Update: NCI/DOE Collaboration

Douglas R. Lowy, M.D.
Deputy Director
National Cancer Institute

FNLAC Virtual Meeting
February 24, 2022

Topics

- *NCI/DOE Collaboration: 2017-2021*
- *Evaluation Task Force,2020; recommendations and implementation*
- *Current projects*

Pilot Projects: started 2017

Pilot 1: Predictive Modeling for Pre-clinical Screening

- Goal: Improve predictive efficacy of preclinical drug studies through computational modeling

Pilot 2: RAS Biology on Membranes

- Goal: deepen understanding of RAS biology through integrated development & use of new simulations, predictive models, and next-generation experimental data

Pilot 3: Population Information, Integration, Analysis, and Modeling

- Goal: modernize NCI's SEER program by developing and deploying scalable deep learning solutions

Task Force Evaluation of DOE-NCI Collaboration: FNLAC presentation by Dr. Joe Gray: October 14, 2020

- NCI-DOE Collaboration is uniquely suited to address certain critical challenges in cancer research and should continue
- Current pilots are really large, full-scale projects; should be evaluated as such
- Future projects should be developed and reviewed by a more structured and rigorous approach; establish project-specific advisory groups
- Increase engagement with NCI extramural community
- **Pilot 1 should be concluded:** Insufficient available and pertinent data, insufficient integration with NCI-supported investigators doing predictive modeling
- **Pilot 2 should be continued**
- **Pilot 3 should be continued**

DOE-NCI collaboration: some 2021 actions

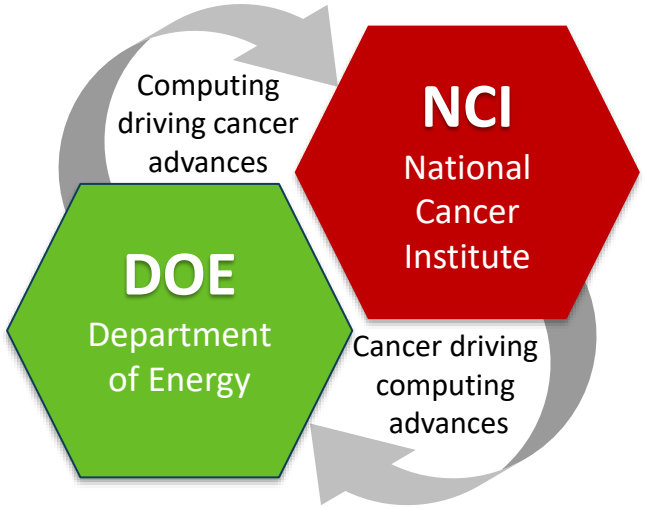
- DOE & NCI signed a new 5 year Memorandum of Understanding
- For new 5 year collaboration (2022-2027), oversight will be under DOE ASCAC (Advanced Scientific Computing Advisory Committee)
- Incorporate recommendations of DOE-NCI task force: increase extramural engagement, increase regular review of projects, workshops & hackathons, drastic revision of pilot 1

New MOU June 2021: Collaboration Governance and Oversight

	U.S. DEPARTMENT OF ENERGY | Office of Science **NCI-DOE ASCAC Subcommittee**	**NCI-DOE Collaboration Scientific & Technical Advisory Committees**	**NCI-DOE Collaboration Executive Committee**
Number	1	1 per project	1
Member composition	Chair: Tony Hey. Members: 8-12 extramural scientists with expertise across collaboration areas (cancer, biology, advanced computing, data science, etc.)	4-6 scientists per committee with targeted, deep expertise relevant to the assigned project	NCI: Drs. Sharpless, Lowy, Singer DOE: Drs. Binkley & Helland (SC), Dr. Anderson & Ms. Hoang (NNSA)
Member selection	per ASCAC guidance with input from NCI and DOE leadership	by project leads in consultation with Exec Committee	by agency leadership
Meeting Frequency	2 times per year or as determined by Subcommittee chair	Quarterly or as needed	3 times per year
Charge/role	- Assessment of current projects - Assessment of opportunities and challenges - Identification of strategies to address challenges and deliver on opportunities	Project-specific, in-depth scientific and technical guidance and advisement	- Interagency strategic partnership status and relationship health - Overall funding - Program priorities - Implementation of ASCAC recommendations

MOSSAIC: Modeling **O**utcomes using **S**urveillance data and **S**calable **AI** for **C**ancer

DOE-NCI partnership to advance exascale development through cancer research



Lynne Penberthy
National Cancer Institute

Georgia Tourassi
Oak Ridge National Laboratory

Formerly pilot 3

This work has been supported in part by the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) program established by the U.S. Department of Energy (DOE) and the National Cancer Institute (NCI) of the National Institutes of Health. This work was performed under the auspices of the U.S. Department of Energy by Argonne National Laboratory under Contract DE-AC02-06-CH11357, Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344, Los Alamos National Laboratory under Contract DE-AC5206NA25396, and Oak Ridge National Laboratory under Contract DE-AC05-00OR22725. [Also adding in the appropriate review and release number]

Research & Development

Rapid Cycle Testing at Scale (IMS using SEER DMS)

Usability Testing & Implementation

Surveillance Community & Federal Partners

NCI Surveillance Program

NCI SRP
3 PMs
1
3 Physicians
2 Epidemiologists
2 Statisticians

DOE Labs

ORNL
2 PM
4 Senior Scientists
14 data scientist/ computational scientists

LANL
1 Senior Scientist
4 computational scientists
1 statistician
1 intern

Cancer Registries

Louisiana	Kentucky
Utah	Seattle
Los Angeles	Greater Bay SF
Greater CA	New Mexico
NJ	New York
CA Central Registry (NonSEER)	
Los Angeles	MN

38 Scientists NCI/DOE
>40 Registry staff/leads
35 Technical Support Staff
Multiple Academic Partners

Specialized Contract Support

IMS
Technical Support & Real World testing of DOE developed tools
2 senior analysts
18 software developer
1 linkage specialist

Westat
Contract Support
Technical Consultants
Pathologists
Registrars
Software developers

Leidos
Contract Support

Academic Collaborators/ SMEs

UK Markey Cancer Center
Eric Durbin/Isaac Hands
API Testing

Vanderbilt CC
Jeremy Warner
HemeOnc.Org

Fred Hutchison CC
Chris Li/Microsoft
Breast Recurrence

Stanford CC
Allison Kurian
Breast Recurrence

Dana Farber CI
Deb Schrag
PRISSMM Consultant

UCSF
Selma/ Scarlett Gomez
SDOH Expertise

Scientific Accomplishments – Epath Auto Extraction

- API to auto-extract structured data from unstructured pathology reports
  - >3 million reviewed and manually screened every year – increasing annually
  - API 18,000 X faster than a human (55 sec/report = **46,000 man-hours**)

- Currently Implementation in 8 SEER registries
  - Results:
    - **17% of all path reports auto-coded with >98% accuracy (7,800 man-hours saved)**
    - Leveraging API to build NLP-assisted manual coding for non auto-coded reports
    - Opportunity to train registrars to increase consistency and accuracy across surveillance
    - New “case level API” in progress, preliminary results **23% of path reports auto-coded with > 98% accuracy**
  - Next steps:
    - Collaboration with CDC - implement Privacy Preserving API in central process for APHL reporting
    - Use beyond SEER (MN Registry)

A current activity – Biomarkers

- **Challenge:** Automated extraction of key biomarkers from pathology reports:
  - **Breast**: ER, PR, HER2
  - **Colon**: KRAS, MSI
- **Next Steps:** Future integration of biomarkers task into SEER workflow:
  - Development and testing of algorithms that can identify HER2 in non-breast cases and KRAS in non-colon cases
  - Transfer learning since no training data
  - Addition of >12 new biomarkers being collected manually in 2020 for use in adding to the multi-task biomarker API

Preliminary algorithm with accuracy ranging from 92-95%

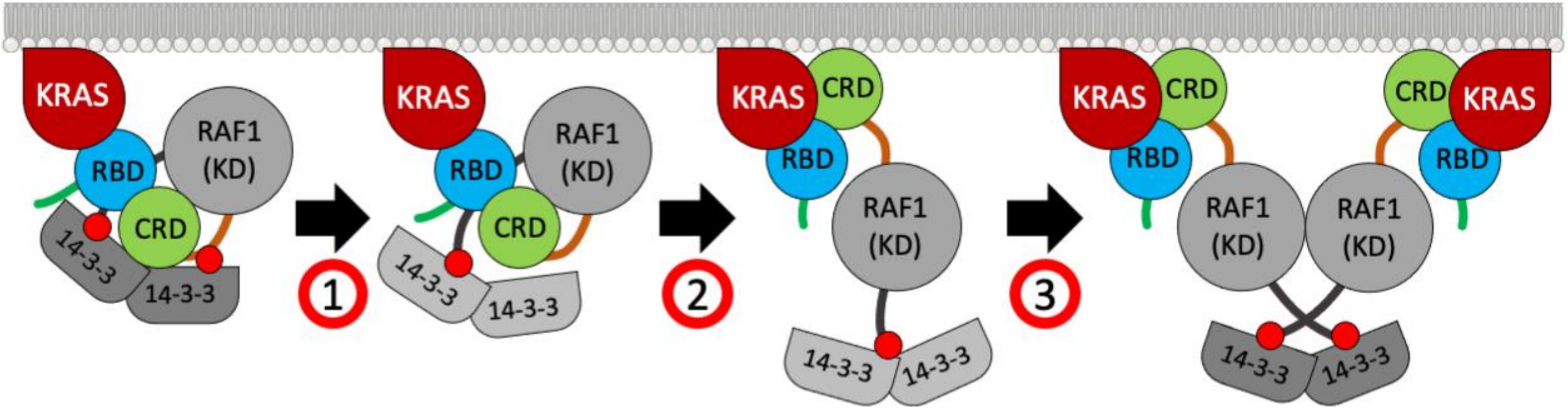
Biomarker	Accuracy / Macro-F
ER	95.26 / 82.03
PR	92.90 / 85.16
HER2	92.62 / 88.71
KRAS	91.86 / 61.23

ADMIRRAL *(**A**I-Driven **M**ultiscale **I**nvestigation of **R**as-**R**af **A**ctivation **L**ife cycle); formerly Pilot 2*

- Leads: Dwight Nissley FNLCR & Fred Streitz LLNL
- Main focus 2017-2021: simulation of K-RAS on a membrane and its interaction with RAF, in context of various lipids by MuMMI (**Mu**ltiscale **M**achine-Learned **M**odeling **I**nfrastructure)
- Main current goal: Greater focus on protein domain movement and mechanism by which K-RAS activates RAF; greater emphasis of bidirectional interaction between simulations and RAS-RAF structure, biochemistry, & biology (Debby Morrison et al)

ADMIRRAL Project: Next Aims for Predictive MD Simulations

AI-Driven Multi-scale Investigation of Ras-RAF Activation Lifecycle



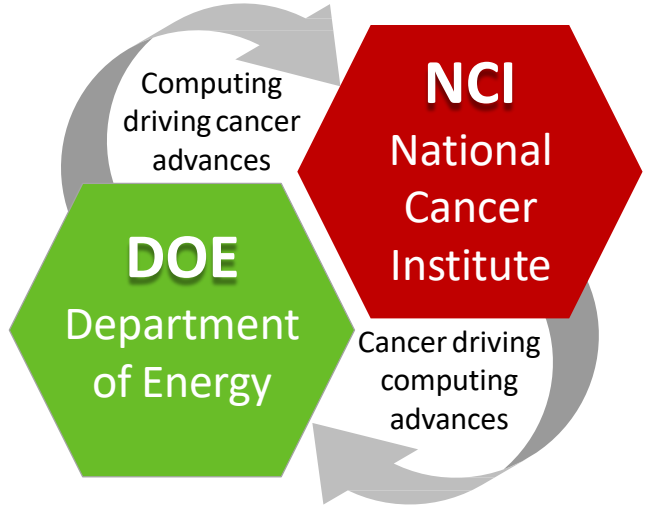
1) **Characterize opening of auto-inhibited RAF protein upon 14-3-3 disengagement**
2) **Delineate large-scale domain rearrangement of the RAS-RAF complex**
3) **Describe engagement and dimerization of the RAF kinase domains.**

IMPROVE: Innovative Methodologies and New Data for Predictive Oncology Model Evaluation

DOE-NCI partnership to advance Exascale development through cancer research

Rick Stevens
Argonne National Laboratory
University of Chicago

Ryan Weil
Frederick National Laboratory for Cancer Research



January 20, 2022

Presented to:
Collaborations Executive Committee Meeting

The IMPROVE Project

- A **new project** building on what was learned in Pilot 1 and designed with a new engagement model with the **cancer research community** and DOE National Laboratories
- Two related goals aimed at IMPROVING deep learning models for predicting Drug Responses in Tumors:
  - **Aim 1:** Development of semi-automatic protocols for comparing deep learning model from various investigators and identifying model attributes that contribute to prediction performance with the goal of IMPROVING future models
  - **Aim 2:** Development of protocols for specifying drug screening experiments and to generate data explicitly aimed at IMPROVING model performance (training and testing)

Anticipated Impact of IMPROVE

- Closing gaps in development and application of deep learning models for predictive modeling of therapeutic response, and potentially generating new treatment approaches:
  - Generate well-curated, clinically relevant, standardized training and testing datasets
  - Utilize standardized, easily-applicable workflow (including software pipeline, performance metrics, data, etc.) for evaluating and comparing prediction models to drive model improvement and new model development where possible, hastening translation to the clinic
  - Understand model attributes related to predictive power, interpretability, and uncertainty quantification (including errors and failure to predict and how this is handled) for guidance on future model design
  - Engage the community for expert opinions and collaborations on developing model evaluation framework and generating benchmark data
  - Potential to generate new hypotheses and identify new treatment targets

Given what we know and the expanding landscape of public models, how can we make progress?

- Addressing two key bottlenecks for making progress and with broad community engagement
- **Bottleneck 1: Comparing a new model to previous N models (Aim 1)**
  - How to quickly and fairly compare N models and learn which are performing better than others and determine each model's relative strengths and weaknesses
  - Determine what aspects of the model formulation/structure/training protocol, etc. are making a difference in performance while holding training data constant
  - Comparison of impact on performance from training and validation data choices
  - Determine the types of errors models are making and why
  - Doing this as automatically as possible
- Go beyond simple validation approaches to more biologically relevant assessment
- Work with the community to develop more standard approaches for evaluation
- *Goal: an "automated" framework to make massive cross-comparisons feasible*

Bottleneck 2: What data need to be generated to improve models? (Aim 2)

- Vast majority of data used to develop current models were **not created for this purpose**
- By studying **model errors and failures** and how they relate to training and validation datasets, what new data would be most useful can be determined
- By understanding **how data quality affects model performance,** the standards needed for new training data can be determined
- By understanding **the learning curve scaling behavior across many models**, the scale of data needed that would improve models can be determined
- By understanding **the feature types and modality of training data,** which assays are needed can be determined
- By understanding **the impact of data diversity in drug and tumor space,** the shape (tumor x drugs) of experiments needed to improve performance can be determined

- *Goal: new datasets explicitly generated to improve models and made widely available*

Engaging the Community

- For Aim 1: Argonne and Frederick plan to use an RFI/RFP process administered by FNLCR to support up to 5 extramural groups to participate in designing and building the “IMPROVE” framework for model comparison and to use that framework to produce an annual assessment of drug response models in Cancer

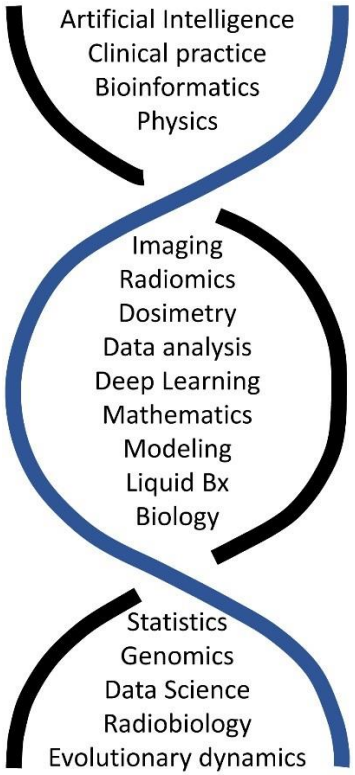
- DOE national laboratories will also be involved. This collaboration will be the “core modeling group,” which is expected to be involved in driving Aim 2. Computing infrastructure will be provided by the DOE labs

- For Aim 2: an RFI/RFP (with a qualification round) process will be used to identify commercial firms (or other third parties) that can be contracted to produce the data specified by the core modeling group

Everything Needs to be OPEN

- The IMPROVE framework, the model analysis results, any improved models, and all data produced will be open source and available to the whole community
- IMPROVE will hold development hackathons that will be open and an annual meeting that will be open to the community
- IMPROVE will work with agencies, scientific associations, and journals to advocate for open models, open data, and open source enabling replication of modeling results

NCI-DOE Collaboration 2021 Virtual Workshops:
Accelerating Precision Radiation Oncology through Advanced Computing and Artificial Intelligence



Why Now?

- Radiation oncology is an area of cancer care that employs rich 4D data to design and deliver highly personalized and technologically advanced treatments.
- Emerging approaches in physics, AI, advanced computing and mathematical modeling can be informed by the growing wealth of 4D data.
- New synergies can be created to predict response at various time scales and thereby support new treatment strategies with the potential for direct translation to the radiation oncology clinic.

Summary & Conclusions

- NCI is continuing its collaboration with DOE
- Recommendations of the evaluation task force are being implemented
- It is anticipated that increased interaction with the extramural research community and regular review by project-specific advisory groups will increase the achievements and impact of the collaboration