Basic, Translational, and Clinical Research Capabilities at the NCI FFRDC

NIH NATIONAL CANCER INSTITUTE

Advanced Scientific Computing and Bioinformatics

Advanced Scientific Computing and Bioinformatics

- ✓ **Infrastructure** - Frederick Research Computing Environment (FRCE) HPC cluster
- ✓ **Scientific Expertise** aligned with programmatic need
  - Data Science
  - Bioinformatics
- ✓ **IT Technical Expertise**
  - High Performance Computing
  - Cloud Computing

⇒ **Comprehensive, cross-cutting, set of advanced computational resources**

- National Mission Programs e.g., RAS, Cryo EM
- Numerous initiatives from the NCI Divisions and other ICs

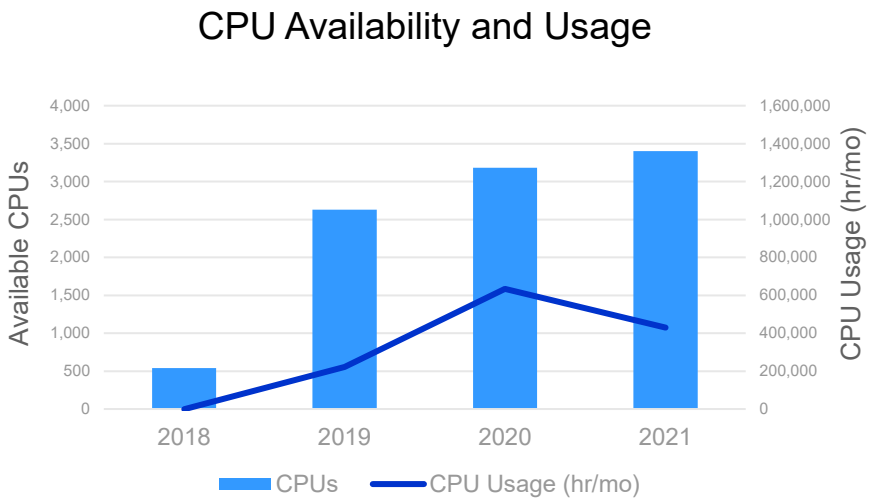
  e.g., The Cancer Research Data Commons

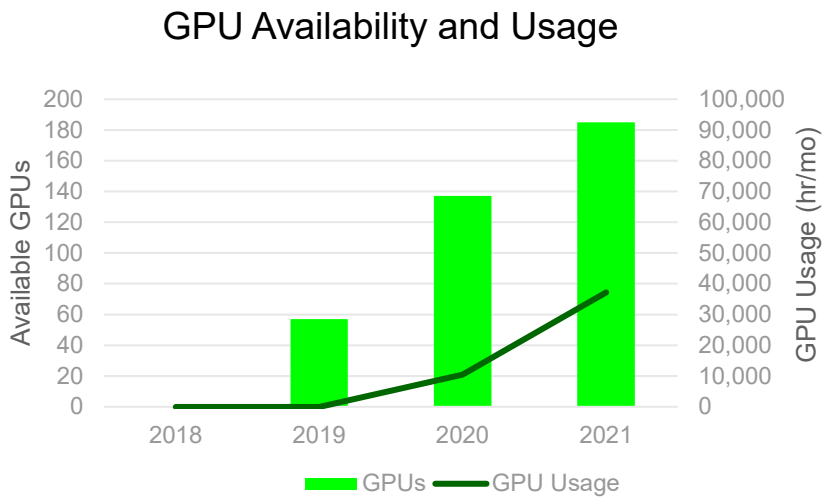
FFRDC Computational Infrastructure

Frederick Research Computing Environment (FRCE)

- FRCE is a Linux-based HPC Cluster ~ 5% the capacity of Biowulf
- Slurm job scheduler to manage allocation of compute resources
- Scientific software for bioinformatics, next-gen sequencing, statistics, multiple modes of image analysis, and computational chemistry applications
- Storage: High-speed flash, longer-term NAS, object, and (soon) cloud tiers
- 100 HPE Gen10 servers housed in a state-of-the-art Data Center provide
  - 3,400 CPU cores, including 192 very high memory
  - 185 GPUs, including 57 NVIDIA P100s and 128 NVIDIA V100s

FRCE Cluster Expansion and Usage



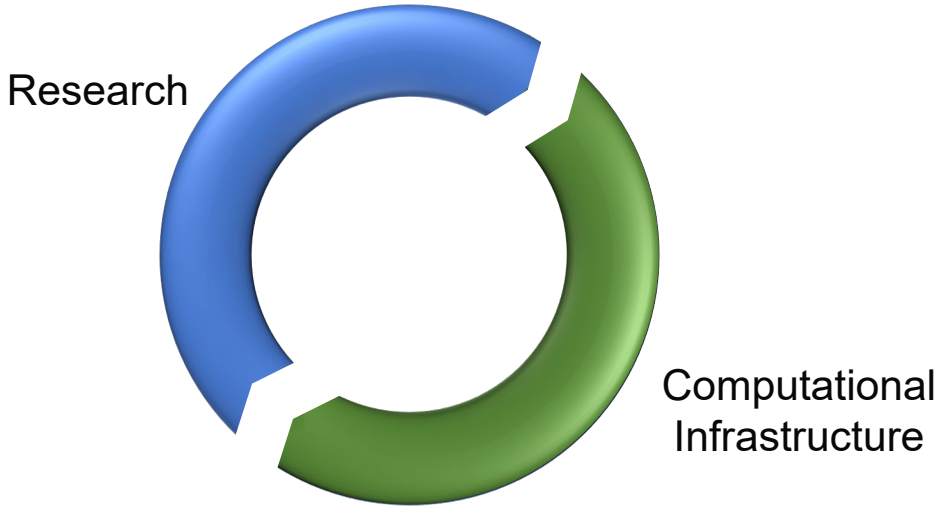


Current: 3,400 CPU cores, including 192 very high memory

185 GPUs, 57 NVIDIA P100s + 28 NVIDIA V100s

Research Drives Innovation of the Computational Infrastructure

- ✓ Cryo EM => Global File System to support HPC data management & auto-tiering
- ✓ Genomics => Integration of data aggregation & analysis UIs for non-Linux users
- ✓ Image analysis => Hybrid local + cloud computing and storage
- ✓ Molecular Diagnostics => Service level agreements to support clinical workflows
- ✓ Chemistry & Drug discovery => Leveraging petascale and exascale compute



FFRDC Data Science

FFRDC Data Science = Interdisciplinary Team Science

- ✓ Aimed at determining the cause-and-effect relationships underlying human disease and leveraging those discoveries to develop precision diagnostics and therapeutics
- ✓ Data Science requires interdisciplinary expertise:
  - In-depth knowledge of the biological system(s) under study and the appropriate computational approaches required to leverage that body of knowledge
  - Bioinformatic statistical correlations
  - Multi-modal data aggregation and analysis (retrospective data mining and prospective cohort development)
  - Deep learning, machine learning, and other AI disciplines
  - Numerous IT domains, e.g. HPC & cloud computing, application programming, UI design, data systems engineering

Numerous FFRDC stakeholders seek to integrate -omics data (genome, transcriptome, proteome, metabolome, microbiome), with imaging, clinical and/or chemistry data to identify new biomarkers and molecular targets and develop novel therapeutics.

Key Scientific and Technical Computational Expertise

Bioinformatics and Statistics
- Next-Gen Sequencing (NGS) design, QC & processing
- Analysis of genomic & transcriptomic data including:
  - Whole genome seq (WGS)
  - Exome-seq
  - RNA-seq
  - Single Cell RNA-seq
  - ChIP-seq
  - Microarray
  - Digital Spatial Profiling (DSP)
- Clinical genomics for precision cancer diagnostics

Multi-modal Aggregation & Analysis (Data Mining)
- Aggregation of large-scale clinical cohorts
- Multi-omic, longitudinal data integration and analysis

Quantitative Image Analysis and Visualization
- High content microscopy, 2D, 3D, 4D
- Brightfield and fluorescence digital pathology
- 3D biomedical visualization (CT, MRI, SPECT, PET)
- Deep learning, machine learning

Simulation and Modeling
- Protein and DNA modeling, drug/substrate interactions
- Molecular Dynamics Simulations
- Electronic structure of proteins and nanoparticles

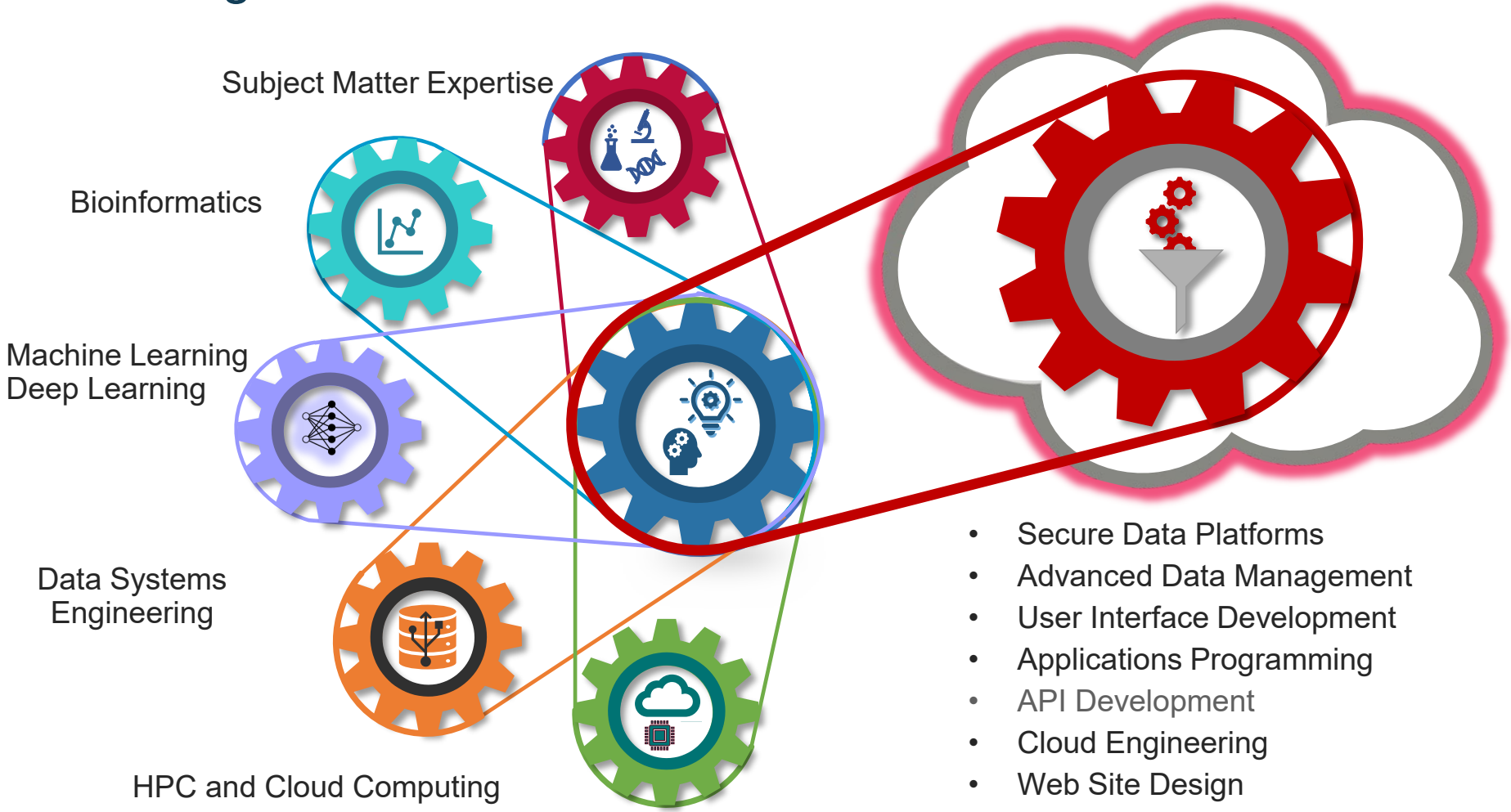
Structural Biology and Chemistry
- Structure determination for numerous modalities:
  - Cryo EM, micro-ED
  - NMR spectroscopy
  - X-ray diffraction, Small angle X-ray Scattering (SAXS)
- Quantitative Structure Activity Relationship (SAR) Analysis

High Performance Computing (HPC)
- HPC application and workflow development
- Petascale computation and capabilities transfer

Cloud Computing
- Cloud engineering & capabilities transfer – all platforms
- Application Programing Interface (API) development
- Advanced data management & database services
- Analytic workflow and applications development
- User Interface design

Scientific Web Development
- Database design, implementation, and management
- User Interface design and graphic development
- Scientific applications design for web and mobile

Scaling Data Science Innovations for Broad Collaboration



- Secure Data Platforms
- Advanced Data Management
- User Interface Development
- Applications Programming
- API Development
- Cloud Engineering
- Web Site Design

Cancer Research Data Commons

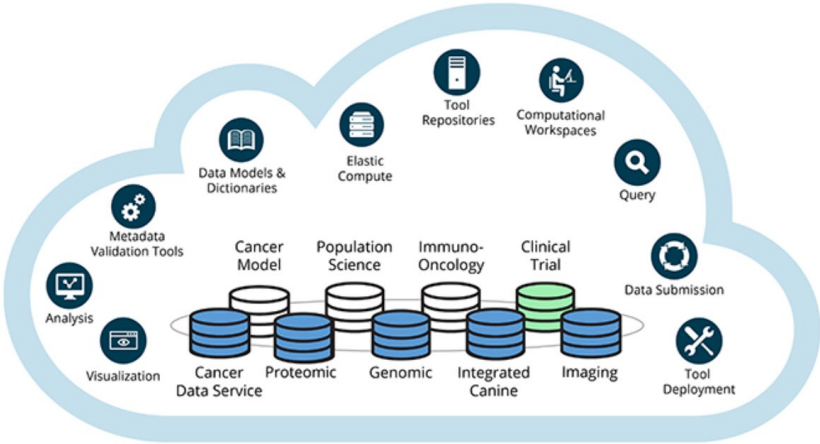
A virtual, scalable cancer data science ecosystem of interconnected data sets and analytics tools

CRDC Components

Data Repositories ~3 PB cancer data

6 Domain- or project-specific nodes: 3 planned nodes:

- ✓ Genomics
- ✓ Proteomics
- ✓ Imaging
- ✓ Clinical Trials
- ✓ Canine Cancer
- ✓ Unstructured Data
- ✓ *Epidemiology*
- ✓ *Immuno-oncology*
- ✓ *Cancer Models*



Infrastructure

- Cancer Data Aggregator (CDA)
- Center for Cancer Data Harmonization (CCDH)
- Data Commons Framework (DCF) Services

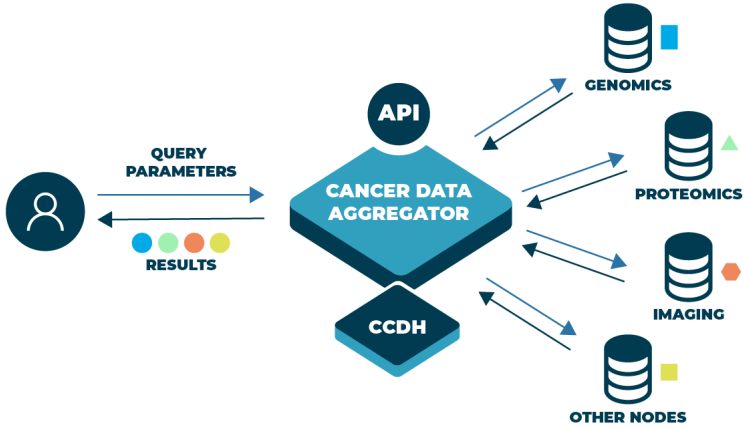
Analytic Resources

- Seven bridges Cancer Genomics Cloud (SB-CGC)
- Broad FireCloud
- Institute for Systems Biology Cancer Genomics Cloud (ISB-CGC)

https://datascience.cancer.gov/data-commons

CRDC Infrastructure Makes Data FAIR

Findable, Accessible, Interoperable, Reusable



Cancer Data Aggregator (CDA)

Consortium led by the Broad Institute

- Central metadata repository
- Provides APIs for querying, retrieval, & integration of data across the CRDC & NCI DCCs

Data Commons Framework (DCF) Services

- Data platforms consisting of open-source software for rapid deployment of new repositories & Data Commons
- Tools for ingesting, QCing, harmonizing & curating data
- Authentication services for controlled access data
- Tools for querying, aggregating, analyzing & simulating data

Center for Cancer Data Harmonization (CCDH)

Consortium led by Oregon State University

- Facilitates semantic harmonization of data across the CRDC
- Leverage existing standards (e.g. FHIR, BRIDG) to enhance interoperability of heterogeneous data types
- Using HTAN to develop a consensus CRDC data model
- Human Tumor Atlas Network (HTAN): Longitudinal molecular and cellular description of specific organs/tissues capturing all relevant spatial, structural, & functional changes during tumor initiation, progression, and metastasis.

NCI Cloud Resources

Three Analytic Resources Connecting CRDC Data to Cloud Compute

The Institute for Systems Biology, Seven Bridges Genomics, & the Broad FireCloud provide access to:

- Large cancer data sets without the need to download
- BYO data and code upload capabilities for large-scale integrated analysis with CRDC data
- Workspaces to create your own workflows or run hosted analysis pipelines & tools
- On-demand, elastic cloud compute
- 3,000 active users per month averaging about 100 analyses/month

Command line UI
Analysis outputs transformed into BigQuery
Any workflow language of choice
Google Cloud
Gen3

Non-technical UI, visual displays
Common Workflow Language (CWL)
Tools for developing pipelines
AWS Cloud
Gen3

Workflow Description Language (WDL)
Methods & processing pipeline repository
Google Cloud
Terra

The FFRDC Supports All Aspects of the CRDC

Data Repositories, Infrastructure, and Analytic Resources

- Development, deployment, and administration of data repositories, infrastructure, & analytic resources
  - Deployment of new Data Repositories
  - Cloud systems architecture and engineering
  - Application Programing Interface (API) development
  - Analytic workflow and applications development
  - User Interface design
  - Systems documentation
  - Web pages & communication to the scientific community
- Advanced data management and analysis services, including support for
  - Data submission and quality control
  - Harmonization to common data elements & models
  - Enterprise Vocabulary Service (EVS) Support
  - Data aggregation and integrated querying
  - Privacy-Preserving Record Linkage/ de-identification
  - Data security

Engagement with Entities Within and Beyond NIH

FFRDC computational experts engage with other data science-focused entities within NCI, NIH, and other Federal and academic institutions to

- Identify and develop potential **computationally-based collaboration opportunities**
- **Leverage unique resources** available through collaboration (e.g., petascale and exascale compute) to expand or develop new computational approaches to accelerate cancer or other disease research for FFRDC stakeholders.
- **Develop assessments and recommendations** on computational resources, future needs, and scientific, computational and technology trends
- **Raise the visibility** of FFRDC data science within the larger biomedical research community

Summit at Oak Ridge NL (world's 2nd fastest computer)

Aurora exascale supercomputer under development at Argonne NL

Japan's Fugaku (world's fastest computer)

www.cancer.gov

www.cancer.gov/espanol

Omics at the FFRDC

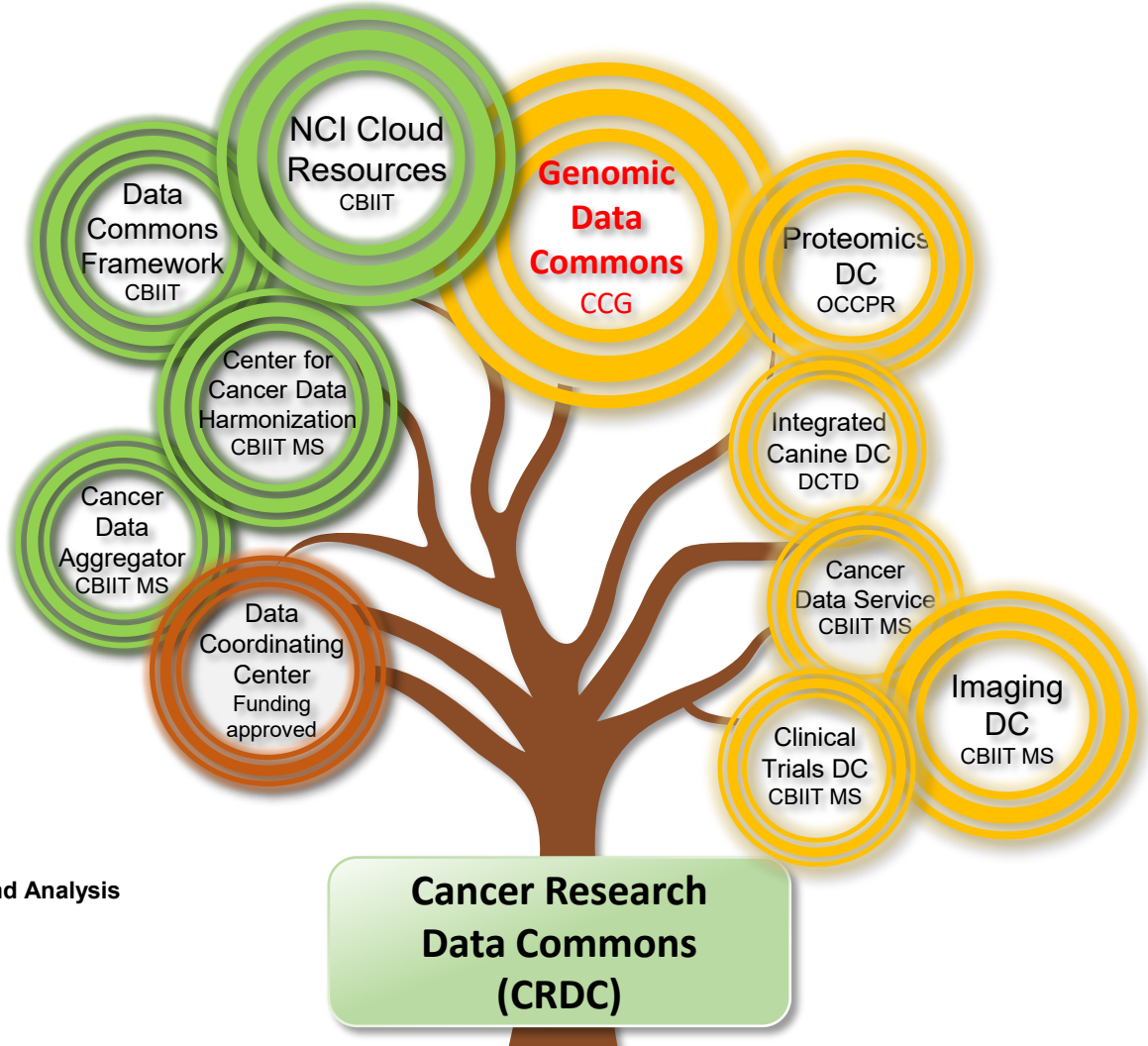
NIH NATIONAL CANCER INSTITUTE

Omics Overview

- Omics research is exploratory and directed at understanding the correlation between molecular properties (e.g., gene and protein markers) and clinical phenotypes (e.g., disease incidence and prevalence, and patient responses to drug treatment) across populations.
- Broad range of omics at the FNLCR supported by state-of-the-art technologies:
  - Genomics, Transcriptomics and Spatial Transcriptomics – Molecular biology techniques, e.g., next-gen sequencing, nanostring, bar-coding, RNAseq, etc.
  - Glycomics - Multiple Reaction Monitoring (MRM), Orbitrap Fusion Tribrid, Q Exactive, Q Exactive HF, LTQ-Velos Pro and TSQ-Triple Quadrupole mass spectrometers
  - Lipidomics - Mass spectrometry, NMR and fluorescence measurement
  - Pharmacogenomics - Various genomic technologies as appropriate
  - Metabolomics - Gas chromatography, HPLC, electrophoresis NMR, and mass spectrometry
  - Epigenomics/Epitranscriptomics - Genomic and chromatin immunoprecipitation techniques
  - Proteomics - HPLC, electrophoresis and mass spectrometry, including data dependent and data independent acquisition methods, and Multiple Reaction Monitoring (MRM) techniques

NCI's GENOMIC DATA COMMONS

NCI Cancer Informatics Vision



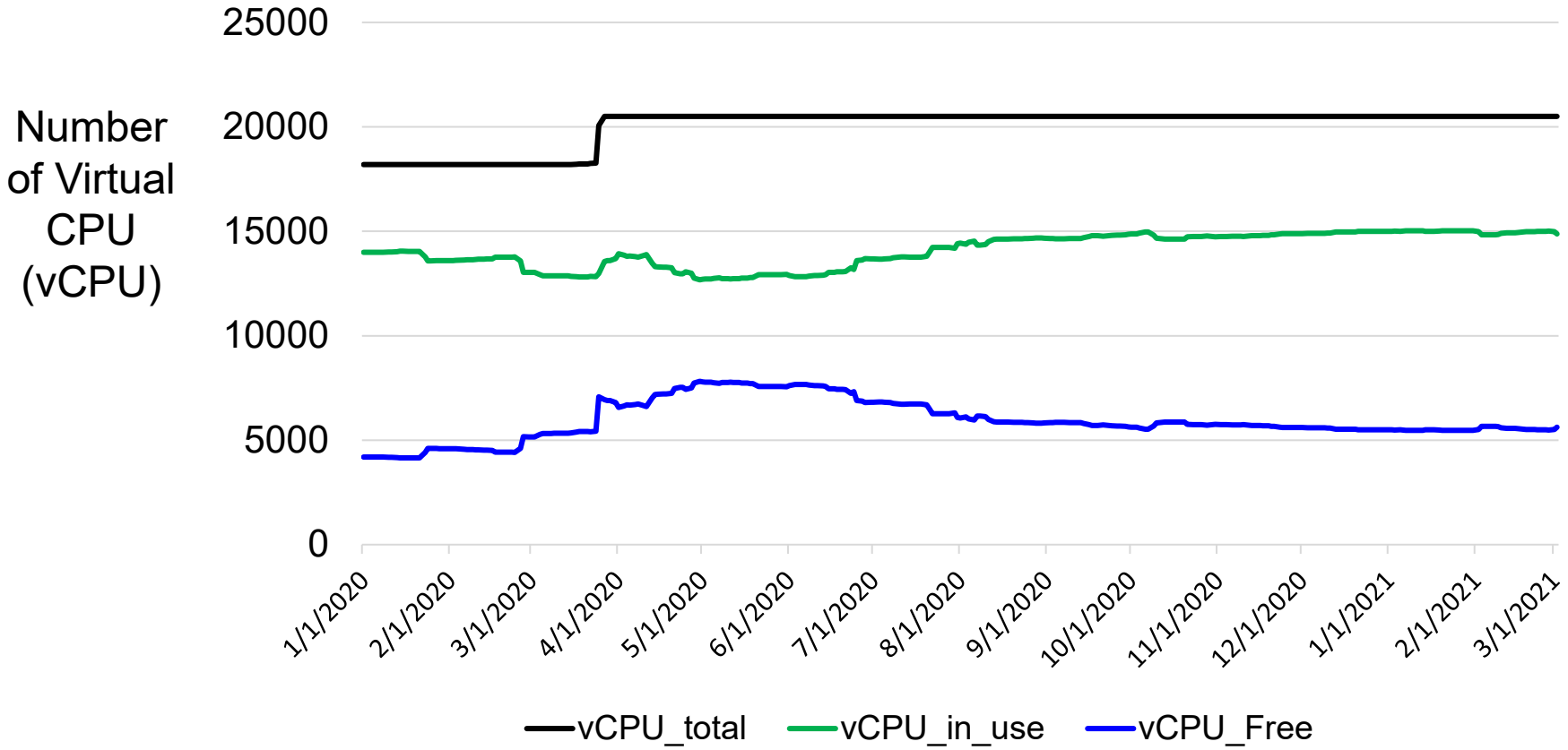
Data Repositories

Data Interoperability and Analysis

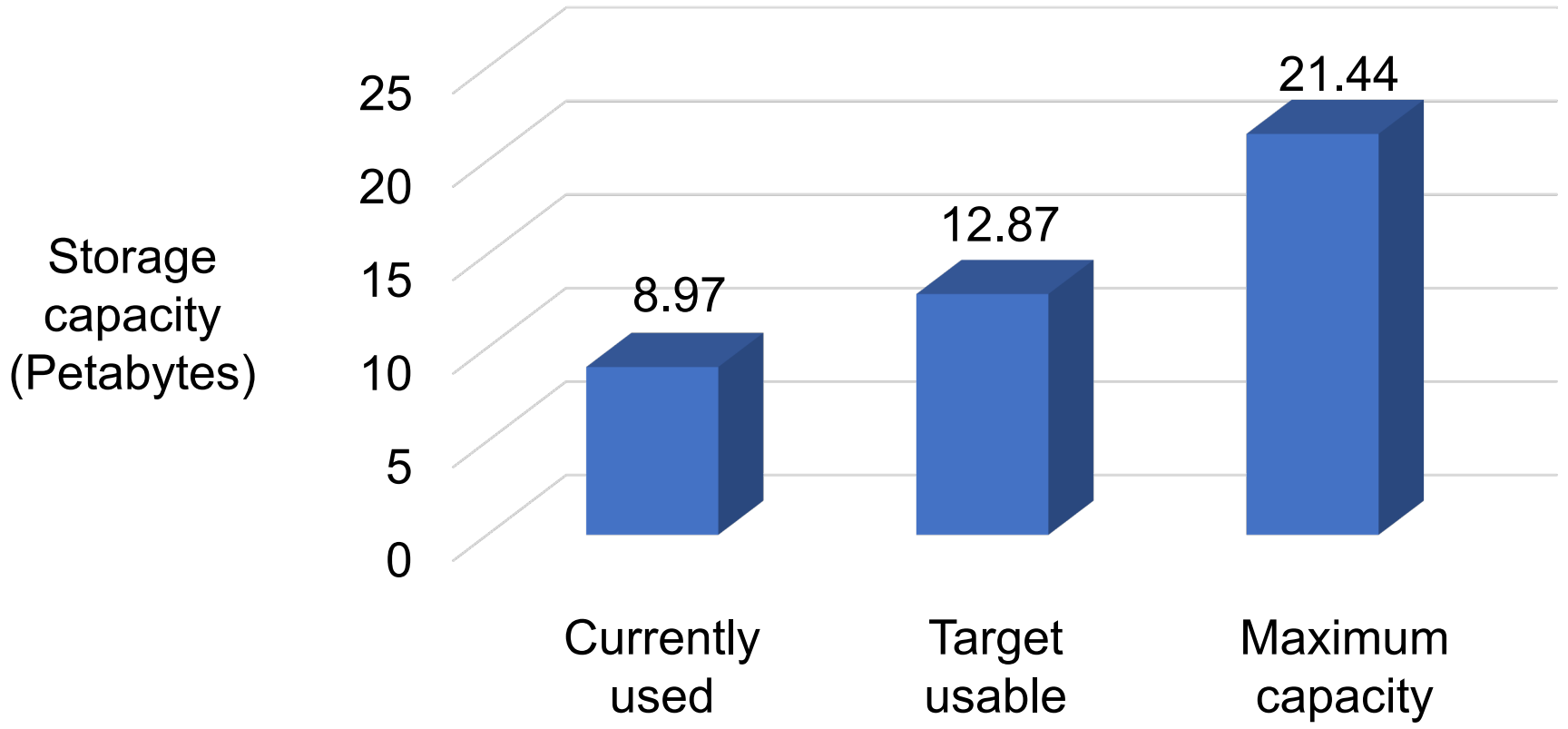
Future Components

**Tree from www.presentationgo.com*

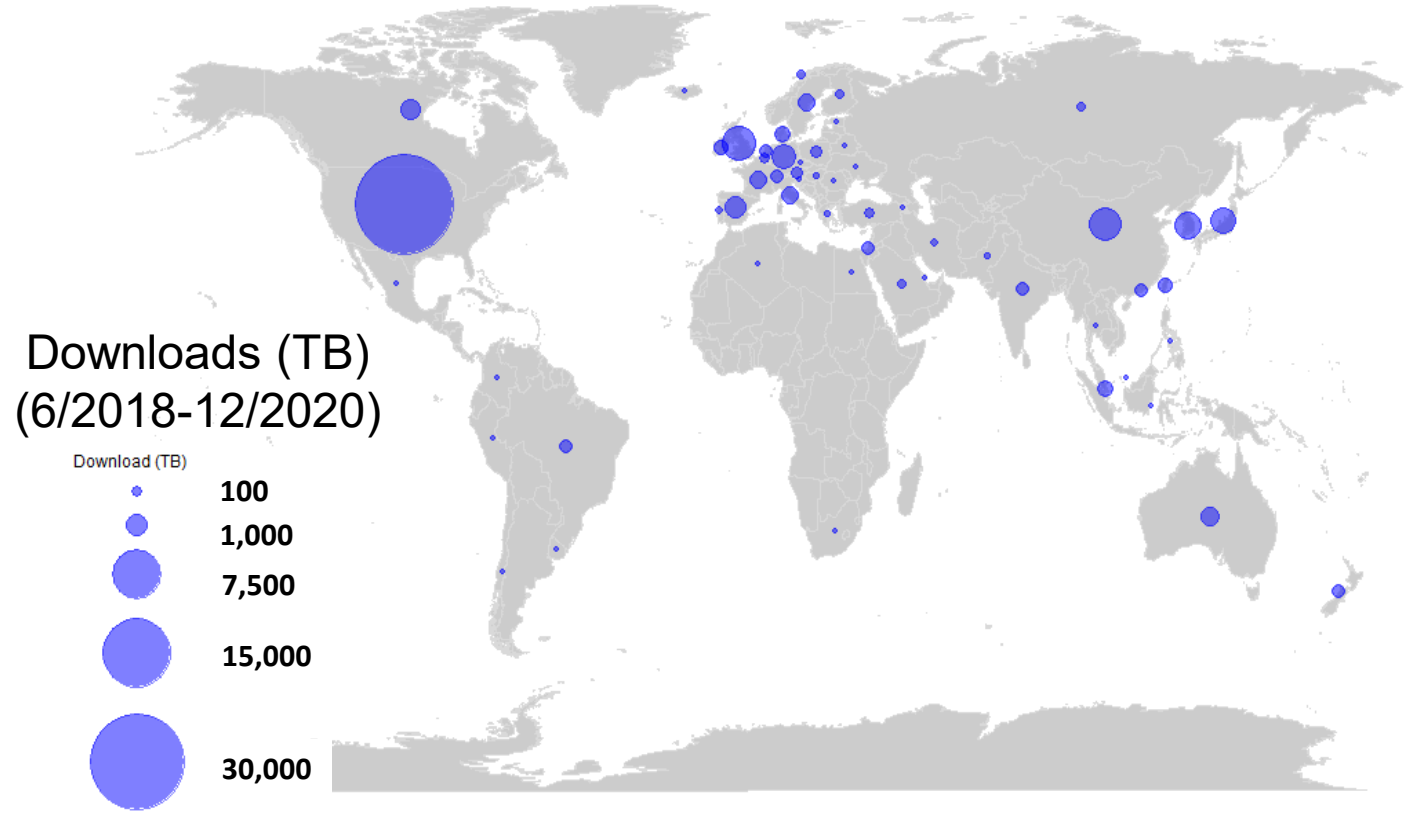
GDC Infrastructure: Univ. of Chicago Computing Power



GDC Infrastructure: Univ. of Chicago Storage Space



GDC Data Sharing: Worldwide Demand for Downloads



Country	Download(TB)
United States	32,894
United Kingdom	3,295
China	2,829
Korea	1,947
Japan	1,607
Germany	1,380
Spain	982
Canada	934
Australia	666
France	657
Italy	654
Sweden	597
Singapore	503
Denmark	448
Taiwan	356
Ireland	330
Switzerland	311
Brazil	290
Netherlands	269
Israel	263

GDC Data Sharing: Worldwide Demand for Downloads

NIH NATIONAL CANCER INSTITUTE GDC Data Portal

Home | Projects | Exploration | Analysis | Repository | Manage Sets | 0

Harmonized Cancer Datasets

Genomic Data Commons Data Portal

Get Started by Exploring:

Projects | Exploration | Analysis | Repository

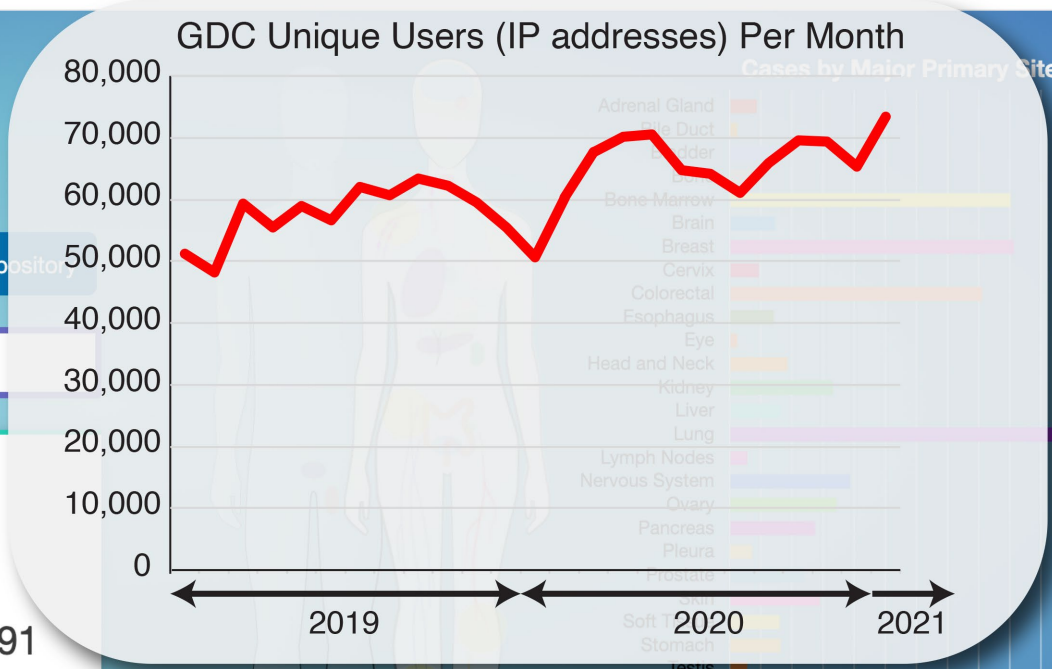
e.g. BRAF, Breast, TCGA-BLCA, TCGA-A5-A0G2

Data Portal Summary

Data Release 28.0 - February 02, 2021

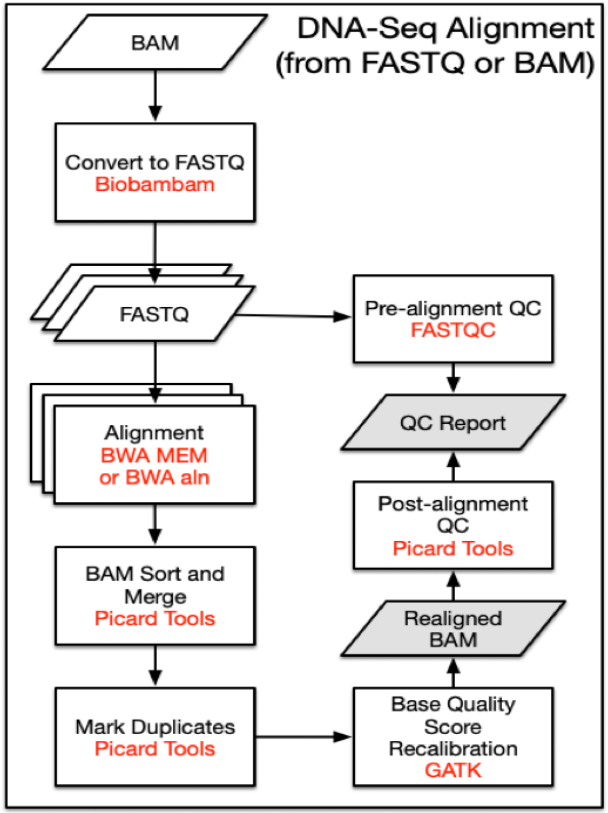
PROJECTS	PRIMARY SITES	CASES
68	67	84,591

FILES	GENES	MUTATIONS
615,761	23,535	3,461,256



GDC Data Harmonization: 51 Workflows and Growing

- DNAcopy
- GENIE Simple Somatic Mutation
- GENIE Copy Number Variation
- BCGSC miRNA Profiling
- ASCAT2
- BWA with Mark Duplicates and Coclea
- SomaticSniper Annotation
- MuTect2 Annotation
- VarScan2 Annotation
- MuSE Annotation
- FM Simple Somatic Mutation
- FoundationOne Annotation
- HTSeq - Counts
- HTSeq - FPKM
- HTSeq - FPKM-UQ
- BWA with Mark Duplicates and BQSR
- SomaticSniper
- MuTect2
- VarScan2
- MuSE
- Liftover
- BWA-aln
- STAR 2-Pass
- STAR - Counts
- Pindel Annotation
- Aliquot Ensemble Somatic Variant Merg…
- Pindel
- STAR 2-Pass Chimeric
- STAR 2-Pass Genome
- STAR 2-Pass Transcriptome
- BWA
- GENIE Structural Variation
- Arriba
- STAR-Fusion
- AscatNGS
- BRASS
- CaVEMan
- BWA with BQSR
- VCF LiftOver
- GATK4 MuTect2
- GATK4 MuTect2 Annotation
- MuSE Variant Aggregation and Masking
- MuTect2 Variant Aggregation and Masking
- SomaticSniper Variant Aggregation and M
- VarScan2 Variant Aggregation and Maskir
- Seurat - 10x Chromium
- FoundationOne Variant Aggregation and .
- GISTIC - Copy Number Score
- CellRanger - 10x Chromium
- CellRanger - 10x Filtered Counts
- CellRanger - 10x Raw Counts



Workflow example: DNAseq alignment

GDC Data Harmonization: Lowering the Bar for Users

22,285 TCGA
Whole exome
sequencing BAM files
(353.08 Terabytes)

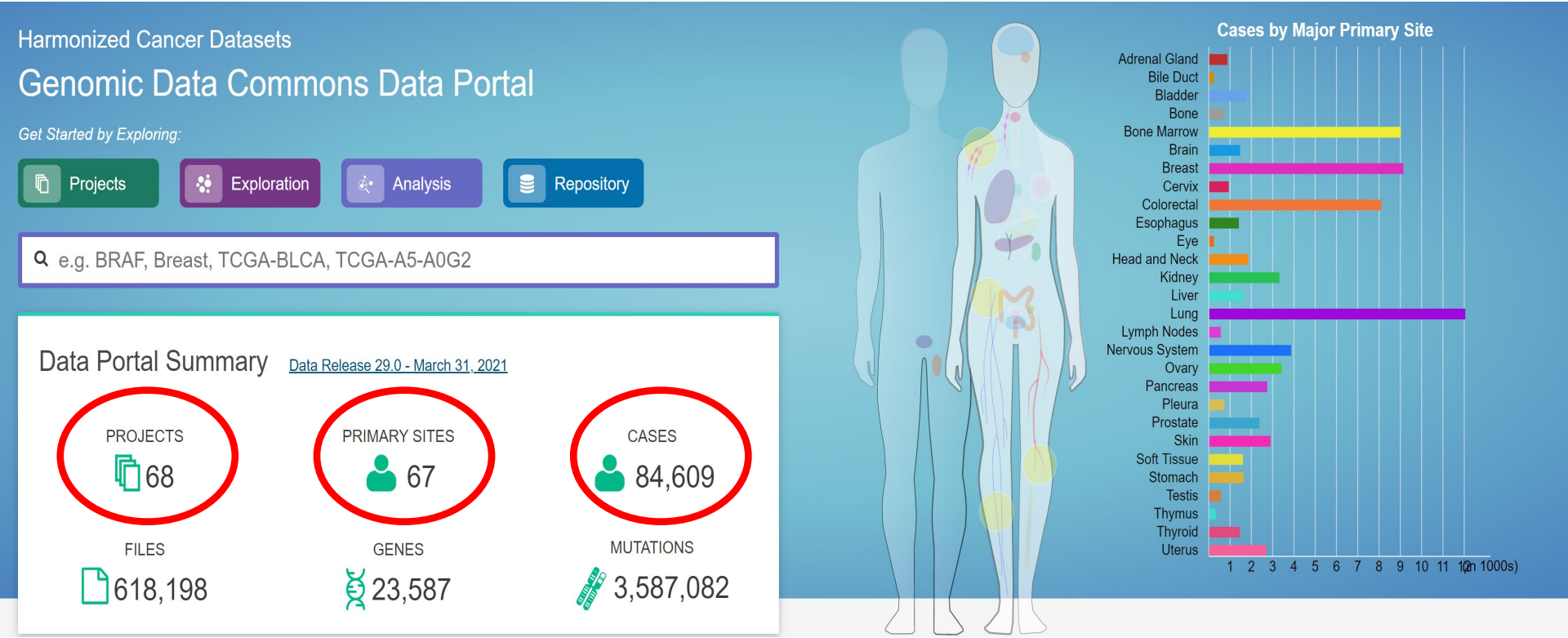
All variants (VCFs)
identified using four
variant callers
(68.56 Gigabytes)

All open access
mutation annotation
files (MAFs)
(2.58 Gigabytes)

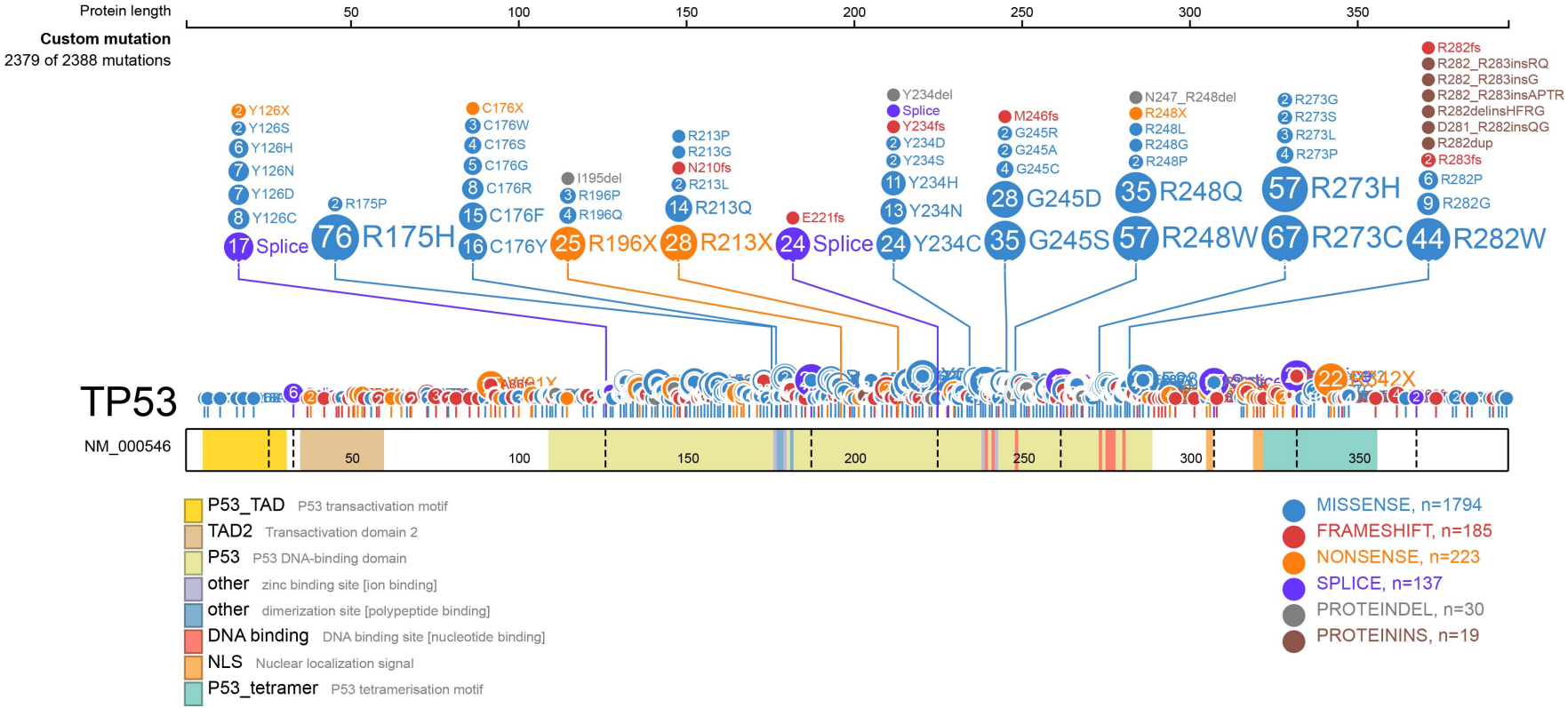
5,150-fold reduction in size

136,853-fold reduction in size

GDC Content: Cancer Genomic Data from >80K Patients

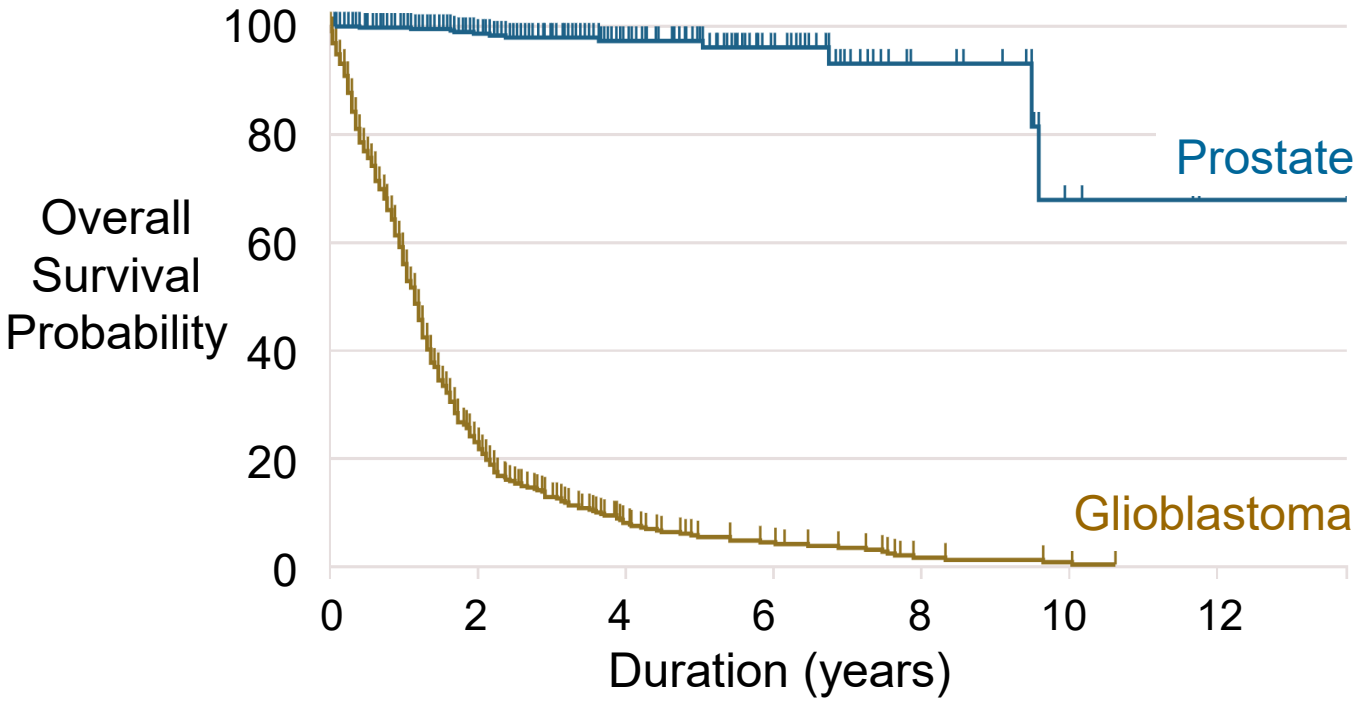


GDC Data Visualization: Protein Coding Mutations



GDC Data Visualization: Clinical Data

Visualize survival via GDC synthetic cohort builder

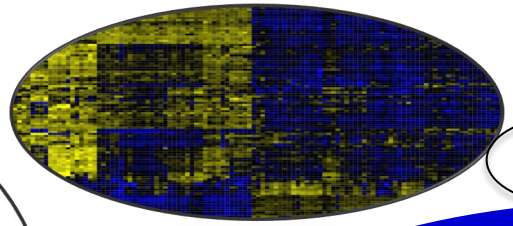


GDC clinical data

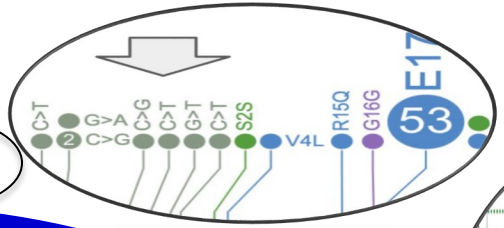
- Demographic
- Diagnosis
- Exposure
- Family history
- Follow-up
- Molecular test
- Pathology report
- Treatment
- Lab tests
- Histological images

GDC Data Visualization: Building an App Ecosystem

Gene Expression



ProteinPaint



API

API

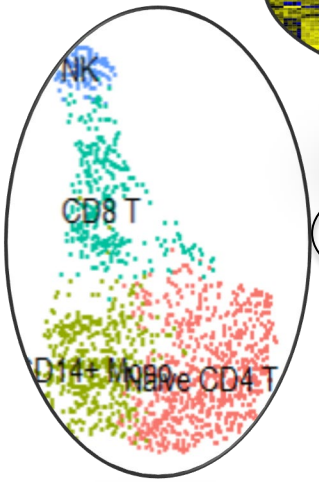
API

API

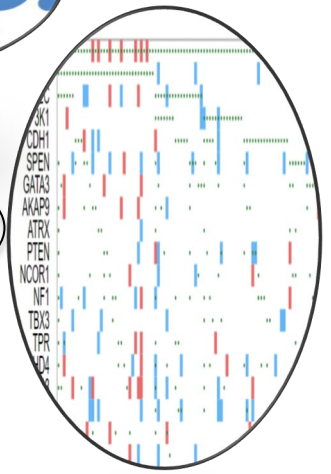
API

API

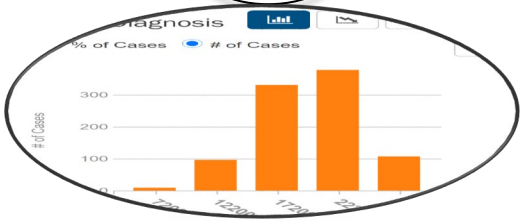
GDC
Backend
Data System



Single cell
RNAseq



OncoGrid



Clinical DAVE

3rd party
R package

TCGAbiolinks

www.cancer.gov

www.cancer.gov/espanol

cGMP Capabilities

Biologics, Small Molecules, Cellular Therapies, and Vaccines

NIH NATIONAL CANCER INSTITUTE

Current Good Manufacturing Practices

FFRDC facilities and subcontractors produce investigational agents according to:

- 21 CFR 210 GMPs for drugs: general
- 21 CFR 211 GMPs for finished pharmaceuticals
- 21 CFR 606 GMPs for blood & blood components
- 21 CFR 820 GMPs for medical devices
- 21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-based Products
- ICH Q7 Good manufacturing practice for active pharmaceutical ingredients
- Relevant and current *Guidance for Industry* applicable to early-phase investigational agents

Current Good Manufacturing Practices (cont'd)

Two cGMP facilities at the FFRDC provide the following:

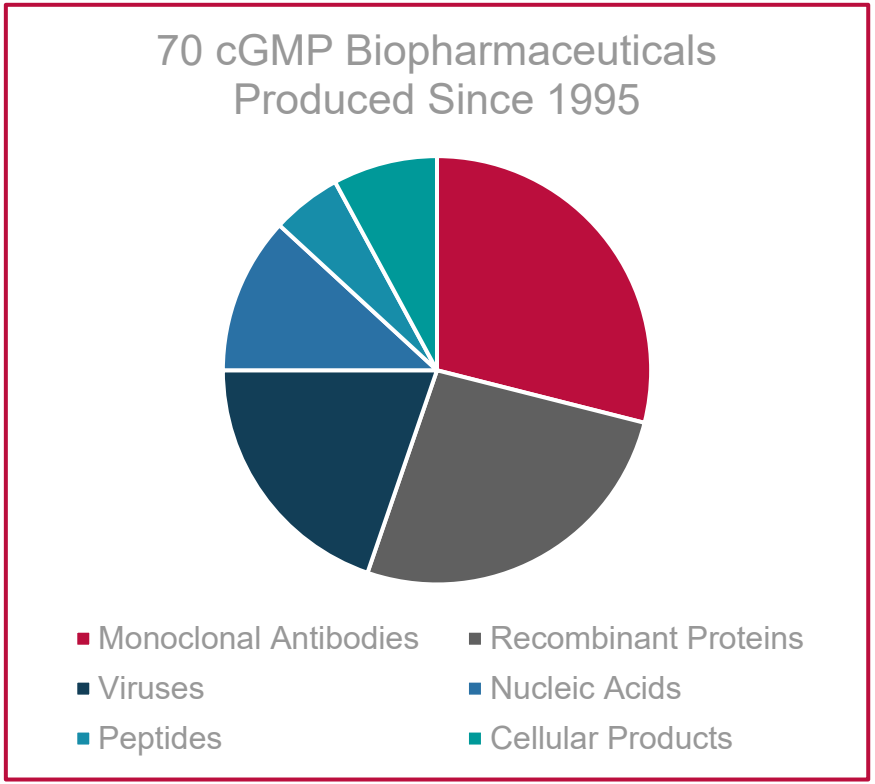
- Multi-product, multi-platform biologics/vaccine manufacture
- Quality Systems: Quality Control, Quality Assurance, Quality Engineering
- Robust scale-up capabilities in fermentation and bioreactor technology
- Regulatory Affairs support
- Operational maintenance, engineering and support for each of the cGMP facilities
- Technology Transfer expertise
- Quality Agreements established with US Government and subcontractors

Biologics and Cellular Therapies

Multi-product Pilot Facility for Biopharmaceuticals and Cellular Products

Capability was established in 1993 to:

- Provide specialized and unique technical expertise and services not available in the commercial market
- Perform feasibility studies of candidate agents
- Develop manufacturing processes and assays
- Conduct GMP manufacturing, filling, testing, and release for early-phase clinical studies
- Generate and submit FDA and international regulatory filings
- Conduct technology transfer to commercial entities
- Provide cGMP training to staff and partners



Multi-product Pilot Facility for Biopharmaceuticals and Cellular Products (cont'd)

- Overall facility size is ~66,000 ft^2
- Main GMP manufacturing area is ~22,000 ft^2
  - Separate trains for eukaryotic and prokaryotic production and purification
  - Suites for fill/finish, vial labeling and inspection up to 10,000 vials per run
- Self-contained virus manufacturing suite is ~2,500 ft^2
- Cell therapy suite is ~750 ft^2
- Multiple labs for analytics, process development, and product and raw material warehousing

Sampling of Equipment: Multi-product Pilot Facility for Biopharmaceuticals and Cellular Products

Chimeric Antigen Receptor T Cell (CART) Bioengineering and Manufacturing to Support Multi-center Clinical Trials

- Selected a closed-system production platform (Prodigy)
- Renovated lab space for GMP cell therapy suites
- Established expertise and bioengineering capability to support multi-center autologous cell therapy clinical trials within 12 months
- Currently supporting two multicenter trials with four CART products produced to date

Vaccines

Vaccine Pilot Plant (VPP)

- Commissioned in 2005
- Drug substance (DS) production and storage
- Drug product (DP) formulation, fill (vialing) and storage
- Analytical release and stability testing of DS & DP
- Adjuvant manufacture including terminal sterilization
- Subcontract mechanisms for viral vector-based vaccines

Tech transfer

Asset or product transfer to licensees

Clinic supply

Vaccine Pilot Plant
Frederick, MD

Vaccine Pilot Plant (VPP) (cont'd)

- Overall facility size is ~130,000 ft^2
- Clean room area is ~50,000 ft^2
  - Four parallel independent trains for eukaryotic and prokaryotic production and purification
  - WAVE and stainless-steel bioreactors (up to 2000L) for mammalian production platforms, and fermenters (100L) for bacterial platforms
  - Isolator technology for formulation, fill and finish
    - Automated systems for vialing, labeling; 100% visual inspection
    - >10,000 vials per run
    - 3 mL to 20 mL vials

Analytical Capabilities

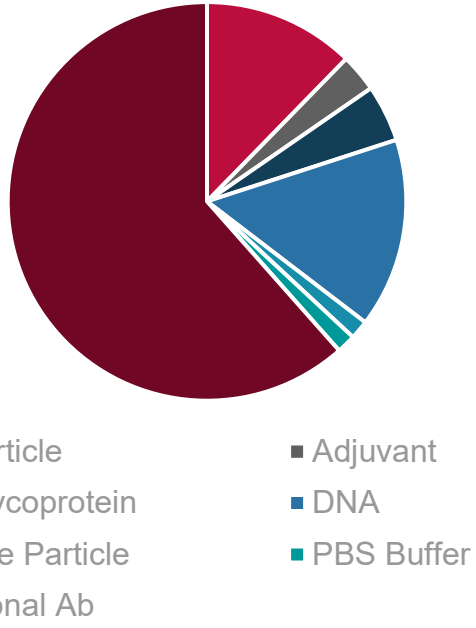
Raw Material testing

Release and stability testing

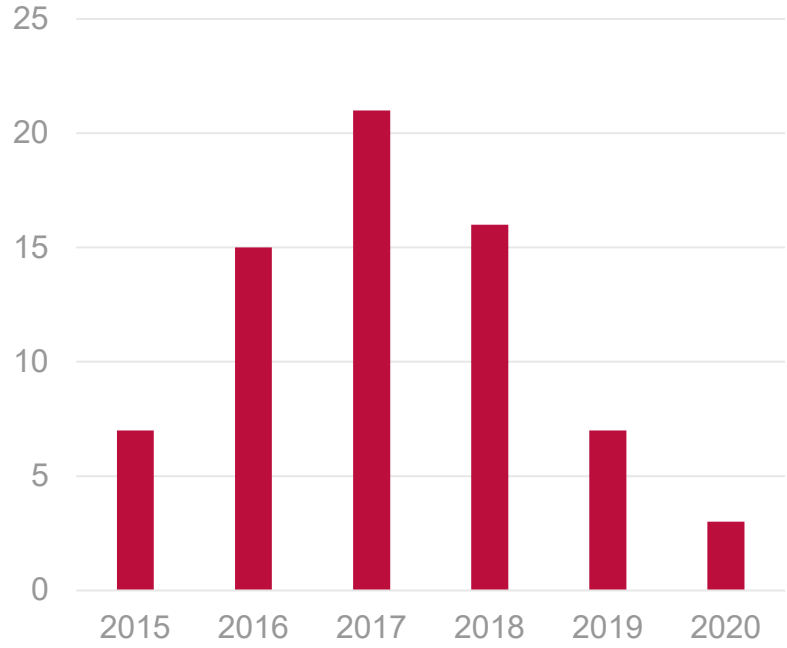
Environmental Monitoring

VPP Output Metrics 2015-2020

PLATFORM



PRODUCT FILLS



Disease Targets and Product Produced at the VPP

INFECTIOUS DISEASE TARGET	PLATFORM(s)
HIV	Recombinant glycoprotein, monoclonal antibody, synthetic peptide
CHIKUNGUNYA	Virus-like particle vaccine
EBOLA	Adenovirus vector, monoclonal antibody
INFLUENZA	Ferritin-nanoparticle, plasmid DNA, Pentamer-MOSAIC nanoparticle vaccines
MALARIA	Monoclonal antibody
MARBURG	Ad vector
RESPIRATORY SCYNCITIAL VIRUS	Recombinant glycoprotein
W/E/V EQUINE ENCEPHALITIS	Virus-like particle
ZIKA VIRUS	Plasmid DNA

Small Molecules

Procurement of Clinical-grade Small-molecule Pharmaceuticals

- The FFRDC does not have on-site facilities for production of small molecule pharmaceuticals
- Expertise is required for:
  - cGMP synthetic processes and purification
  - Solubility and formulation development

www.cancer.gov

www.cancer.gov/espanol

Chemistry – Drug Discovery/Screening/Development

NIH NATIONAL CANCER INSTITUTE

Molecular Pharmacology Laboratories

3D and 2D cell culture models and HTS screening

Automated High Throughput Screening Laboratories: NCI60 Production Screen

- Mission: Provide drug, investigational agents and compound screening service to global cancer research community
- NCI60 2D production screen tests small molecules, proteins and other investigational agents submitted by external investigators and provides the cell-based assay data back to them confidentially
- Provide external investigators with NCI60 cell line RNA, DNA, frozen cell pellets, live cells upon request
- Provide public-facing websites with NCI60 drug and compound response (20 years of data), genetic characteristics such as mutations, DNA methylation and gene expression

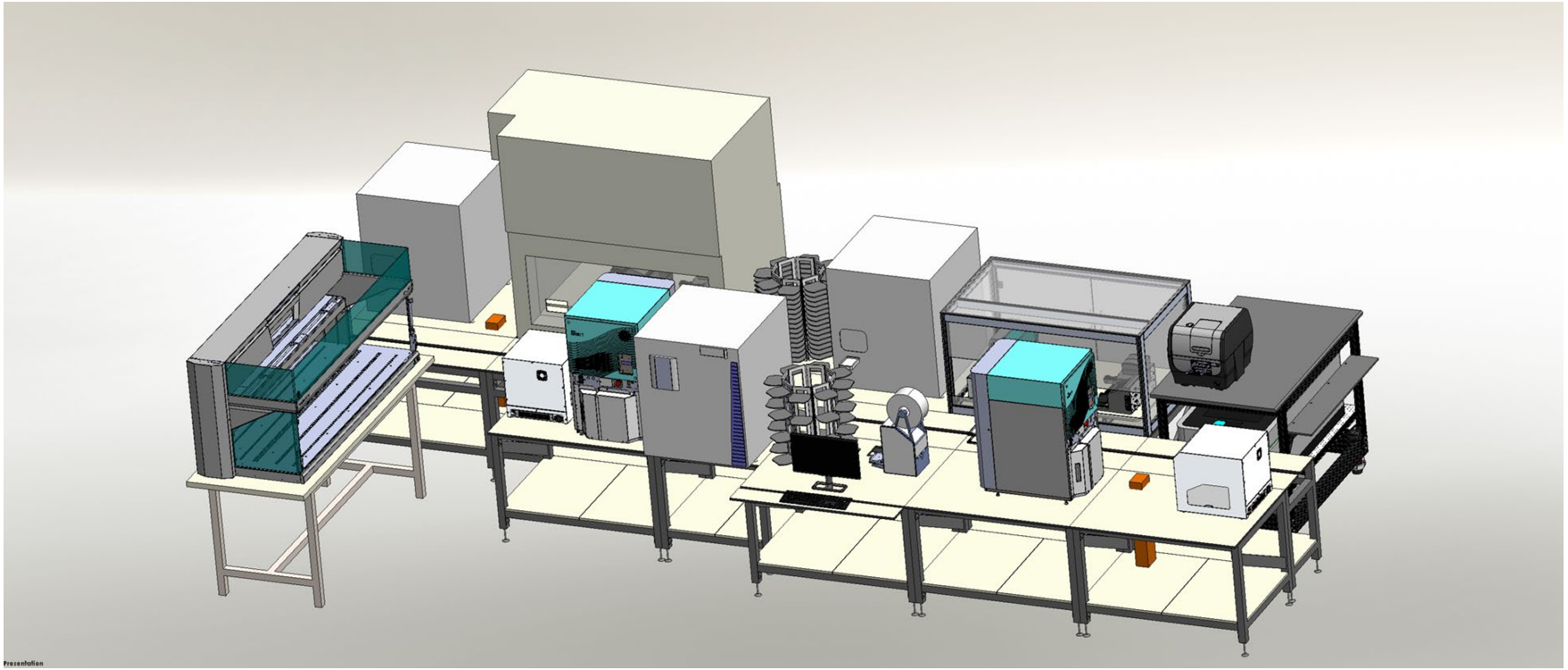
Automated High Throughput Screening Laboratories

- Mission: Provide service to global cancer research community
- Disease specific screens: 60 small cell lung cancer (SCLC) cell lines, 60 pediatric and adult sarcoma cell lines, 20 pancreatic cancer cell lines. SCLC and sarcoma lines have been screened with FDA approved anticancer agents and 400 or more investigational anticancer agents and data provided to the community on public facing websites. Gene expression, microRNA and DNA methylation data also provided.
- https://sclccelllines.cancer.gov/
- https://sarcoma.cancer.gov/sarcoma/
- These screens and databases must be updated periodically

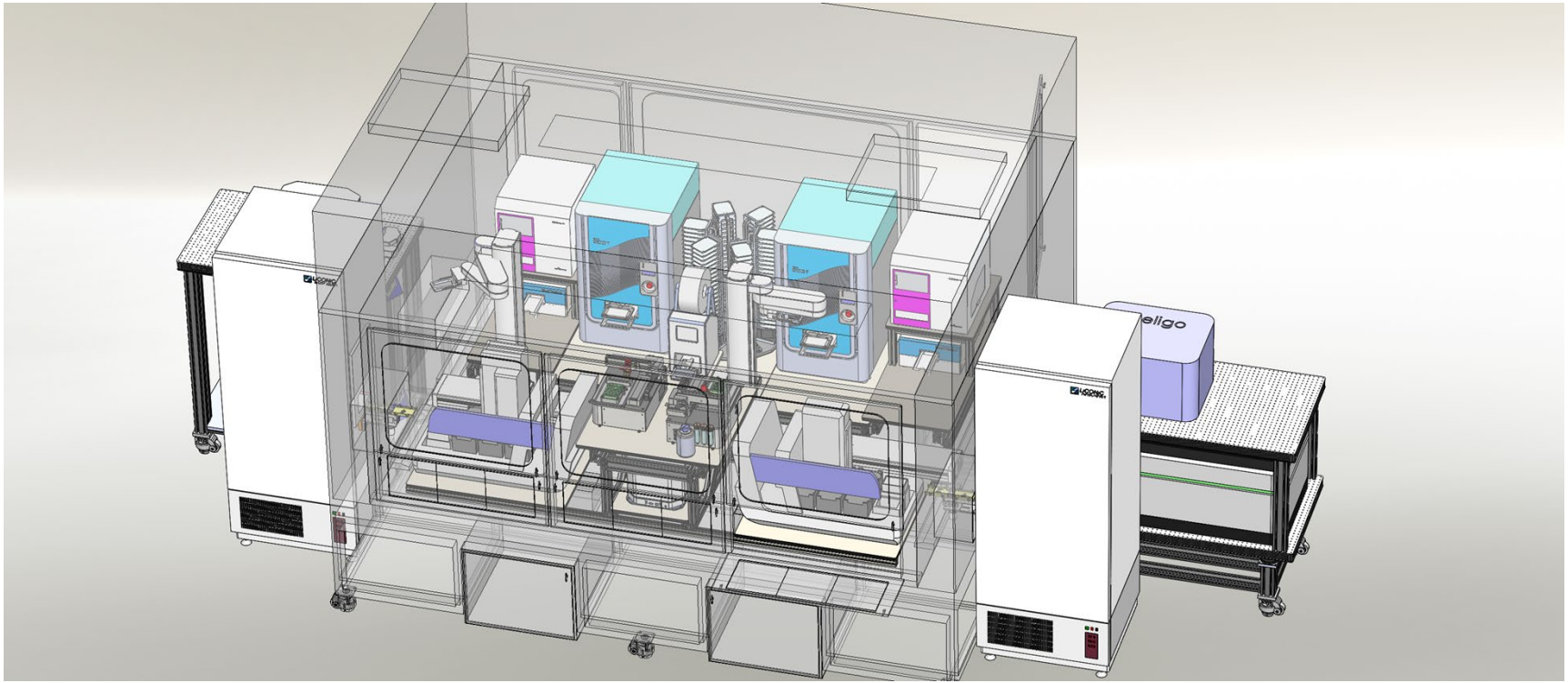
Automated High Throughput Screening Laboratories

- 3D cell culture screens: complex spheroids and organoids using cultures derived from patient clinical specimens or patient-derived xenografts (PDX) including cell lines and organoid cultures
- Patient-derived cell lines and patient-derived organoids https://pdmr.cancer.gov/
- Conduct single agent and combination 3D culture screens with a goal to provide robust data to Cancer Therapy Evaluation Program (CTEP) and other physicians to inform early clinical trial designs
- Develop an automated organoid screen to be made available as a production screen to screen compounds submitted by external investigators

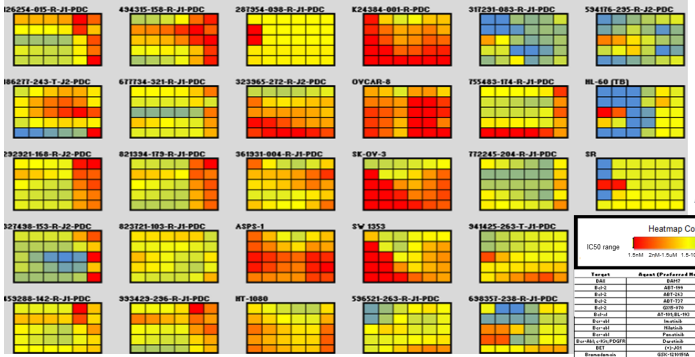
Automated High Throughput Screening Laboratories: System #1



Automated High Throughput Screening Laboratories System #2



Automated High Throughput Screening Laboratories: Database development and Maintenance



Heatmap of Selected Agents IC50s in SCLC lines in the single agent screen

Cmax = 74 uM	0.00914 uM	0.0274 uM	0.0823 uM	0.247 uM	0.741 uM	2.22 uM	6.67 uM	20 uM
NCI-H1876	-2	-2	-0	0.8	0.7	0.7	0.6	0.4
NCI-H1618	0.4	1.2	2.1	2.5	1	0.8	0.6	0
NCI-H209	-0	-0	1.4	1.6	1.8	1.5	1.4	1.4
NCI-H187	-1	-0	-2	1.2	1.1	0.3	0.7	0.6
NCI-H719	2.6	3.8	3.9	4.9	1.9	1.8	0.9	1
NCI-H1048	0.9	-0	-1	-0	-2	0.8	-2	-1
NCI-H526	3.4	-1	0.9	1.3	0.9	0.9	0.9	0.6
NCI-H211	-13	-0	2.2	1.1	0.1	0	0.2	-0
COLO 668	2	-1	6.7	6.8	7.5	6.6	4.7	2.7
NCI-H2107	2.4	4.6	4.6	17	15	12	10	7.8
LXFS 650L	6.6	9.2	24	3.8	0.4	0.4	0.2	0.1
COR-L32	0	2	3	8.4	3.2	5.2	-1	-1
NCI-H2081	-5	-11	2.8	4.1	13	13	12	14
NCI-H1882	4.3	3.8	12	15	19	16	20	17
NCI-H1963	1.8	6.6	7	16	5.3	3.7	3.6	2.5
NCI-H1694	0.1	1.1	20	21	16	14	9.1	7.1
DMS 79	4.3	2.8	10	17	10	8.5	7.4	4.3
NCI-H1092	-4	-1	1	7.2	10	21	20	7.2
NCI-H1105	10	11	27	21	25	23	26	17
NCI-H510	9.2	12	19	32	16	9.3	10	4
LXFS 605L	9.9	16	7.1	18	8	1.8	0.7	-0
NCI-H847	-5	4.1	15	21	5.1	1.7	0.6	0.1
NCI-H146	7.3	5.9	0.8	15	9.2	22	15	2.2
A549	3.3	5.6	13	9.3	11	6.4	8.7	7.9
DMS 114	-19	-17	-10	-4	-5	-5	-4	-3
NCI-H2171	3.9	9.6	36	40	9.8	3.2	1.6	0.2
COR-L47	-4	-3	-5	15	-0	-2	-0	0.1
NCI-H841	0.1	-3	6.8	6	8.7	13	9.6	3.5
NCI-H69	-1	-7	4	0.8	-4	-8	-4	-4
NCI-H69 CPR	-2	-8	7.4	15	8.9	3.7	1.9	1.5
NCI-H524	6.4	4.2	17	29	3.4	1.8	1.3	-0
NCI-H1417	3.3	16	24	26	7.7	3	1.6	0.5
NCI-H2066	-11	-16	-5	-9	-1	-6	4	6.5
NCI-H250	19	14	14	51	25	22	13	10
NCI-H2330	1.4	2.9	15	40	40	27	20	9.6
COR L88	-10	-10	-15	-22	-7	1.4	1.4	2.5
NCI-H865	-2	-10	-2	7	0.5	2.8	3.2	5.4
DMS 273	-2	-5	6.7	9	-15	-13	-7	-6
NCI-H1522	-16	-26	-5	8.5	0.7	4.6	2.5	3.8
DMS 53	10	3.8	-5	-5	-7	-8	-2	-3
NCI-H711	-6	-3	-6	-2	-2	-7	-5	-4.4
NCI-H2198	-2	-0	2.2	21	45	48	42	46
NCI-H1836	-3	0.5	-6	-2	4	-6	4.6	-4
NCI-H720	14	10	11	20	16	20	23	13
NCI-H69VCR R	5.9	11	11	7.9	4.2	-5	-9	-7
NCI-H1436	-2	0.2	0.2	3.5	22	27	33	34
NCI-H660	9.4	8.5	8.2	13	7.1	1	-2	-2
NCI-H1650	4.6	0.2	-3	-3	0.3	7.2	7.2	-2
NCI-H735	-15	-10	1.6	6.5	-10	-55	-22	-27
SW 1271	7.9	4.7	9.2	27	-3	-1	-0	0.3
NCI-H220	-4	-5	-1	19	45	32	23	24
NCI-H345	3.4	14	42	41	43	33	31	56
SHP-77	9.4	6.9	6.6	16	13	9.6	13	12
NCI-H889	0.4	3.4	-5	-7	-3	-5	-2	14
NCI-H1341	-12	-10	-5	-15	5.0	0.7	2.1	-0
NCI-H69 LX10	-0	0.6	-2	10	-1	-6	-7	-6
NCI-H196	1.9	-6	-6	-6	-4	-4	-3	-7
DMS 187	2.1	1.2	-1	-2	8.4	-1	2.7	7.2
NCI-H378	7.2	4.1	-3	4.7	-6	-36	-7	13
NCI-H28	-9	1.4	-0	0.4	-2	-0	-2	3.8
NCI-H1672	4.6	4.4	1.7	-1	-4	-9	-4	3.1

	0.00914 uM	0.0274 uM	0.0823 uM	0.247 uM	0.741 uM	2.22 uM	6.67 uM	20 uM
NCI-H1876	0.8	0.6	0.6	0.5	0.8	0.5	0.4	0.3
NCI-H1618	0.6	0.6	1	0.8	0.2	0.2	0	0.2
NCI-H209	0.1	0.7	1.5	1.9	1.2	0.8	0.6	0.3
NCI-H187	1.0	1.1	4.4	1.8	2	1.5	1.1	1.2
NCI-H719	3.4	2.7	4.9	4	1.7	0.8	0.7	0.7
NCI-H1048	2.1	-0	-2	1.5	1.3	0.1	0.8	-2
NCI-H526	1.6	2.6	1.3	0.6	0.7	1	0.2	1
NCI-H211	0.8	2.1	1.5	-1	-1	-0	-0	0
COLO 668	13	15	22	16	16	10	7.3	4.3
NCI-H2107	0.8	7.2	17	14	12	9.7	5.6	6.9
LXFS 650L	8.2	22	20	0.1	0.2	0.3	0.3	0.3
COR-L32	4.2	2.7	9.1	2.7	3.2	0.1	-0	0.9
NCI-H2081	-0	-0	5.7	12	13	10	9.7	10
NCI-H1882	5	6.5	15	17	12	13	8.5	10
NCI-H1963	-4	-1	6.2	11	5.4	7.8	2.9	4
NCI-H1694	15	23	23	20	17	14	12	11
DMS 79	14	30	26	30	17	9.8	5.8	5.7
NCI-H1092	7.4	9.5	14	15	25	24	22	20
NCI-H1105	14	26	33	27	24	22	16	16
NCI-H510	2.6	4.5	15	10	7.8	13	2.9	4.1
LXFS 605L	3.7	6.4	7.7	11	0.8	0.4	2.1	1.5
NCI-H847	11	15	21	14	5.8	1.3	0.5	0.7
NCI-H146	4.6	7.8	6.1	15	15	15	20	15
A549	4.9	6.5	9.9	11	8.7	9.3	4.9	6.3
DMS 114	6.7	-0	-7	-4	-3	-3	-3	-2
NCI-H2171	3.4	13	34	12	5.8	4.3	1.3	1.6
COR-L47	-3	-8	-3.5	-7	-2	-0	-0	0.6
NCI-H841	10	15	23	15	12	12	9.4	5
NCI-H69	8.2	4.1	7.9	4.5	-0	-1	-1	-0
NCI-H69 CPR	0.8	1.7	8	8.2	5.8	1.9	0.2	1.4
NCI-H524	-2	-0	26	5.6	2.1	1.1	1.2	1.4
NCI-H1417	9.4	24	31	10	3	1.4	0.7	0.8
NCI-H2066	-1	-5	-10	-6	-1	0.5	2.5	4.7
NCI-H250	6.1	12	29	14	26	12	6.5	11
NCI-H2330	8.1	19	47	44	52	45	25	34
COR L88	4.8	4.7	-11	-17	1.7	2.1	0.5	3.6
NCI-H865	-6	0	-2	-5	0.8	-0	0.5	3.3
DMS 273	4.3	-5	5.9	5.5	-6	-3	-3	0.6
NCI-H1522	16	13	20	12	14	14	5.8	8.9
DMS 53	2.9	-0	-8	-12	-10	-8	-6	-2.5
NCI-H711	-6	-10	-7	-2	-2	-5	-4	-1.4
NCI-H2198	3.9	8	29	27	46	44	39	39
NCI-H1836	-5	-4	-4	-7	-7	3.4	-0	18
NCI-H720	12	11	10	19	18	19	23	14
NCI-H69VCR R	3.2	6.6	4.3	10	9.8	10	0.4	15
NCI-H1436	-3	-7	-6	6.3	18	30	17	16
NCI-H660	12	16	14	23	15	8.8	10	10
NCI-H1650	11	11	12	4	9.3	6.7	15	11
NCI-H735	-6	-6	-12	-10	-10	-12	-9	-3
SW 1271	3.9	4.8	5.7	23	11	12	13	11
NCI-H220	-2	0.2	28	11	42	40	23	27
NCI-H345	4.3	16	27	28	26	31	27	20
SHP-77	7.5	6.5	5.1	20	14	20	22	17
NCI-H889	4.3	7.4	-7	3.2	4.2	2	12	6.6
NCI-H1341	0.7	-2	4.1	2.8	6.5	5.8	6.3	6.4
NCI-H69 LX10	-2	-3	1.7	3	8.8	9.4	15	22
NCI-H196	1.3	-2	-1	-7	-3	-3	-6	0.2
DMS 187	-3	0.6	0	5.1	15	15	15	12
NCI-H378	3.9	10	-12	-4	-9	-2	-4	13
NCI-H28	4.5	-0	-3	2.6	4.3	1.6	5.3	3.3
NCI-H1672	1.2	-3	-6	-3	-14	-8	-2	6.7

www.cancer.gov

www.cancer.gov/espanol

Natural Products

Natural Products Support Group Mission

Laboratory support for the Natural Products Branch, DTP, DCTD

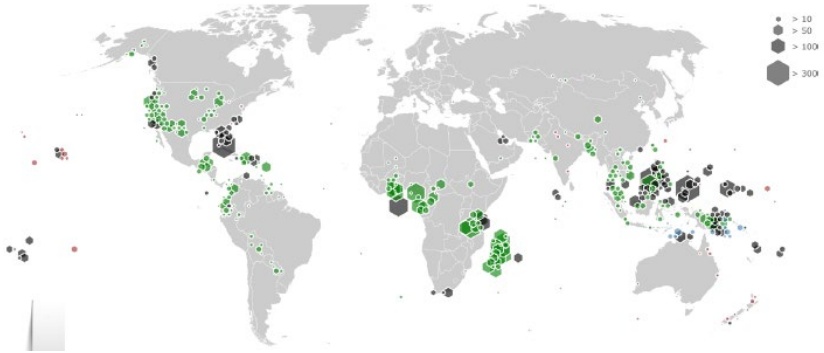
- Extraction of plant, marine and microbial biota
- Prefractionation of natural product extracts
- Isolation and structure identification of biologically active natural products
- Microbial natural product culture and extraction

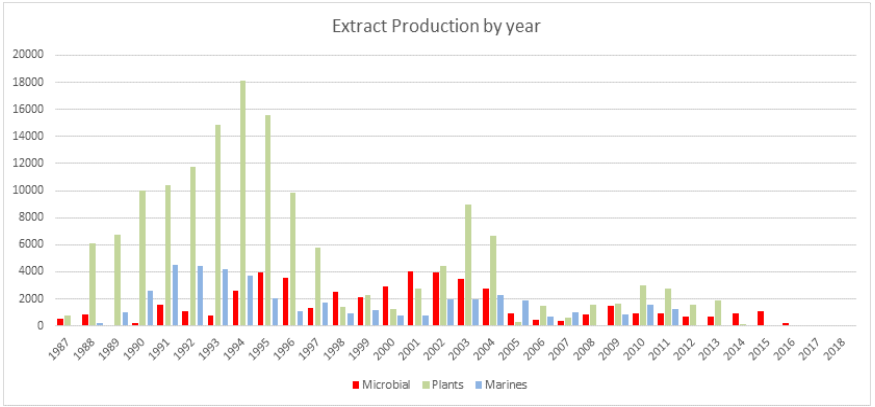
Natural Product Extraction Laboratories

Capability established in the 1980s.

Specialised laboratories for high throughput extraction of plant, marine invertebrate and microbial material.

To date 230,000 natural product extracts generated.

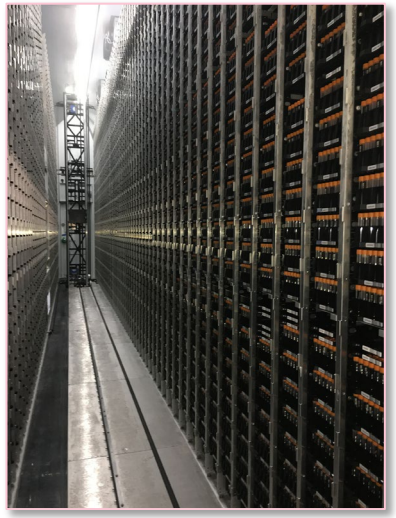




Prefractionation of Natural Product Extracts

Capability established in 2016. Custom-built automation laboratory capable of:

- Generating a library of 1,000,000 natural product fractions.
- Replicating the library into >55 copies of 384 well plates suitable for high throughput screening
- Automated sample storage and recovery

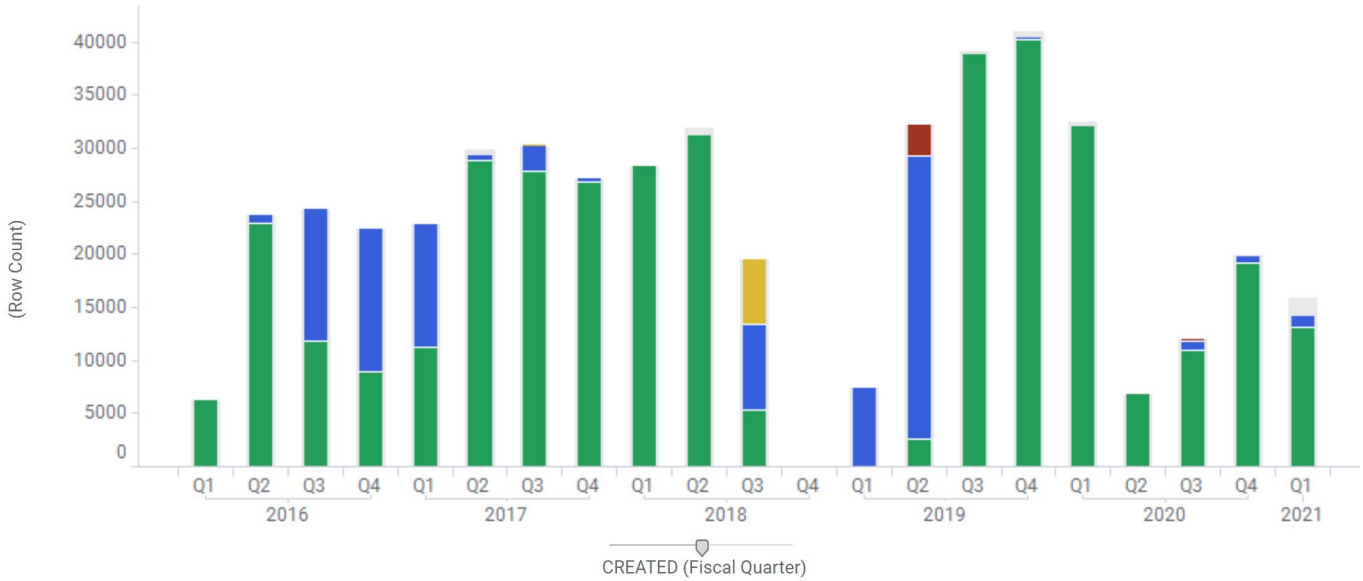


Fraction Library Production Metrics

A total of 464,464 fractions produced to date.

326,000 fractions released for distribution on 384 well plates.

Fractions Produced by Date



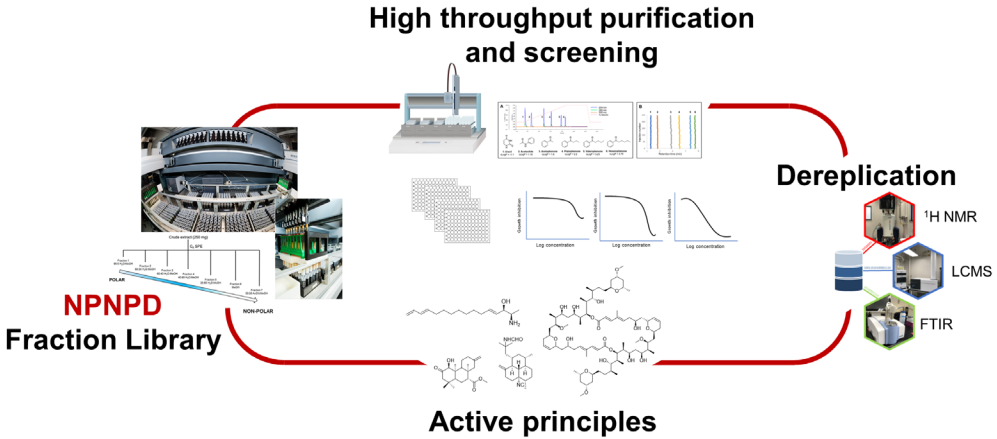
Fractions, Extracts per CREATED ...

Year	Quarter	Month	Grand total of Fractions	G
2020	Q1	Jan	10,472	
		Feb	11,704	
		Mar	9,856	
	Q2	Jun	6,776	
	Q3	Jul	3,080	
		Aug	3,080	
		Sep	5,880	
	Q4	Oct	7,392	
		Nov	8,008	
		Dec	4,312	
2021	Q1	Jan	4,928	
		Feb	3,696	
		Mar	2,464	
Grand total			464,464	

Isolation of Biologically Active Natural Products

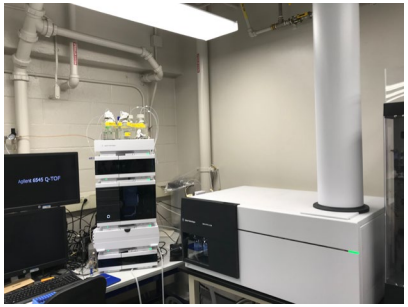
Chemistry laboratory focused on:

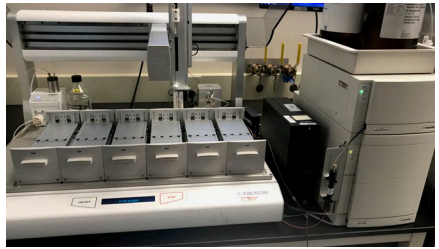
- Isolation of biologically active natural products as part of prefractionated library high throughput screening efforts.
- Ability to capture, store, and generate libraries of high-quality analytical chemistry data on the prefractionated library and the isolated natural products.

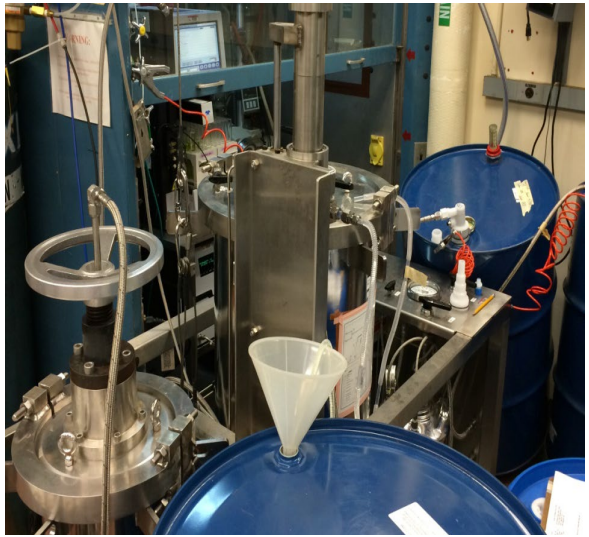


Large-scale Isolation of Natural Products

- Ability to perform medium- and large-scale compound isolations from natural product extracts.
- Specialized chemistry equipment for spectroscopic and spectrometric characterization of small molecules.

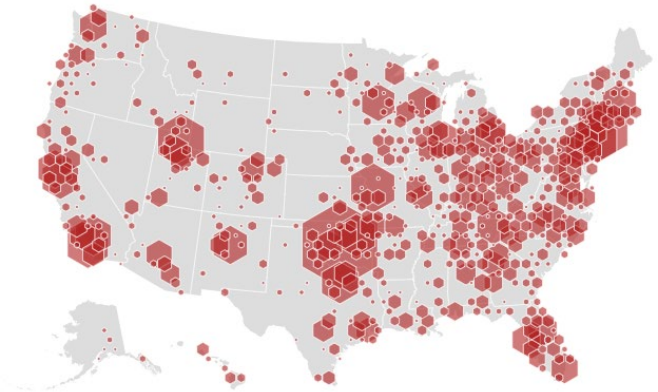


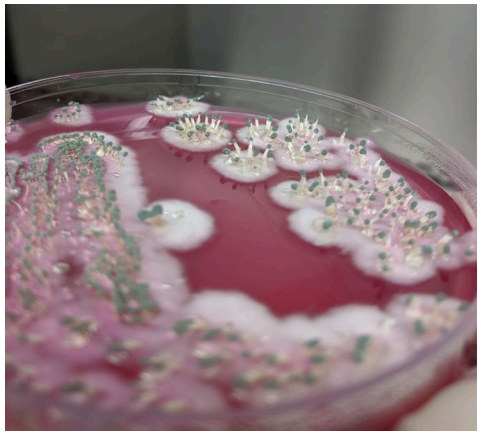




Microbial Strain Collection Expansion

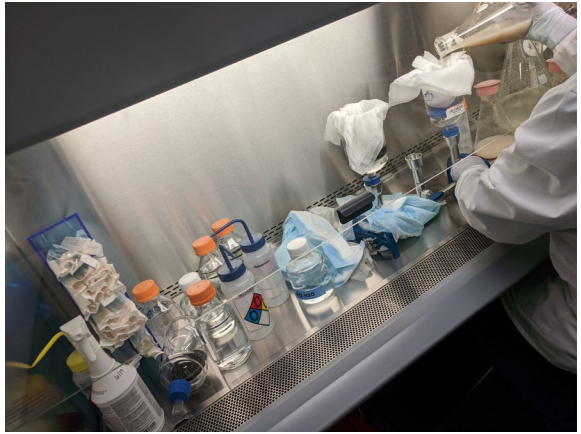
- Program focused on expanding the diversity of the microbial strain collection in the Natural Products Repository
- Processing of new isolates includes plating, assessing viability and contamination, photographing, and generating 7 replicate vials.
- 20,000 US-sourced new fungal strains received since 2015.





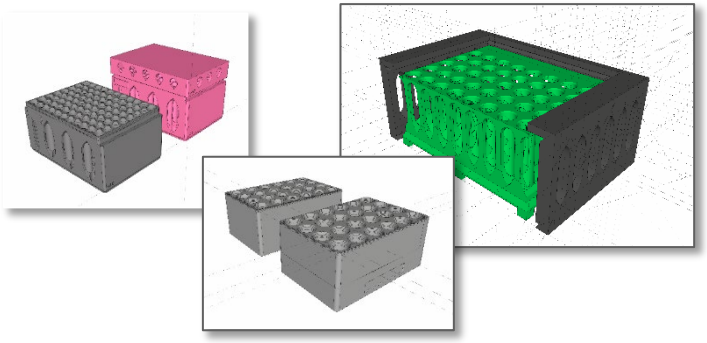
Microbial Natural Product Culture and Extraction

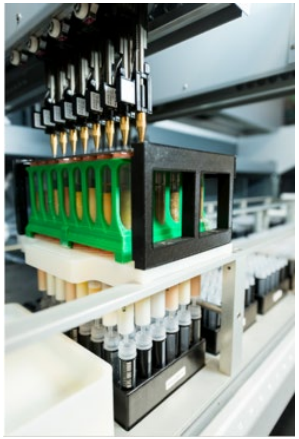
- Specialized laboratories able to perform small- and medium-scale fermentations of microbial cultures.
- Capacity to perform 100 x 1L cultures per week.
- Capacity for high-throughput extraction of microbial cultures.

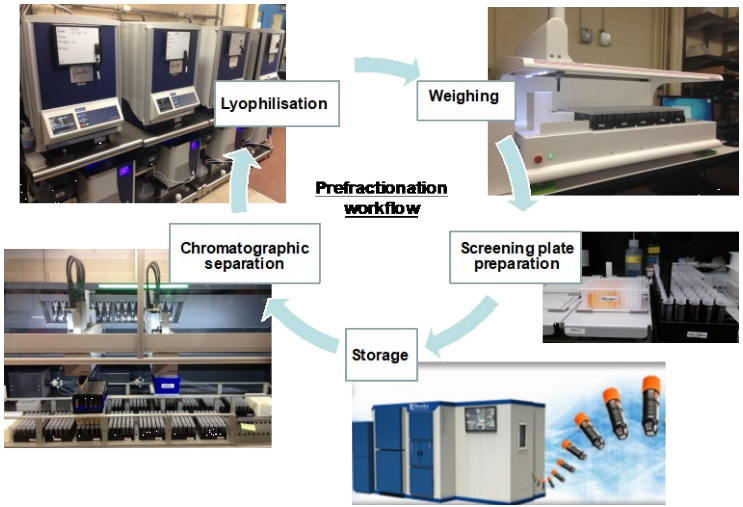


Ability to Design new Labware and Implement New Experimental Procedures

- 3D printed labware
- Customization of lab instrumentation
- Large integrated infrastructure development

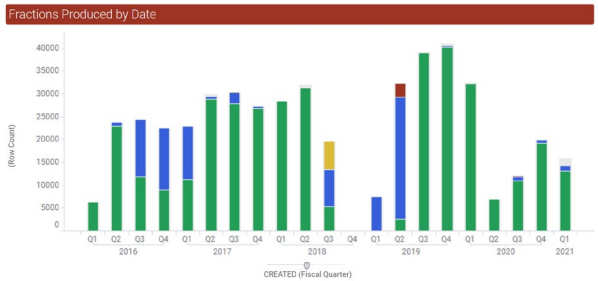


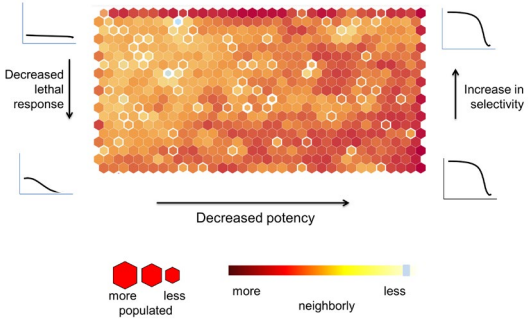


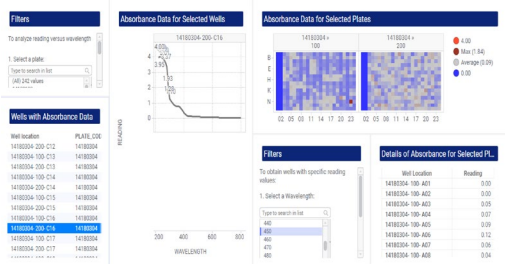


Development of a Public Database and Bioinformatics Platform

- Development of web interfaces integrating taxonomy, analytical chemistry, biological activity, and genomic data.
- Creation of databases for fraction production, plating, and chemical annotation of the prefractionated library.
- Integration of legacy database structures into a new stable and user-friendly interface.







www.cancer.gov

www.cancer.gov/espanol

Clinical Studies Support

Relevant Areas of the SOW (1)

- Provide a management infrastructure that includes oversight and mentoring of good clinical practices
- Provide the broad range of technical support, administrative management services and program-dedicated research support programs, based domestically and internationally (typically government-to-government engagements), as requested.
- Mounting an initial effective rapid response to urgent and compelling public health concerns; then, post-event, establishing the capacity to sustain these programs and ensure readiness for future event response.
- Provide general programmatic support to the clinical research efforts (e.g., subcontracting, logistics and procurement)

Relevant Areas of the SOW (2)

- Provide physicians, medical affairs scientists, expert nursing care, pharmacy and laboratory technicians, clinical project managers, regulatory and clinical trials staff, biostatisticians, and consultants/subject matter experts (including, but not limited to, physicists, Artificial Intelligence specialists, medical technologists, and chemists) who shall:
  - Serve as a liaison with clinical, regulatory and laboratory personnel on assigned protocols
  - Serve as associate investigators
  - Document patient care per protocol requirements
  - Participate in clinical rounds

Relevant Areas of the SOW (3)

- Who shall (cont'd)
  - Order diagnostic and related procedures, such as imaging per protocol
  - Assist in skilled procedures performed by medical affairs/physicians (e.g., phlebotomy and IV catheter placements)
  - Coordinate patient schedules to meet the requirements of protocol interventions and data collections
  - Collect clinical samples per protocol requirements
  - Provide overall study coordination
  - Coordinate courier services

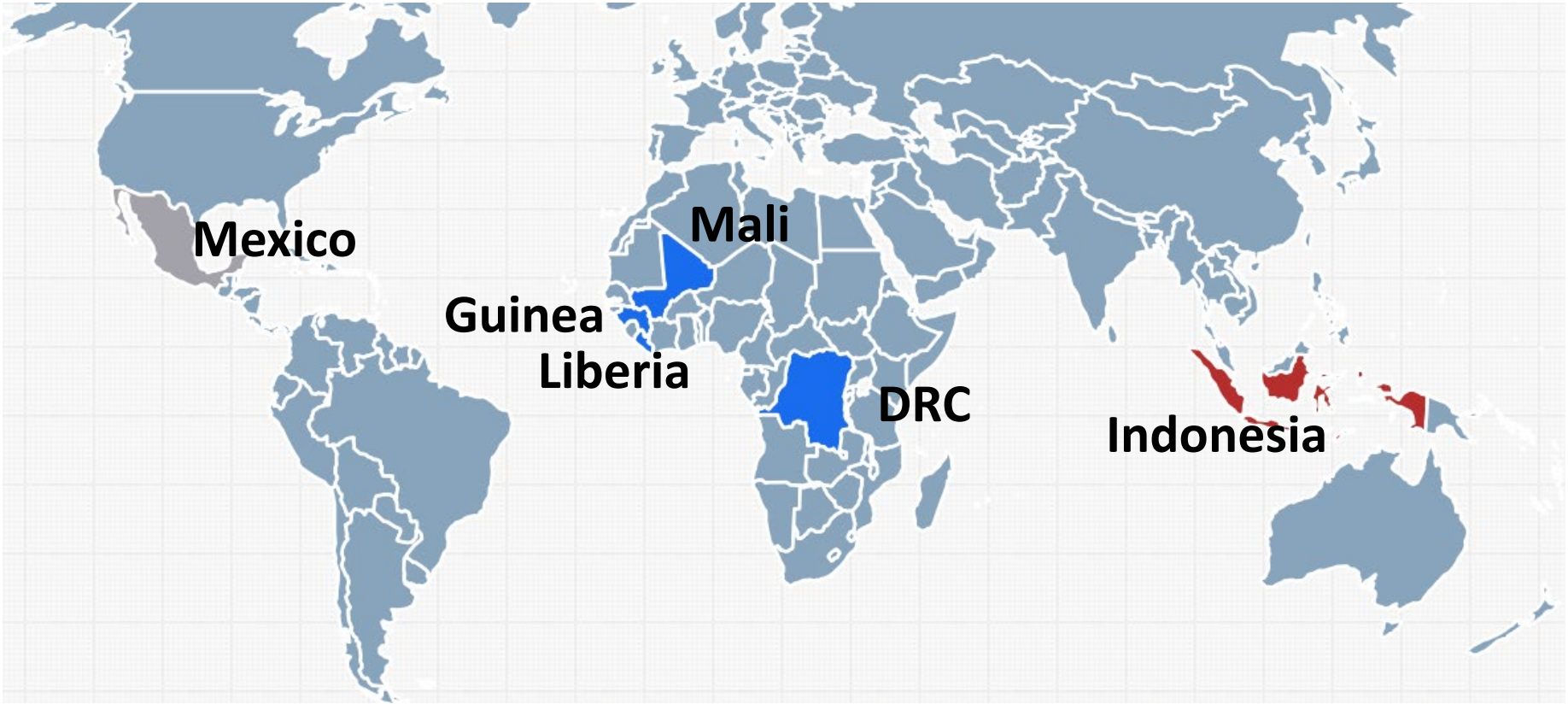
Relevant Areas of the SOW (4)

- Who shall (cont'd.)
  - Provide protocol lifetime support (e.g., clinical research training and education)
  - Manage clinical trial research portfolios
  - Select clinical trial sites
  - Provide data warehousing, management and analysis, including biostatistics
  - Provide monitoring and quality assurance
  - Provide medical and technical writing for clinical trials (e.g., protocol development, regulatory communications and publications)

Support to Clinical Research

- Typically in areas not supported in other ways
- Often international, high-priority, urgent
- Include staffing and physical infrastructure
- Laboratory activities include routine monitoring (at the sites) as well as implementation of new technologies (often at the FNL)
- Regulatory Support

NIAID International Clinical Research Programs Supported by the FNL/FFRDC

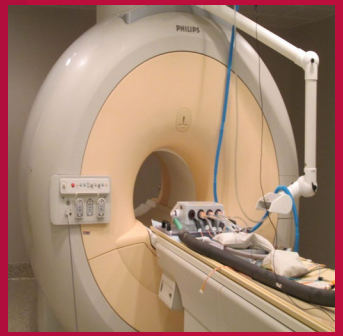


Recent Examples of Clinical Research Supported by the FNL/FFRDC

- West Africa Ebola outbreak (2015-17)
- Democratic Republic of the Congo Ebola outbreak (2018-19)
- COVID-19 (2020-Present) in US, UK Europe, West Africa, DRC, Indonesia and Mexico

www.cancer.gov

www.cancer.gov/espanol



Imaging Technologies

NIH NATIONAL CANCER INSTITUTE

Overview

In vivo and *in vitro* imaging facility
Supply of non-commercial imaging agents
Imaging informatics

In vivo and in vitro imaging

State-of-the-art *in vivo* and *in vitro* imaging facility

- Provide investigators with the ability to develop and characterize:
  - New animal models
  - Molecular markers, and theranostics
  - Monitor tumors in vivo
- Assist in nanotechnology characterization:
  - Assay cascade of nanoplatforms
- Support initiatives in:
  - Developing standards in small animal imaging
  - Integrating imaging into drug development
  - Characterizing Patient Derived Models
  - Evaluating new imaging agents/probes for investigators

Minimum equipment/capabilities

MAGNETIC RESONANCE IMAGING

Image Resolution (175 µm); Sensitivity (10^{-3}-10^{-5} mol/L)

- Dynamic Contrast Enhanced (DCE)-MRI (Permeability)
- Dynamic Susceptibility Contrast (DSC)-MRI (Perfusion)
- Tracer Kinetics
- Anatomical volumes

Virtual Colonoscopy

NUCLEAR (PET/CT, SPECT/CT)

PET Resolution (1400 µm); Sensitivity (10^{-11}-10^{-12} mol/L)

SPECT Resolution (500-2000 µm); Sensitivity (10^{-10}-10^{-11} mol/L)

CT Image Resolution (5 µm)

- Imaging disease-related biomarkers and pathways
- Tracer Kinetics

Internal Radiation Dosimetry

BIOLUMINESCENCE

Image Resolution (>1000 µm); Sensitivity (10^{-15}-10^{-17} mol/L)

- Cell Tracking
- Tumor Growth

Metastasis

BIODISTRIBUTION

Distribution of tagged probes in organs

FLUORESCENCE

Image Resolution (>1000 µm); Sensitivity (10^{-9}-10^{-5} mol/L)

- Cell Tracking
- Phenotyping
- Tracer Kinetics
- Imaging disease-related biomarkers and pathways
- Receptors
- Angiogenesis
- Apoptosis
- Other probes as needed

ULTRASOUND

Image Resolution (30 µm); Sensitivity

- Anatomical volumes
- Blood Volume
- Blood Flow (Doppler)
- Cardiac Function
- Tissue Doppler

Image guided injections

Imaging disease-related biomarkers and pathways

HYPERPOLARIZED CARBON 13 SUBSTRATES (MRSI)

Metabolic Imaging: e.g., HP 13C-Pyruvate/Lactate

Minimum supporting capabilities

- Qualified staff with training in handling radioactive materials
  - for instrument operation & maintenance
  - for animal handling and drug administrations
- Provide imaging agents as needed
  - Qualify vendors for commercial agents: e.g., FDG, Ga agents
  - Synthesize non-commercial agents: e.g., FLT, tagged antibodies
  - Assure quality and performance of all agents
  - Provide regulatory support for imaging INDs
- Develop analytical methods for image processing

Example Projects

Some typical projects

Methods

- Virtual Colonoscopy
- Ultrasound Image Guided Injections (Liver and Cardiac)
- Collaborate: Short-Wavelength Infrared Fluorescence)
- Awake Mouse Cardiac Imaging
- High Throughput Image Acquisition Techniques
- Metabolic Magnetic Resonance Spectroscopy Imaging (MRSI)
- Quantitative hi-resolution ultrasound
- Image segmentation & radiomics
- Collaborate: small animal DICOM standards

Characterize Animal Models

- Leptomeningeal Disease
- Diffuse Intrinsic Pontine Glioma
- Pancreatic Cancer
- Metastatic Cancer (Brain, prostate, lung, liver)
- Lung Cancer
- Ovarian
- Patient derived xenografts

Characterize Imaging Agents/Therapeutics

- Labeled antibodies (89Zr and 111In)
- Labeled drugs (F-18, gadolinium)
- Metabolic reporters (F-18 tracers, hyperpolarized C-13)
- Nanoparticles

Zr-89 Panitumumab

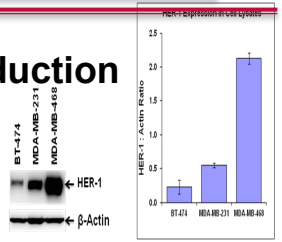
- **Vectibix® (panitumumab-Amgen), targets EGFR (HER1, Erb-1)**
  - Approved for metastatic CRC
  - Significant toxicity issues
- **Imaging probe**
  - Non-invasive, in vivo, quantitative biomarker of EGFR expression
  - Investigate for patient selection and monitoring of EGFR-targeted therapies, e.g., panitumumab or cetuximab
- **Project**
  - Labeled panitumumab with Zr-89
  - Tested in three animal models – high, medium, low expressors
  - Assisted in documentation for IND filing
  - Prepared GMP labeled drug for a small clinical trial

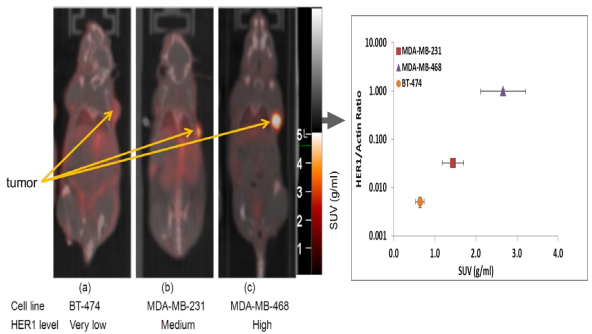
Zr-89 Panitumumab

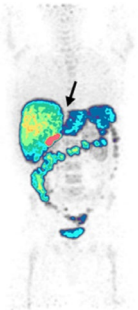
- **Vectibix® (panitumumab-Amgen), targets EGFR (HER1, Erb-1)**
  - Approved for metastatic CRC
  - Significant toxicity issues
- **Imaging probe**
  - Non-invasive, in vivo, quantitative biomarker of EGFR expression
  - Investigate for patient selection and monitoring of EGFR-targeted therapies, e.g., panitumumab or cetuximab
- **Project**
  - Labeled panitumumab with Zr-89
  - Tested in three animal models – high, medium, low expressors
  - Assisted in documentation for IND filing
  - Prepared GMP labeled drug for a small clinical trial

Nuclear Medicine and Biology 2013; 40(4): 451-457
https://doi.org/10.1016/j.nucmedbio.2013.01.007

- **Tracer synthesis and GMP production**
  - Panitumumab + DFO, purify
  - Add Zr-89, purify
- **Animal Model**
  - Xenograft tumor model
  - Cells: BT-474, MDA-MB-231, MDA-MB-468
- **File IND**
  - Phase one trial



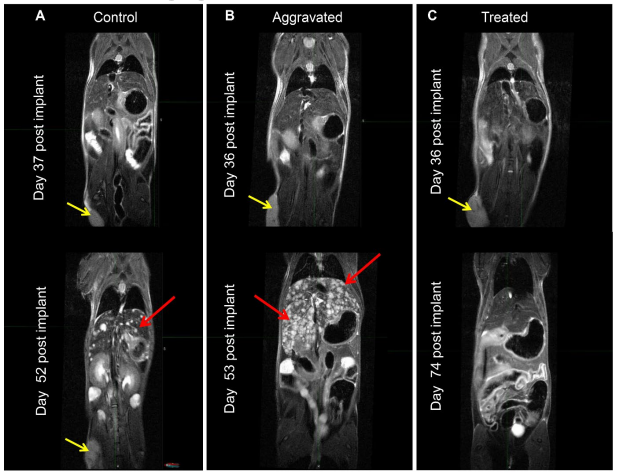




Am J Nucl Med Mol Imaging 2017;7(4):195-203
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0056289

Characterizing BL0293–a metastatic PDX model

- Bladder cancer model, grown in nude mice
- Imaged with T1 MRI, T2 MRI, contrast enhanced MRI, FDG-PET, FLT-PET and 3D-ultrasound to evaluate best method
- Three cohorts: control, aggravated by resection, non-aggravated and treated with one therapy cycle
- Monitored with multiple MRI imaging sessions
- Confirmed metastases with pathology
- Therapy prevented metastases
- Similar approach to multiple PDX models



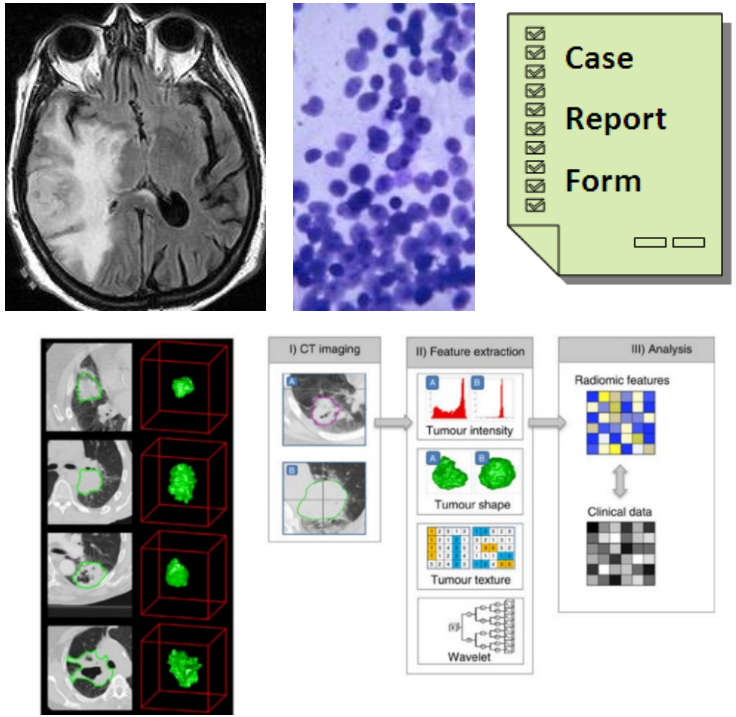
J Transl Med 17, 425 (2019). https://doi.org/10.1186/s12967-019-02177-y

THE CANCER IMAGING ARCHIVE

Imaging Informatics

Supporting Image Archives

Current archive –The Cancer Imaging Archive



- 121 Collections consisting of ~48,000 subjects with over 50 million images
  - 6 mice collections (4 PDMR models)
  - Canine GBM pilot dataset from ICDC
- 32 Analysis Result datasets based on TCIA collections
- Radiology, radiation therapy, and histopathology image modalities
- Wide variety of cancers + phantoms
- Most have associated supporting data
  - Demographics/outcomes/therapy
  - Image analyses (e.g., segmentations)
  - Genomics/Proteomics
- COVID-19 initiative

Integrated Project Data

- MR, CT, X-ray, PET medical images in DICOM format
- Histology slide images
- Robust de-identification
- Curation
- Human, phantom, mouse, canine, synthetic, analyses
- Annotation and segmentation to prepare for machine learning analyses

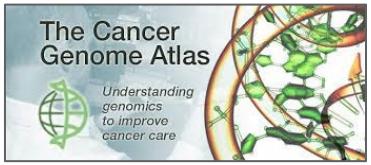
Integrated Projects

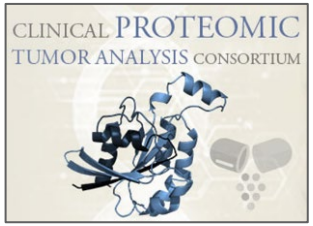
- MR, CT, X-ray, PET
- Histology slides
- Robust de-identification
- Curation
- Human, phantom, mouse, canine, synthetic, analyses
- Annotation and segmentation to prepare for machine learning analyses

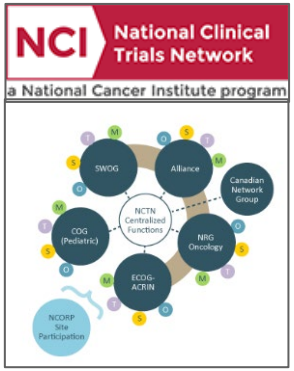
- TCGA
- CPTAC
- NCTN
- APOLLO
- BIOBANK
- IDC
- ICDC
- PDMR

TCIA Datasets

NCI data collection initiatives

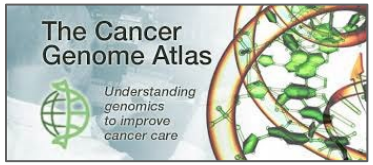


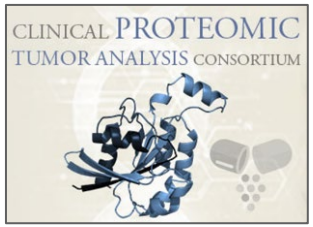


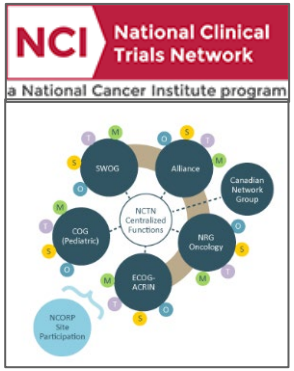


TCIA Datasets

NCI data collection initiatives







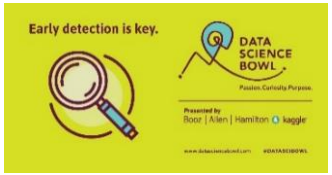
NIH NATIONAL CANCER INSTITUTE
Cancer Moonshot Biobank

PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology Initiative℠ Resource

"Community" proposals
reviewed monthly

NIH All About Grants

Data generated by NCI/NIH Grants



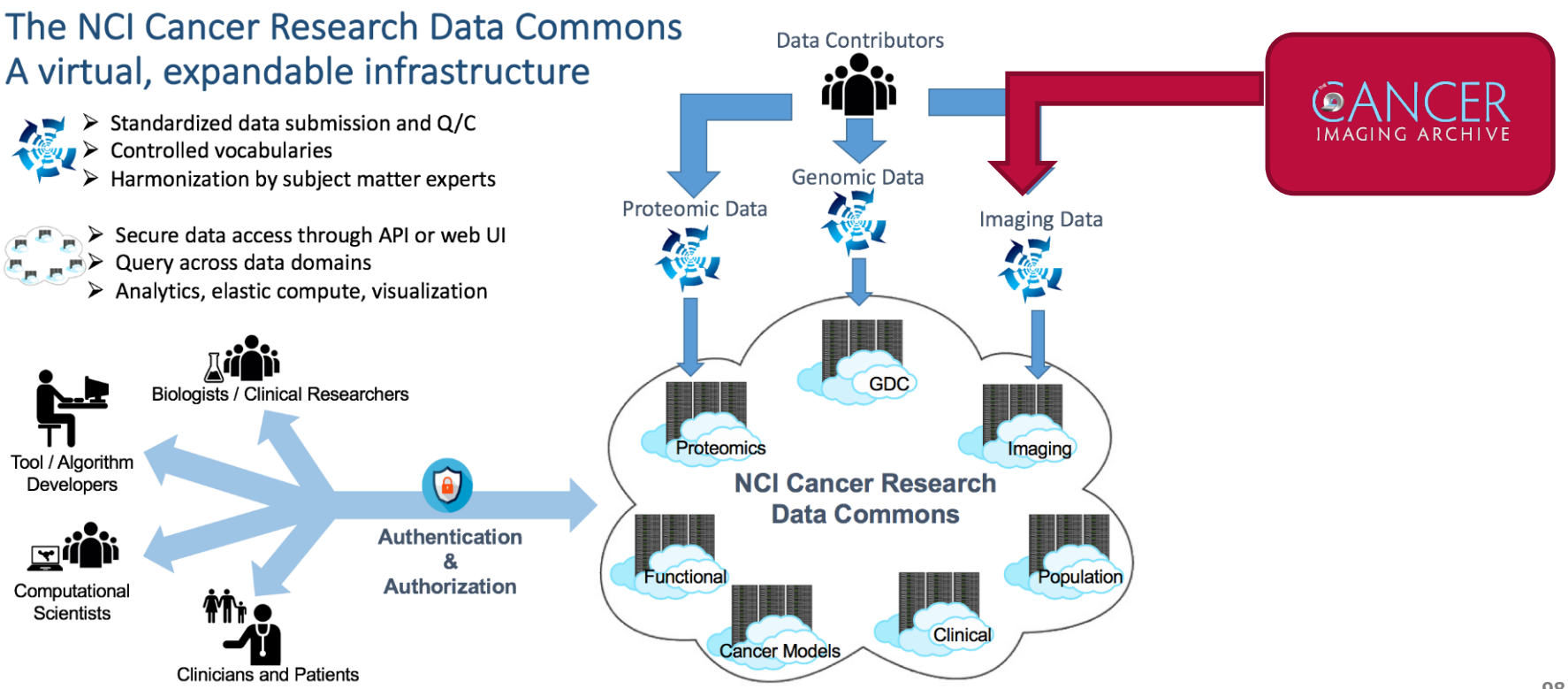
Challenge competitions

SCIENTIFIC DATA

PLOS ONE

Publication data sharing requests

Data in TCIA will be mirrored in Imaging Data Commons



www.cancer.gov

www.cancer.gov/espanol

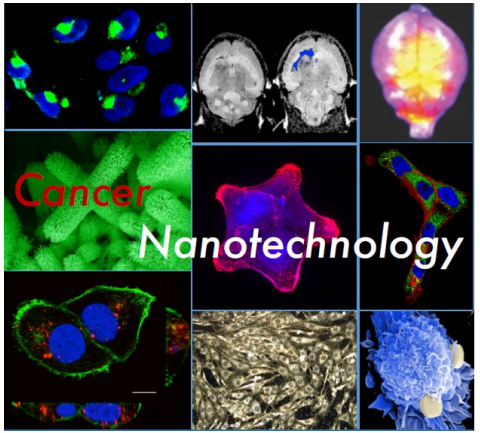
Nanotechnology Characterization Laboratory (NCL)

Characterizing nanomaterials and nano-devices to enhance understanding of nanomedicines and aid their clinical translation

NIH NATIONAL CANCER INSTITUTE

Cancer Nanotechnology: The Opportunity

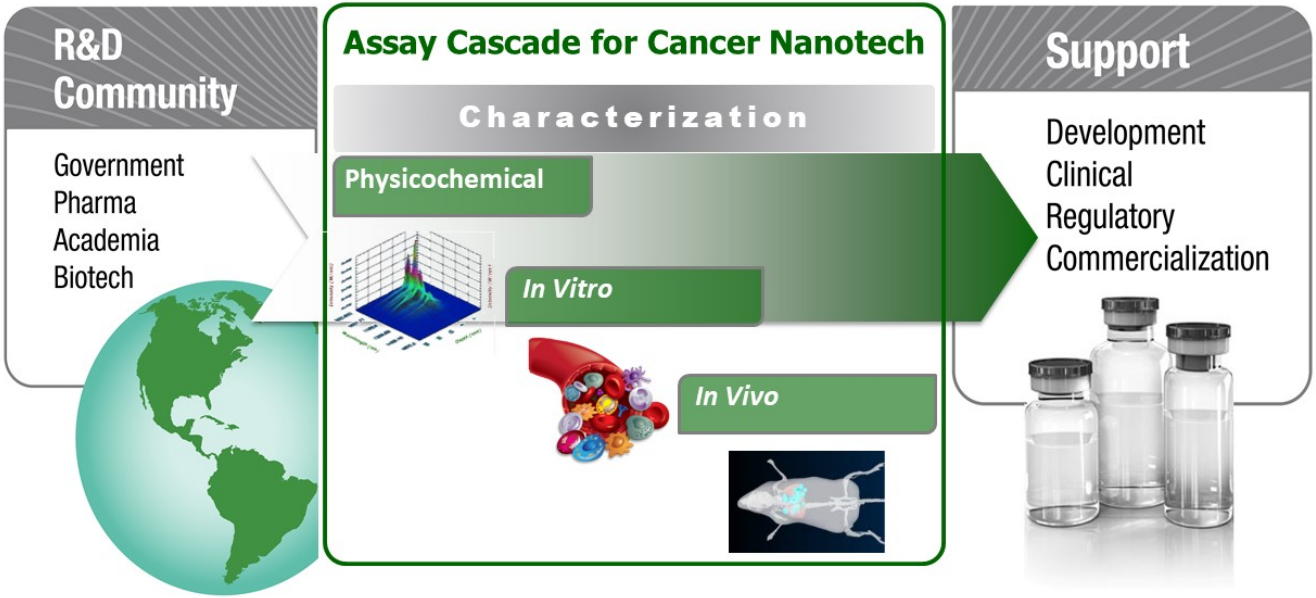
- Combine power of innovation in nano-materials and cancer biology to develop new solutions in cancer
- Detect Disease Early
  - Sensors
  - Imaging
- Deliver Treatment
  - Local delivery
  - Combination therapies
  - Post-therapy monitoring
- Develop Research Tools to Enhance Understanding of Biology and the Disease



Cancer Nanotechnology: The Need

- Successful progression of nanomedicines to the clinical space requires:
  - Further, in-depth nanomaterials characterization in *in vitro* and *in vivo* setting
  - Standardization of characterization assays
  - Data and information sharing

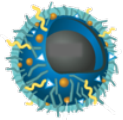
Nanotechnology Characterization Lab (NCL)



- NCL was established in 2004 as an interagency collaboration among NCI, FDA, and NIST.
- Lab's primary mission is to advance the science and enable translation of promising nanomedicines with a support of a standardized "Assay Cascade".
- 'Assay Cascade' characterization is **FREE** of charge to submitting investigator

NCL's Assay Cascade

FREE Service for cancer nanotechnology concepts, by application



Physicochemical Characterization

Applicable to CMC section of IND

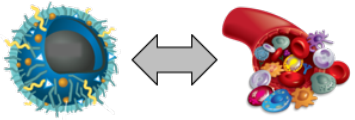
Size/Size Distribution
- Dynamic Light Scattering (DLS)
- Electron Microscopy (TEM, SEM, cryo)
- Atomic Force Microscopy (AFM)
- Field Flow Fractionation (FFF), SEC-MALS

Composition
- TEM with EDS
- Inductively coupled plasma-mass spec. (ICP-MS)
- Spectroscopy (NMR, CD, Fluorescence, IR, UV-vis)

Purity
- Chromatography
- Capillary Electrophoresis

Surface Chemistry
- Biacore
- Zeta Potential

Stability
- Stability can be measured with any number of instruments with respect to time, temperature, pH, etc.



In Vitro Characterization

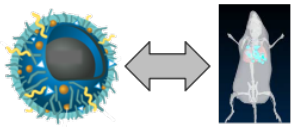
Applicable to vaccines, immunotherapies

Sterility
- Bacterial/Viral/Mycoplasma
- Endotoxin

Hematology
- Hemolysis
- Platelet Aggregation
- Coagulation
- Complement Activation
- Plasma Protein Binding

Immune Cell Function
- Cytokine Induction
- Chemotaxis
- Phagocytosis
- Leukocyte Proliferation
- Leukocyte Procoagulant Activity

Toxicity
- Cytotoxicity
- Autophagy



In Vivo Characterization

Comprehensive animal studies

Pharmacology
- Clinical Tx cycle
- NP Quantitation methods
- PK Parameters

Immunotoxicity
- Local lymph node proliferation assay
- T-cell dependent antibody response
- Adjuvanticity
- Rabbit pyrogen test
- Immunogenicity
- Inflammatory response
- Autoimmunity

Single and Repeated Dose Toxicity
- Blood Chemistry
- Hematology
- Histopathology (42 tissues)
- Gross Pathology

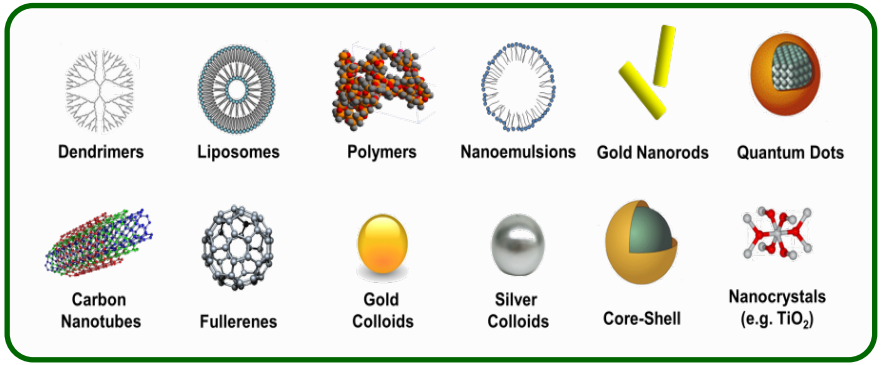
Not GLP

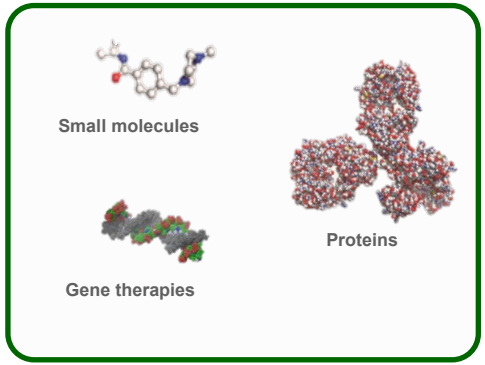
Inter-disciplinary approach to link physicochemical attributes to biological outcomes

72 protocols available online: https://ncl.cancer.gov/resources/assay-cascade-protocols

NCL by the Numbers

>430 Different nanomaterials characterized with a wide range of nanotechnologies and APIs





>200 Peer-reviewed publications covering nanoparticle characterization, immunotoxicity and safety

>150 Collaborations with academia, industry, and government labs

>70 Protocols standardized for various nanoparticles

17 NCL collaborators reached clinical trials

Cumulative experience of providing NCL Assay Cascade for 16 years has made NCL a unique resource

NCL's Assay Cascade Application Process

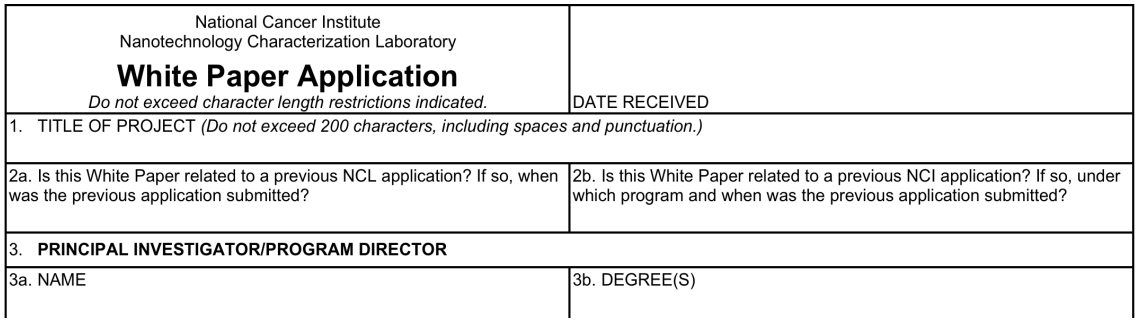
Two-phase application process

Phase 1: Brief (3-4 page) White Paper

- Abstract, Background, Strategy/Concept, Data on Synthesis, Characterization, In Vitro & In Vivo Testing, Novelty, Clinical Impact & Scale Up.
- Applications are accepted and reviewed quarterly.
- Decisions are remitted within 45 days of the application deadline.

Phase 2: Oral or Written Proposal

- Expansion of data presented in White Paper; addressing reviewer questions.
- Inputs due within 3 months of receiving invitation letter.
- Decisions are remitted within 2 weeks.



National Cancer Institute
Nanotechnology Characterization Laboratory

White Paper Application

Do not exceed character length restrictions indicated.

DATE RECEIVED

1. TITLE OF PROJECT *(Do not exceed 200 characters, including spaces and punctuation.)*

2a. Is this White Paper related to a previous NCL application? If so, when was the previous application submitted?

2b. Is this White Paper related to a previous NCI application? If so, under which program and when was the previous application submitted?

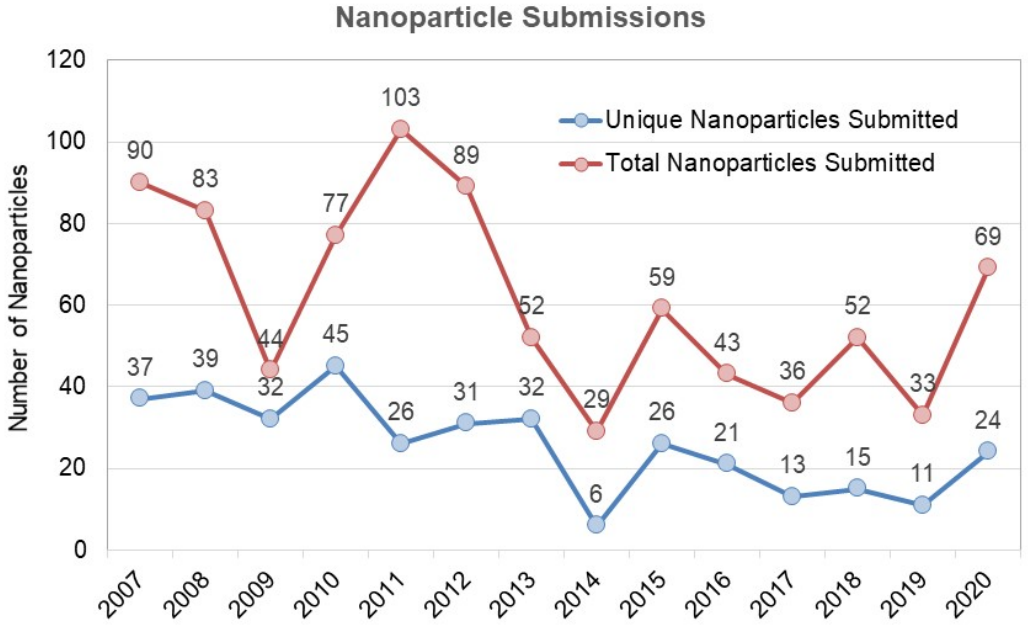
3. **PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR**

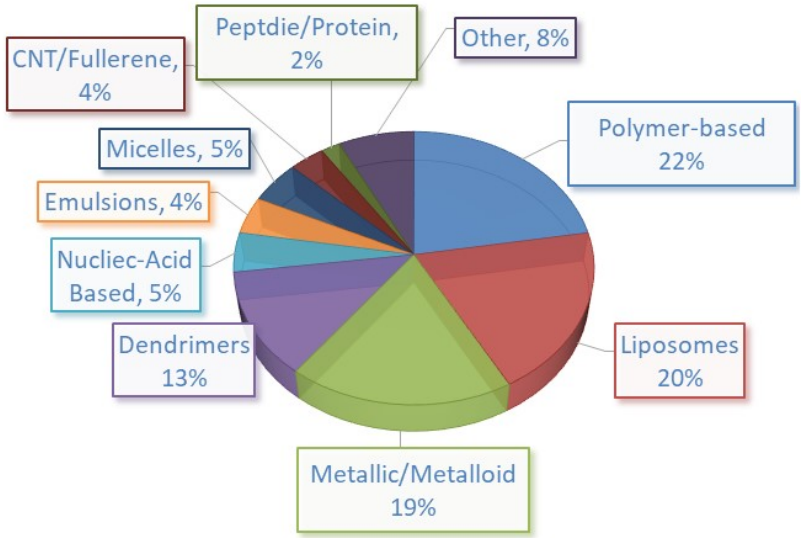
3a. NAME

3b. DEGREE(S)

https://ncl.cancer.gov/working-ncl/ncl-assay-cascade-application-process

Nanoparticle Submissions



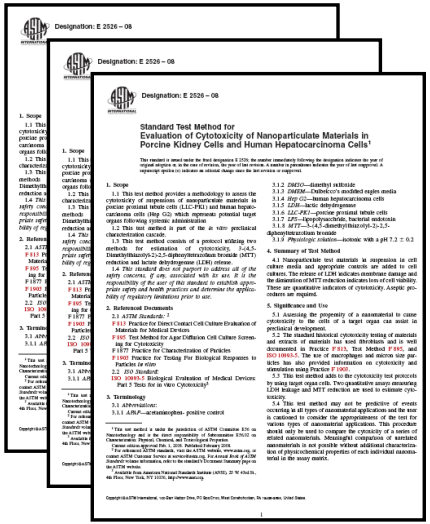


- **Average number of total nanoparticles per year - 61**
- **Average number of unique nanoparticles per year - 26**

Polymer-based nanomaterials, liposomes and metal-based nanoparticles dominate the NCL nanoparticle portfolio

Standards Development at NCL

- Standards development with ASTM and ISO
  - Three NCL protocols are ASTM standards
  - Multiple NCL protocols are ISO PASs
- NCL supported the production of NIST's colloidal gold RM
  - Gold selected for calibration and biocompatibility
  - 10 nm, 30 nm, and 60 nm diameters
- NCL participates in inter-laboratory studies (ILS)


Designation: E 2526 – 08

Standard Test Method for
Evaluation of Cytotoxicity of Nanoparticulate Materials in
Porcine Kidney Cells and Human Hepatocarcinoma Cells[1]

Beyond the Assay Cascade:
Collaborative Research Projects (cCRADA)

FEE-based Services

Nanotech Formulation

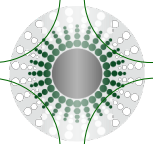
- Reformulation of both traditional and novel APIs.
- Incorporation of active targeting ligands.
- Address previously disqualifying toxicity or missed metric.
- Concurrent in vitro and/or in vivo testing for toxicity, efficacy, PK.

NCL has unique expertise for matching APIs with nanotech-based formulations.

Non-oncology Nanomaterials

- Several nanomedicines are being developed for non-oncology indications.
- Leverage assays developed for cancer nanomedicines.
- Generate predictive toxicity profiles based on the physicochemical properties of nanomaterials.

Knowledge/Assays for cancer nanomedicines address similar gaps for non-oncology.



Method Development

- Methods for evaluating nanomedicines in biological matrix, assessing polydispersity, etc.
- Collaborations with instrument manufacturers to improve nanotech bioanalytical tools.
- Methods to support clinical trials and BE studies.
- Collaborates with multiple standards organizations on protocol standardization.

Methodologies to inform/contribute to translation & regulatory approval.

Safety & Mechanistic Studies

- Exploring common reasons for preclinical and early clinical failure of nanoformulated drugs:
  - Endotoxin contamination
  - Cytokine storm
  - Hypersensitivity reactions
  - Complement activation
  - Thrombogenicity (DIC)
  - Exaggeration of API immunotox by NP carrier

Ensuring nanotech keeps pace with the improved understanding of cancer biology.

https://ncl.cancer.gov/working-ncl/ccrada-application-process

Beyond the Assay Cascade:
Fixed Services (TSA)

FEE-based Services

Technical Service Agreements (TSA) – Fee-for-service for select assays

NCL-01

In vitro drug release study in human plasma using the stable isotope tracer ultrafiltration assay (SITUA) to provide concentrations of:

- **Encapsulated drug**
- **Free/unbound drug**
- **Protein-bound drug**

Ideal for formulation optimization, lot release, & estimation of in vivo PK.

Nanomedicine In Vitro Drug Release

J Control Release, **2015**, 220(PtA), 169-174.
Methods in Molecular Biology, **2018**, 1628, 223-239.

NCL-02

Nanomedicine PK study in rats using the SITUA. Blood samples collected at various timepoints for analysis of:

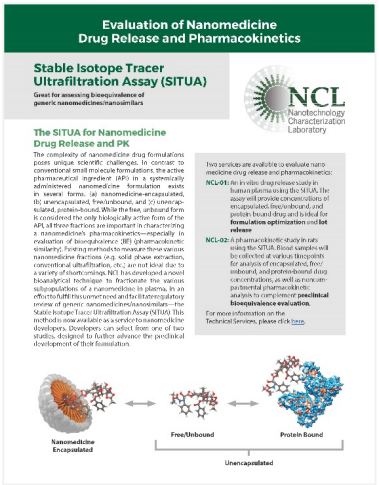
- **Encapsulated drug**
- **Free/unbound drug**
- **Protein-bound drug**
- **Noncompartmental pharmacokinetic analysis**

Complements preclinical bioequivalence evaluation.

Nanomedicine Pharmacokinetic Studies

Drug Metab Dispos, **2016**, 44(12), 1934-1939.
ACS Pharmacol Transl Sci, **2020**, 3(3), 547-558.

Unique services not offered at CROs



https://ncl.cancer.gov/working-ncl/technical-services

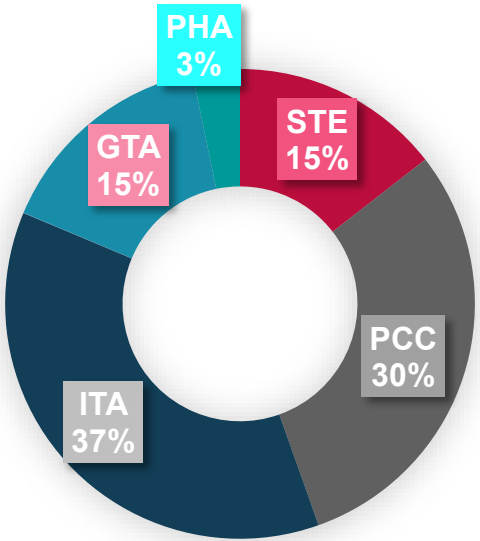
Education and Knowledge Sharing: Method Dissemination

72 total protocols published on the NCL website

2243 protocol downloads last year

6 new protocols were added to the NCL website in 2020

Protocol Downloads by Category



New Protocols in 2020

- STE-4: Detection of β-Glucan Contamination
- PCC-18: Quantitation of APIs in Polymeric Prodrug Formulations
- PCC-19: Asymmetric-Flow Field-Flow Fractionation
- PCC-20: Particle Concentration & Size using the Spectradyne nCS1
- PCC-21: Measuring Size and Number Concentration of Metallic Nanoparticle using single particle-ICP-MS
- ITA-27: Multiplex Enzyme-Linked Immunosorbent Assay (ELISA) for Detection of Human Cytokines in Culture Supernatants

https://ncl.cancer.gov/resources/assay-cascade-protocols

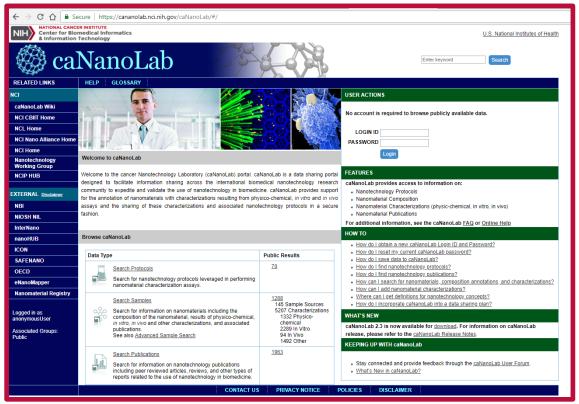
All protocols now have unique DOI

STE = sterility; PCC = physicochemical characterization; ITA = immunotoxicity assay; GTA = general toxicity assay; PHA = drug release assay

caNanoLab Data Portal: A Resource for Data Sharing

caNanoLab Goal

To provide a nanotechnology resource that facilitates data sharing in the community to expedite and validate the use of nanomaterials in biomedicine



Home Page

- Provides support for the annotation of nanomaterials with composition information, and physico-chemical, *in vitro*, and *in vivo* characterizations
- Provides access to curated information from nanomaterial and nanomedicine samples, protocols, and publications

https://cananolab.nci.nih.gov/caNanoLab/

Cancer Nanotechnology
Summary

- Nanotechnology presents a strong potential for the development of potent cancer therapeutics and diagnostics
- NCL is a laboratory with unique set of capabilities supporting characterization of nanomaterials and nano-devices used in nanotechnology-based medical interventions
- Over last 16 years, NCL characterized over 430 different nanomaterials and established body of literature on nanoparticle designs and their design correlations with safety and toxicity
- NCL educates research community and disseminates knowledge on evaluation of nanomedicines
- NCL is involved in standardization of nanomedicine characterization tools and nanomaterial standards
- NCL has a diverse arsenal of contractual mechanisms to conduct its collaborations:
    - Assay Cascade White Paper submissions
    - Interagency Agreements - IAA
    - Collaborative Research Projects - cCRADA
    - Technical Service Agreements – TSA
- caNanoLab facilitates data sharing in the nanomedicine community to expedite and validate the use of nanomaterials in medicine.

www.cancer.gov

www.cancer.gov/espanol

Virology

NIH NATIONAL CANCER INSTITUTE

Virology - Overview

The FFRDC supports:

- PI/Investigator initiated research and core laboratories. These contribute to both intramural and extramural research
  - Immunological, pathological, and cellular/molecular/biochemical aspects of AIDS-associated viral diseases
  - Vaccine development and translational research
- Technology/reagent/assay development. Proactive sharing of technology with the broader research community
  - Standardized and validated serological assays and reagents
  - Virus, viral vector, and virus-like particle generation/production
  - Viral genotyping and sequencing

Investigator-Initiated Virology Research

- **Retroviral Evolution**

Retroviral evolution research uses molecular biology approaches to generate, manipulate, and employ novel viral systems to take full advantage of the benefits of nonhuman primate (NHP) models to test specific hypotheses in vivo.

- **Viral Oncology**

The overall aim of viral oncology research is to study the role of viruses in cancer. Studies are focused primarily on Kaposi's sarcoma-associated herpesvirus (KSHV) and related malignancies. The approach encompasses epidemiology, molecular virology, immunology and translational studies.

- **Retrovirus-Cell Interactions**

Research on retrovirus-cell interactions seeks to study the interactions between AIDS viruses and their host cells using both the HIV-1/human T cell and SIV/ rhesus macaque T cell systems.

Investigator-Initiated Virology Research (cont'd)

- **Retroviral Pathogenesis**

Carries out in vitro and in vivo studies are aimed at improving the understanding the basis of lentiviral pathogenesis, particularly aspects relevant to the development and evaluation of interventions intended to prevent and treat HIV infections and AIDS.

- **Viral Persistence**

Persistence research uses in vivo non-human primate models of HIV infection, in vitro and ex vivo cell culture, virology, and molecular biology to study the establishment, spread, and maintenance of persistent AIDS virus infections and evaluate novel treatment approaches to reduce viral reservoirs.

Virology Core Support

Core Support for Virology Research

- **HPV Serology**

Carries out standardized measurements of immune responses and immuno-bridging for the academic and commercial HPV vaccine trials.

- **Viral Evolution**

Provides specialized sequencing techniques, molecular cloning, and studies viral evolution to support intramural and extramural investigators conducting a broad range of AIDS-research studies, including HIV-cure research, viral reservoir identification/elimination, viral transmission/ dissemination, and viral adaptation.

- **Tissue Analysis**

Carries out state-of-the art tissue analysis (i.e. immunofluorescence, immunohistochemistry, in situ hybridization, quantitative image analysis, laser capture microdissection), with an emphasis on analyzing specimens from non-human primate (NHP) models.

Core Support for Virology Research (cont'd, 1)

- **Retroviral Protein Chemistry**

  Provides state-of-the-art preparative and analytic protein chemistry for the characterization of retroviral virions and related samples. This core pioneered the use of HPLC for the purification of retroviral proteins.

- **Biological Products**

  Provides the AIDS research community with large quantities of high-quality purified preparations of various strains of Human Immunodeficiency Virus (HIV) and Simian Immunodeficiency Virus (SIV).

- **Quantitative Molecular Diagnostics**

  Provides state-of-the-art quantitative molecular analyses of specific nucleic acid sequences in specimens provided by intramural and extramural laboratories.

Core Support for Virology Research (cont'd, 2)

- **Nonhuman Primate Research Support**

Supports virological studies conducted by FFRDC scientists and their collaborators in nonhuman primates. Support includes ongoing scheduling for all study events, drug preparation, and specimen collection, handling, processing, and transportation support for AIDS vaccine, pathogenesis, and treatment studies.

- **HIV Molecular Monitoring**

Provides state-of-the-art molecular quantitation and sequence analysis of HIV from clinical specimens obtained from intramural and extramural scientists. These include ultrasensitive HIV plasma viral load measurements and cell-associated HIV RNA and DNA quantitation.

- **Cellular Immunity**

Provides comprehensive flow cytometry, cell sorting, and cellular immune analysis to support FFRDC scientists and their collaborators in studies of non-human primates using advanced flow cytometry methods, instrumentation and software.

Examples of Recent Virology Research

Integration Site Analysis is Used to Monitor the Clonal Expansion and Persistence of HIV Infected T Cells in Humans

- The clonal expansion of HIV infected T cells plays an important role in the persistence of infected cells during effective anti-retroviral therapy.
- When an infected cell clonally expands, all the progeny cells have an HIV provirus integrated in the same position in the genome.
- Can the SIV/macaque system be used to do experiments monitoring the clonal expansion and persistence of infected T cells that cannot be done using samples from HIV infected human donors?

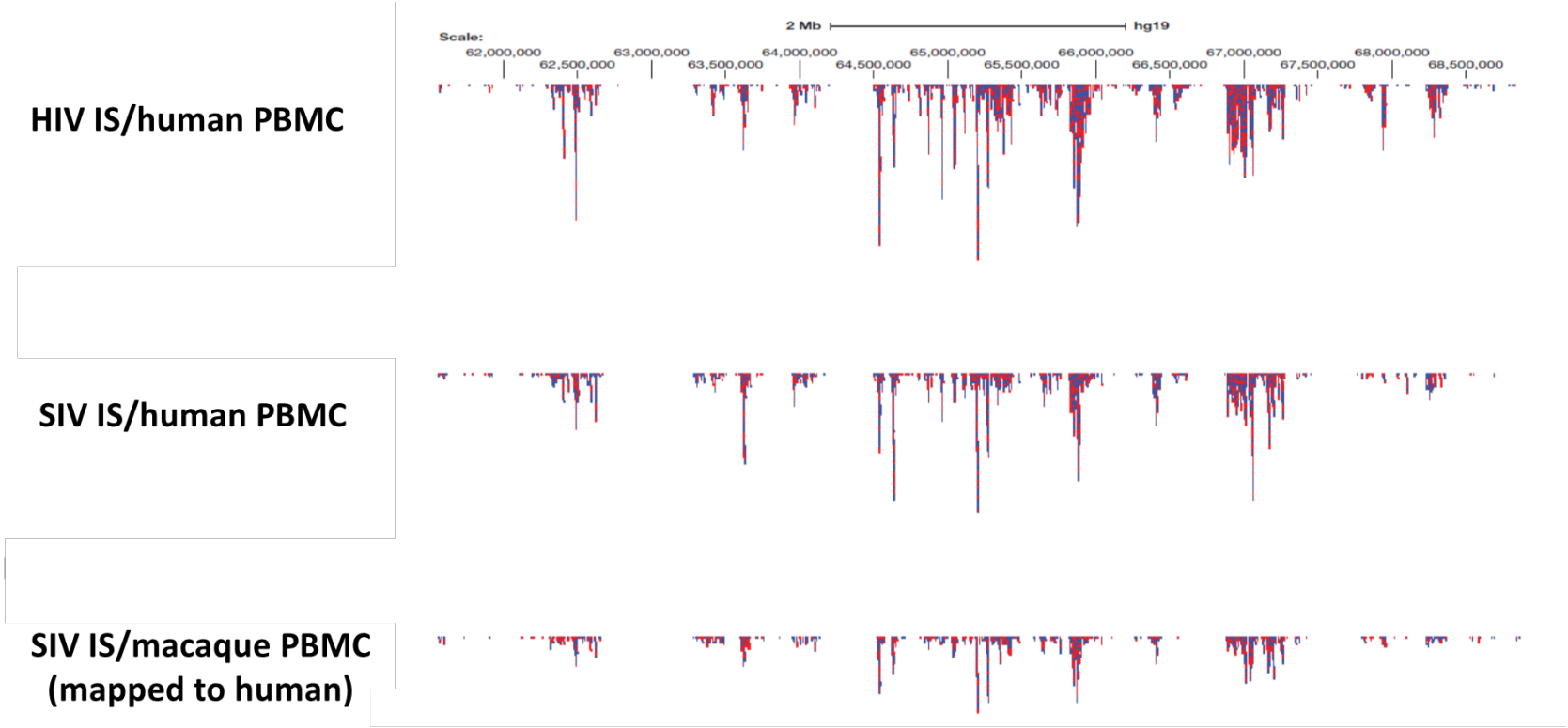
Macaque/SIV Model Has Advantages for Integration Site Analysis

- Control timing of infection and therapy
- Barcoded viruses
- Can manipulate the immune system
- Tissue sampling
- The SIV/macaque model needs to be validated for integration site analysis both in vitro and in vivo

Validating the SIV/Macaque Model to Study Clonal Expansion of Infected T Cells In Vivo

- How similar is the integration site distribution in HIV infected human cells and SIV infected macaque cells?
- Is there clonal expansion of SIV-infected T cells in macaques, and is it similar to the clonal expansion of HIV infected cells in humans?

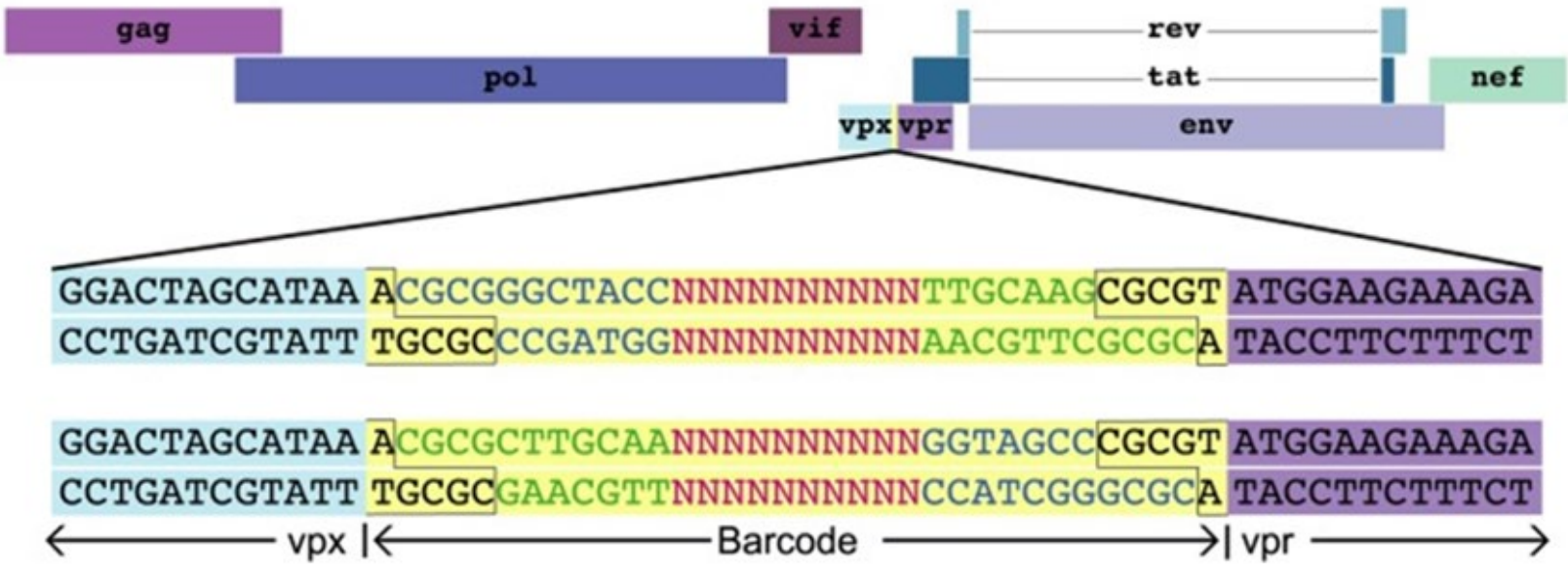
SIV and HIV Integration Sites Are Similar in Human PBMCs and in SIV Infected Macaque PBMCs (Chr 11)



There is Clonal Expansion of SIV Infected Cells in Macaques

- More than 100 separate clones of SIV infected cells were found in samples from macaques. ~20% of the proviruses in the on-therapy samples were in clones. 6 of the 7 largest clones were found in at least 2 different tissues.
- One clone that was found in a sample taken 2 weeks after the initial infection was also seen in a tissue sample taken at 1 year. 5 clones (18 total integration sites) were seen at 4 weeks.
- Clonal expansion of SIV infected cells in macaques is similar to the clonal expansion of HIV infected cells in humans.

Barcoded SIVs: Tracking Thousands of Viruses in Vivo



www.cancer.gov

www.cancer.gov/espanol

Questions?

All questions must be entered into the WebEx chat