Report from the Acting Director

Douglas R. Lowy
Acting Director, National Cancer Institute,
National Institutes of Health

NIH NATIONAL CANCER INSTITUTE

Joint NCAB/BSA Meeting
December 1, 2015

Outline of Presentation

- FY15 RPG success rates
- New research specialist award
- New cryo-EM user facility at FNL
- Cancer health disparities workshop
- New pilot project with Department of Energy
- MATCH trial update (Jim Doroshow)

RPG Success Rates FY12-FY15

Table 2:

	FY2015		FY2014		FY2013		FY2012	
	Funded	Success Rate	Funded	Success Rate	Funded	Success Rate	Funded	Success Rate
R01 – Unsolicited [1]	623	14%	578	15%	582	15%	620	15%
R01 RFAs	12	12%	51	13%	29	17%	41	10%
Total R01	635	14%	629	15%	611	15%	661	14%
R21 – Unsolicited	325	11%	302	12%	241	10%	200	11%
R21 RFAs	38	15%	53	13%	30	13%	28	7%
Total R21	363	12%	355	12%	271	11%	228	10%
R35 [2]	43	19%	-	-	-	-	-	-
R03	67	12%	93	15%	100	15%	101	20%
Other RFAs [3]	34	11%	35	15%	23	21%	19	16%
Other RPGs [4]	94	14%	95	19%	90	20%	76	17%
Total Competing RPGs:	1,236	13%	1,207	14%	1,095	14%	1,085	14%

[1] R01s include competing board supplements
[2] Outstanding Investigator Awards (R35) new in FY2015
[3] RFAs include UM1, R33, U01 and UH2
[4] RPGs include R00, R15, R37, R56, P01, U01, U19, UH2, UM1 and DP2

http://www.cancer.gov/about-nci/budget/plan; thanks to Carol Leigh Smith, Tenille McCatty, Nelson Garcia, and Paulette Gray

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FY12-FY15 NCI Budget Changes

Dollars (Millions)				
	FY12	FY13 Sequestration	FY14	FY15
Competing RPGs	414	404	450	508
Change from Previous FY	-10	-10	+46	+58
Total NCI Budget	5,067	4,789	4,932	4,953
Change from Previous FY	+9	-278	+143	+21

R50 Research Specialist Award: Applications due Feb 9, 2016

- To support a new career path, with stable salary support, for accomplished scientists (eg lab, core, bioinformatics) who want to continue to do research but do not want to be a PI
- 5 year awards, renewable. Would support that portion of salary dedicated to NCI-funded cancer research. Would not cover research expenses, but could include travel funds up to $5K/year
- Application requires letter from sponsoring PI, but grantees would have independence to move to another lab or institution, with prior NCI approval

Thanks to Dinah Singer & Chris Siemon

Establishing a Cryo-EM user facility at FNL

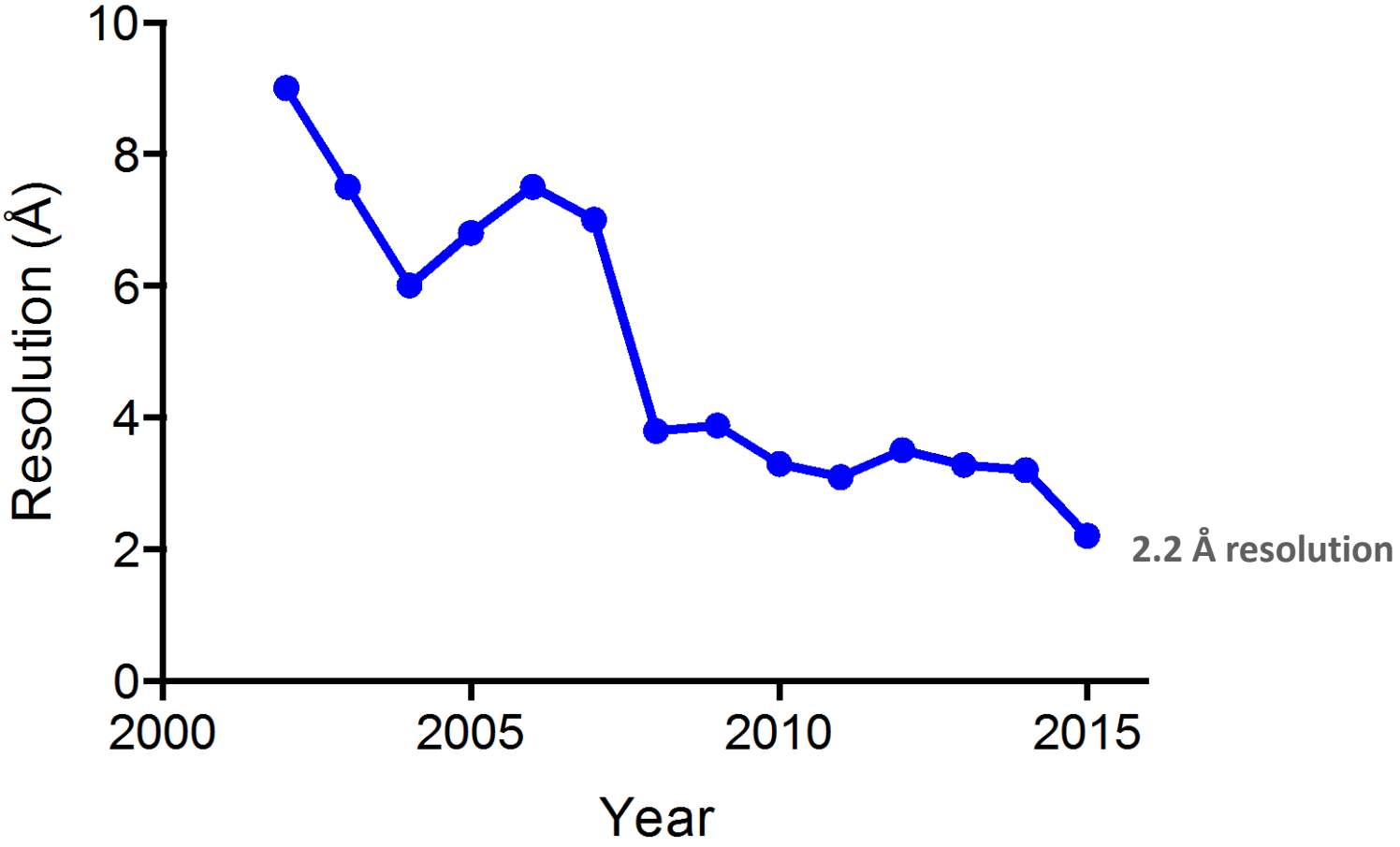
- **Goal**: To provide extramural research community access to high quality cryo-EM
- **Purpose**: to determine structures of macromolecules of importance in cancer research
- **Recommended** by FNLAC
- **Steering committee** for user facility: FNLAC members, Cryo-EM community, structural biology community
- **Facility director**: Sriram Subramaniam, CCR, NCI (subramas@mail.nih.gov)
- **Proposed user fee** (far lower than cost recovery)

The increasing potential of cryo-EM

- Structure determination at high resolution without 3D crystals
- Structural analysis of dynamic protein assemblies
- Progressively higher resolution
- Mapping conformational states of integral membrane proteins
- Localization of drug binding sites
- High degree of automation in data collection and processing

Thanks to Sriram Subramaniam, NCI

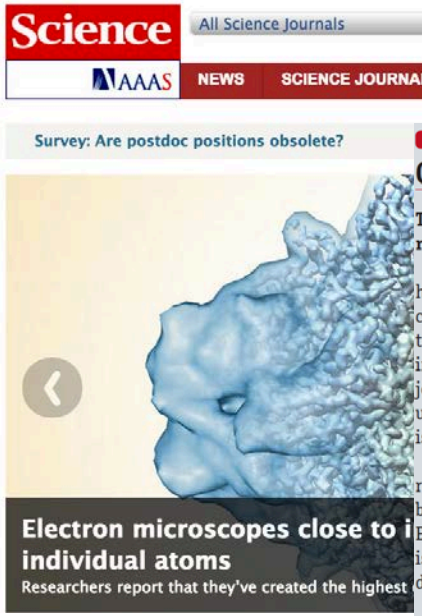
Resolution trends in single particle cryo-EM



From the Protein Data Bank website: pdbe.org/emstats

Thanks to Sriram Subramaniam, NCI

Protein structure determination by cryo-EM



Science
June 2015


STRUCTURAL BIOLOGY

CRYO-EM GOES HIGH-RESOLUTION

The highest-resolution structure solved by cryo-electron microscopy to date reveals what it takes to reach the resolution realm of X-ra

Recent, rapid technical advances to microscopes, detectors have substantially improved the resolution of cryo-electron m causing the broader biology community to sit up and take not technique. An increasing number of near-atomic-resolution st interesting protein complexes solved by cryo-EM are being rep journals. But these advances notwithstanding, the cryo-EM co unable to penetrate the 3-Å resolution barrier, despite predict is no theoretical limit to reaching atomic (~2-Å) resolution.

X-ray crystallography is routinely used to solve protein stru resolution, which allows visualization of fine details such as h bridges and ordered water molecules. The ability to attain suc EM—which uses samples frozen in a thin layer of ice rather th is particularly suitable for studying large protein complexes— doors in structural biology.

In recent work, Sriram Subramaniam of the US National Can colleagues reported the highest-resolution structure solved by complex between *Escherichia coli* β-galactosidase and an inhi thiogalactopyranoside) (Bartesaghi *et al.*, 2015). The reported

Just last year, Subramaniam's group reported a 3.2-Å struct β-galactosidase, a fairly ordinary enzyme of about 460 kDa wh solved by crystallography, allowing the researchers to vet the Reaching 3.2 Å was commendable, but Subramaniam was eage group might do to break through the 3-Å barrier. "There are s

Nature Methods
July 2015

Nature
September 2015

NCI Workshop on Cancer Health Disparities

- Held Nov. 11-13; co-chairs: Lisa Richardson, CDC; Edith Mitchell, Thomas Jefferson; Sandy Markowitz, Case-Western; Michelle Bennett, NCI
- One part of our efforts to develop research priorities for NCI in cancer health disparities
- Focused on a few cancers: breast, prostate, colorectal, liver, multiple myeloma

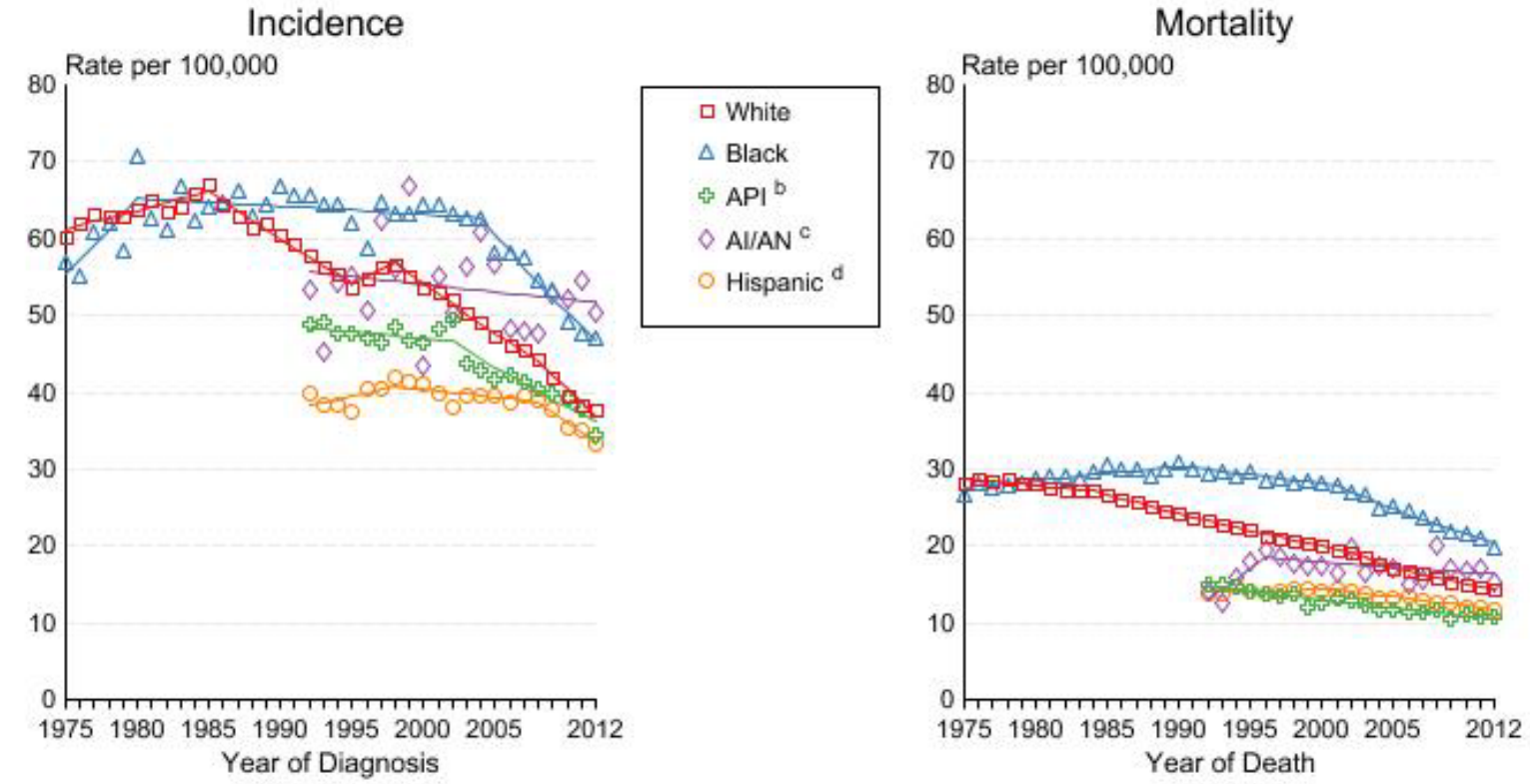
High-risk populations for various cancers

- What accounts for the elevated risk
- Biology, life-style, access/utilization
- Reducing risk: What factors can be mitigated (short term, intermediate term, long term)?

Two Possible Overarching Research Areas

- Develop and study a cohort focused on minority individuals who develop cancer at an unusually early age. Could address roles of genomics, environment, biology, screening, treatment, etc.
- “Financial toxicity.” Understanding it and how to overcome it.

SEER Incidence and US Death Rates[a]
Cancer of the Colon and Rectum, Both Sexes
Joinpoint Analyses for Whites and Blacks from 1975-2012
and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 1992-2012



Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from US Mortality Files, National Center for Health Statistics, CDC.

[a] Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute. Joinpoint analyses for Whites and Blacks during the 1975-2012 period allow a maximum of 5 joinpoints. Analyses for other ethnic groups during the period 1992-2012 allow a maximum of 3 joinpoints.

[b] API = Asian/Pacific Islander.

[c] AI/AN = American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

[d] Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from New Hampshire and Oklahoma.

Some Colorectal Cancer Research Issues

- What are the best algorithms to follow for screening and follow-up?
  - Effective, acceptable, feasible, scalable?
- Effectiveness of prevention? Chemoprevention, lifestyle factors

Aspirin to Prevent Colorectal Cancer

- The final USPSTF recommendations for colorectal cancer reduction (expected in 2016) are likely to be for all populations eligible for aspirin for reducing risk of cardiovascular disease, within a certain age range (probably 50-59)
- Aspirin uptake for reducing risk of cardiovascular disease (recommended by USPSTF since 2002) is lower among African Americans
- A possible joint NHLBI-NCI project to promote the use of aspirin to prevent cardiovascular & colorectal disease

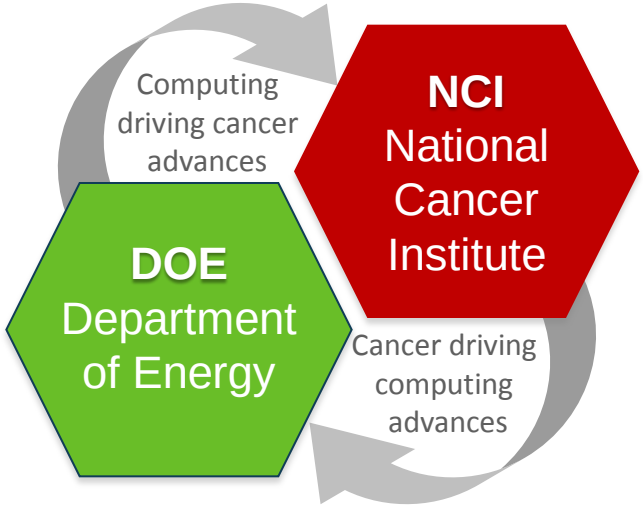
Cancer Currents Blog – November 5, 2015 (www.cancer.gov/cancer-currents)

L. Michelle Bennett, Worta McCaskill-Stevens, Sanya Springfield, NCI

- Join the conversation
- Share your thoughts, ideas, and recommendations
- Submit a comment on *Cancer Currents* Blog (www.cancer.gov/cancer-currents)
- E-mail Center for Research Strategy (Michelle Bennett): ncicrs@nih.gov

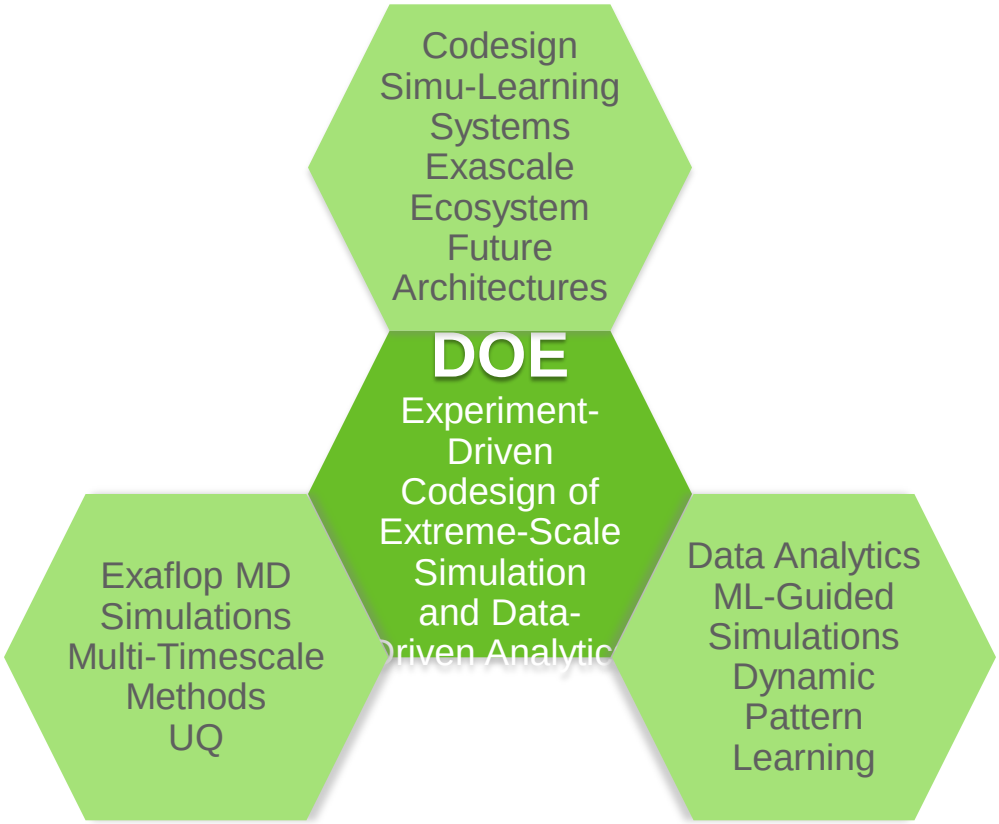
Joint Design of Advanced Computing Solutions for Cancer

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

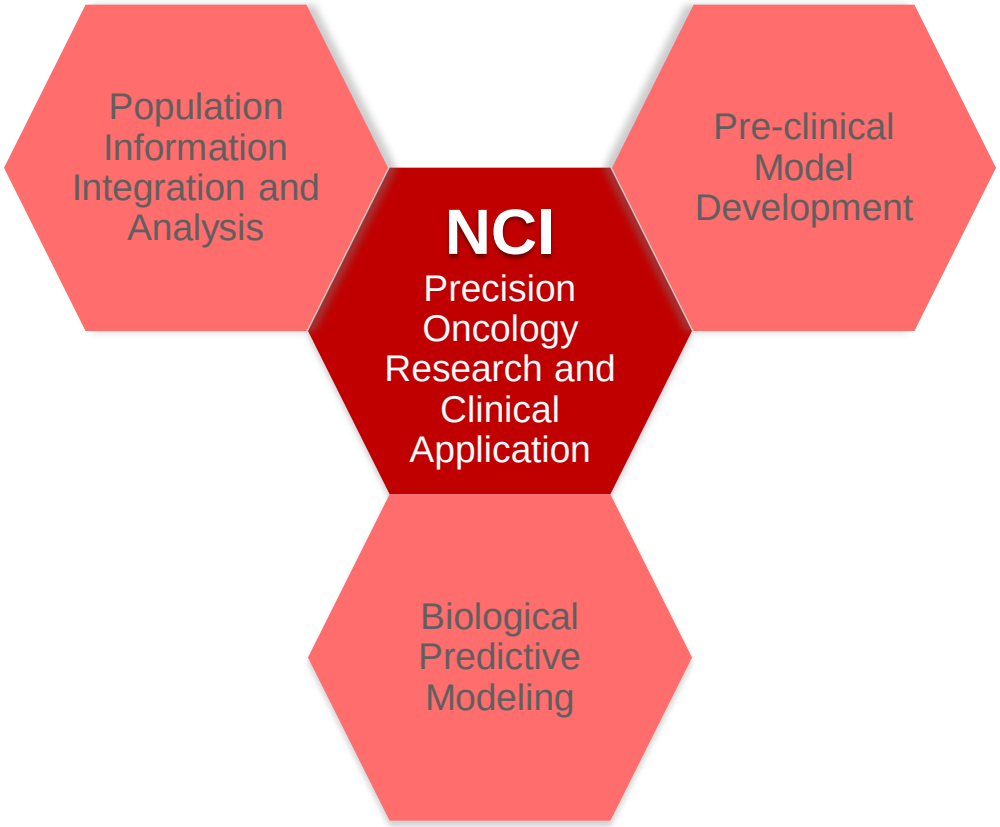


Thanks to Warren Kibbe, NCI, and Dmitri Kusnezov, DOE

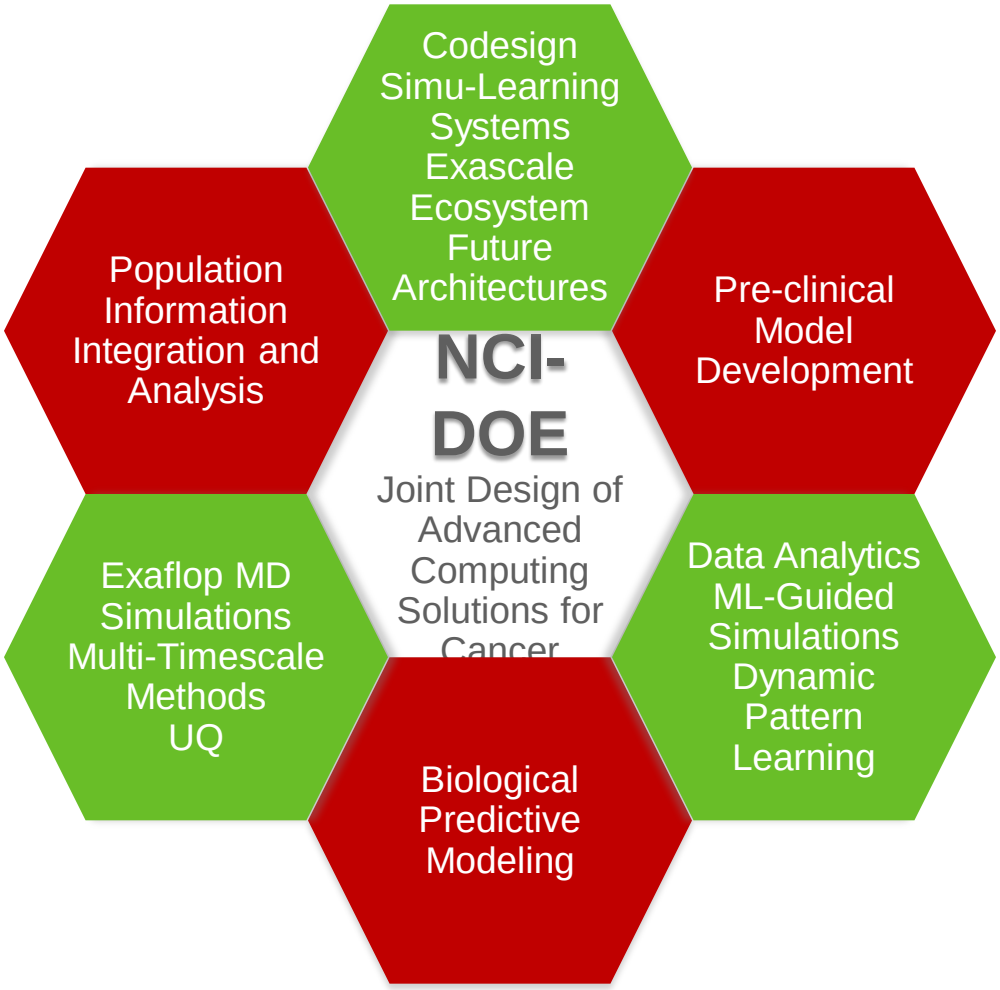
DOE Interests



NCI Interests



JDACS – Joint Design for Advanced Computing Solutions for Cancer

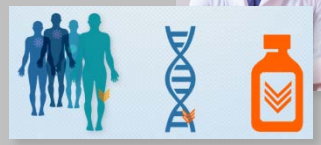


Predictive Models for Preclinical Screening

Modeling framework established

Machine-learning-based predictors

Patient-derived cell lines and xenografts



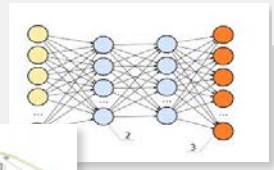
Populating cell line and PDX database with 1000s of samples

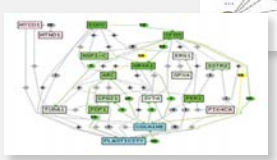
FY16

Project cell line screen results to PDX models

Optimal predictor design using CORAL

Coupling ML models to biological interactions





Testing hypotheses generated by models

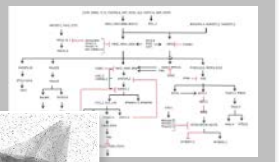
Adding imaging data to molecular assays

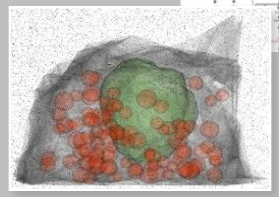
FY17

Coupling machine learning and mechanism

Automated-imaging-based phenotype assessment

Multiscale cancer pathway models with inhibitors





Modeling supported precision medicine trial demo

Patient-specific inhibitor proposed

FY18

Exascale search for optimal models enabling precision medicine trials

DOE

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www.cancer.gov/espanol