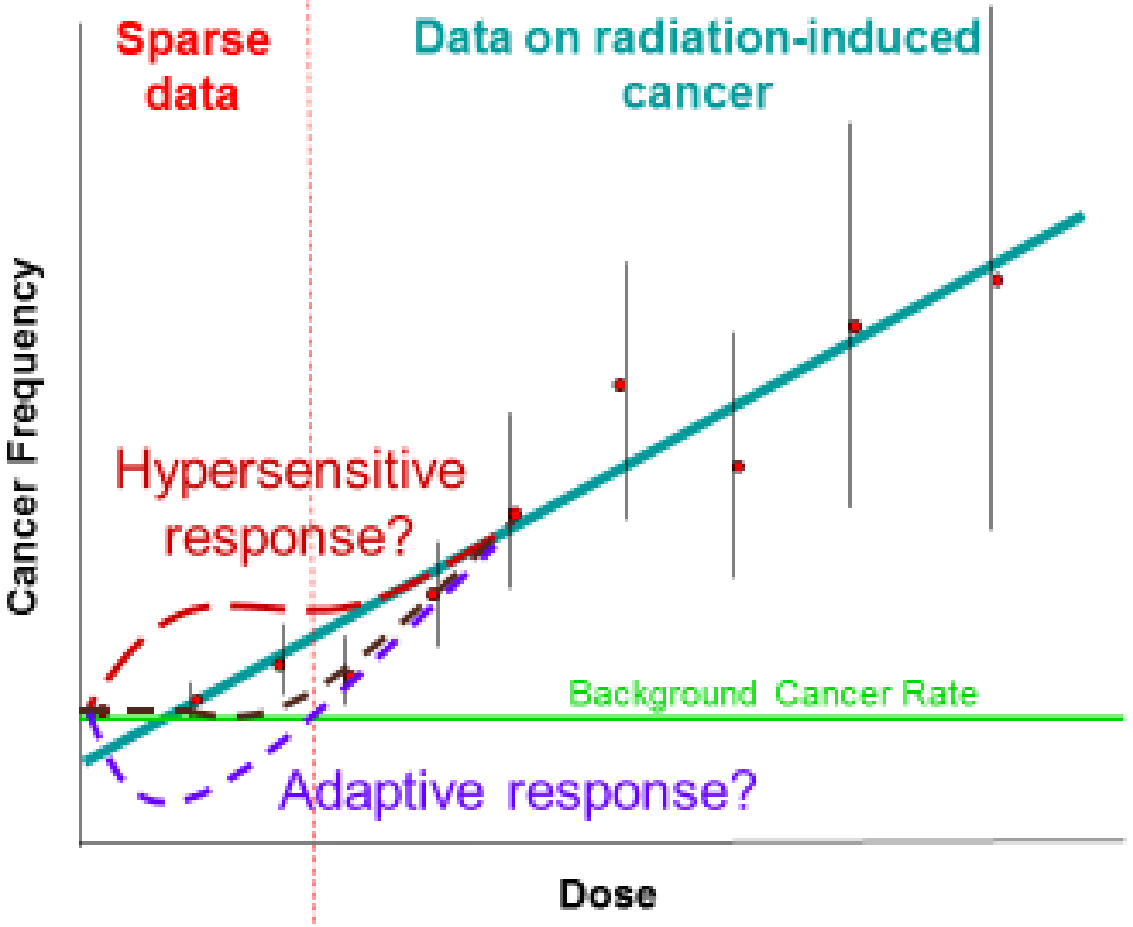
David Relman, Stanford

Isotopes and radio-biology: DOE and university production sites



Radiobiology

Linear Non-Threshold Radiation Dose-Response Model – Good for High Doses



The NNSA labs have played key roles in all facets of biodefense for decades

Threat Awareness

Prevention and Protection

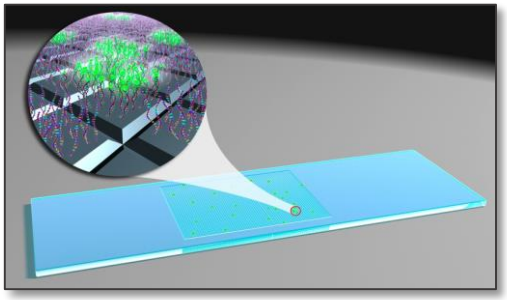
Surveillance and Detection

Response and Recovery *

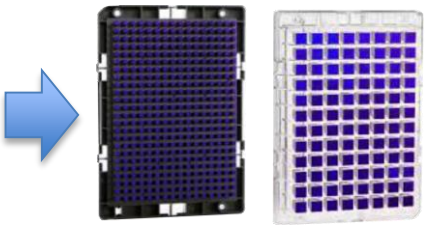
*Four "Pillars" from HSPD 10: Biodefense for the 21st Century

(

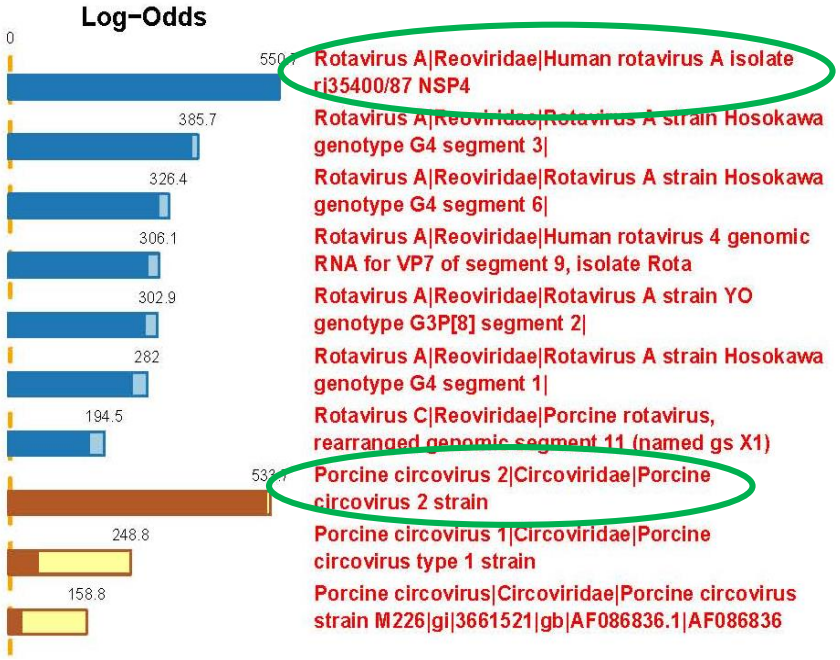
High Density DNA Microarray That Detects Over 10,000 Microbial Species for Wide Range of Applications



15 years of R&D and applications



384- and 96-sample array formats



Domain	# families	# species	# sequences*
Archaea	29	**293**	517
Bacteria	265	**5,367**	24,945
Fungi	101	**265**	395
Protozoa	32	**117**	191
Virus	94	**4,219**	86,931
Total	**521**	**10,261**	**112,979**

Biodefense versions of the arrays include markers for virulence, antibiotic resistance, genetic engineering and other forensic markers.

(D. Lindner, NNSA)

High throughput, high information content and low cost format enables new approaches in surveillance systems

RECOMMENDATIONS AND IMPLEMENTATION PLANS

#1 Identify areas for joint research programs

--DOE and NIH should impanel experts for this purpose on a regular basis

A bottoms-up approach to collaborative work!

RECOMMENDATIONS AND IMPLEMENTATION PLANS

#2 Bring diverse researchers together and co-train the young

--Cross-agency assignments

--Summer gatherings

--Grant supplements

--Novel training programs

Overcoming cultural differences!

RECOMMENDATIONS AND IMPLEMENTATION PLANS

#3 Establish facilities, such as "foundaries," for desirable large scale collaborative projects

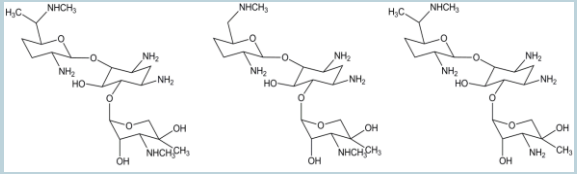
--Recognize the virtues of past efforts

--Act on recommendations of informed panels

--Negotiate with relevant parties

Biofoundry: Rapid Production of Antimicrobials

New antibiotic-resistant pathogen



1 ✘ 2 ✔ ... N ✘

Screen drug variants for efficacy

Stockpiled vials of cells to produce drug variants

Distributed fermentation drug production facilities

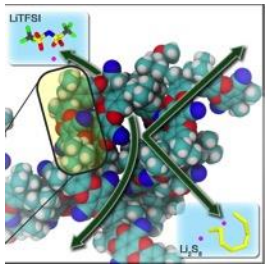
Rapid surge production of effective drug variant

Grand Challenge:

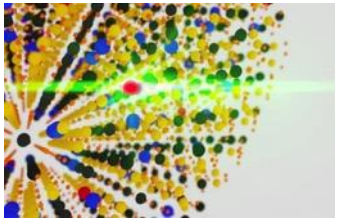
- Discover new and improved antimicrobials for human, animal, and plant pathogens
- Rapidly identify an effective antibiotic and surge its production at distributed sites

High Impact Science by Users and Staff…

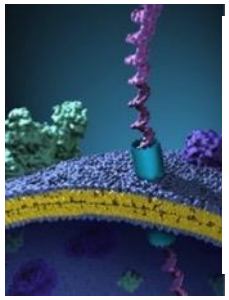
FY 2015
Budget: $26.4M
Publications: 326
(41% "high impact")
Proposals: 515
Users: 677



C. Li, *et al.,* **Nano Lett.** (2015)



D. J. Gargas, et al. **Nature Nano.** (2014)



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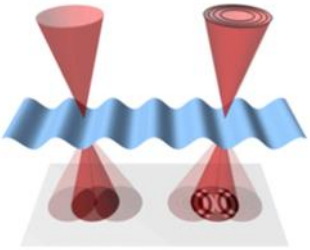
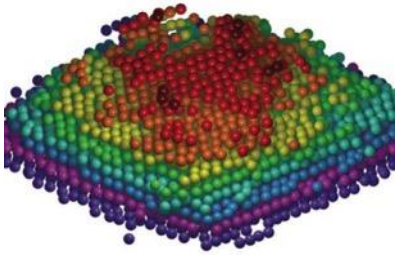


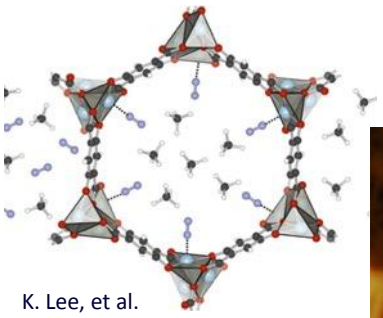
C. Ophus, et al**. Nat Commun**. 2016

M. Bagge-Hansen, et al., **Adv. Mater.** (2015)



R. Xu, *et al.,* **Nature Mat.** (2015)

A. Llordés, et al. **Nature** (2013)



K. Lee, et al.
J. Am. Chem. Soc. (2013)

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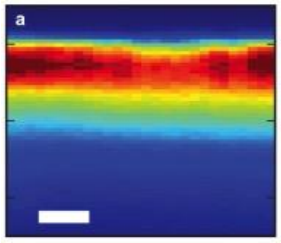
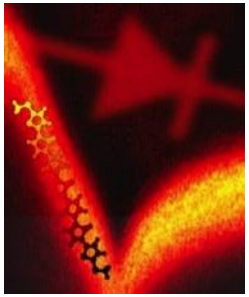
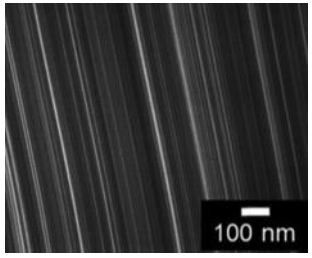


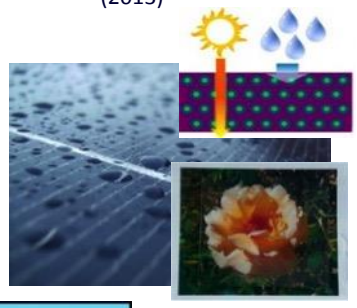
E. S. Barnard, et al. **Scientific Reports** (2013)



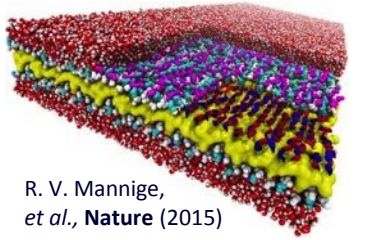
B. Capozzi, *et al.* **Nature Nano.** (2015)



S. Babin, et al. **J. Vac. Sci. Technol. B** (2015)
V. V. Yashchuk, et al. **Rev. Sci. Instrum.** (2015)



E. S. Cho, *et al.* **ACS Macro Lett.** (2015)



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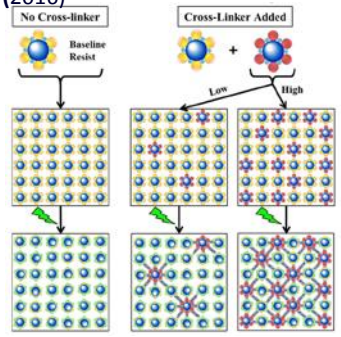
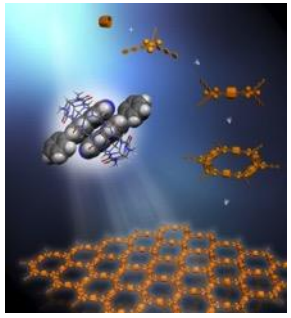
Mecklenburg *et al.*, **Science** (2015)



P. K. Kulshreshtha, et al. **Nanotechnology** (2014)



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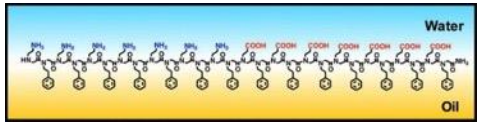
J. Am. Chem. Soc. (2013)



E. J. Robertson, et al. **Proc Natl Acad Sci** (2014)

…at LBL Molecular Foundry

RECOMMENDATIONS AND IMPLEMENTATION PLANS

#4 Inform OMB, Congress, and the public about strategies, proposed activities, and virtuesmof enhanced collaboration

ACKNOWLEDGEMENTS

TASK FORCE MEMBERS

WORKSHOP PARTICIPANTS

NIH/DOE STAFF

SEAB (AND ITS CHAIRPERSON)

SECRETARY MONIZ AND DIRECTOR COLLINS