Carcinogenicity Testing for the 21st Century

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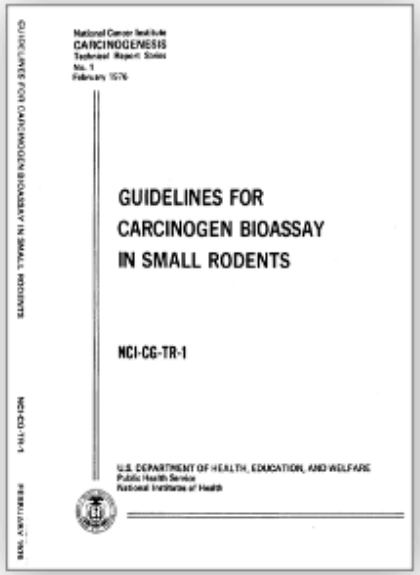
Chief (Acting), Predictive Toxicology Branch

NIEHS / DNTP

05.26.2022

Guidelines for Rodent Carcinogenicity Studies

Protocols for conducting carcinogenicity testing in rodents were developed > 50 years ago and remain virtually unchanged.



OPPTS 870.4200 Carcinogenicity

OECD TG 451: Carcinogenicity Studies

ICH S1 Carcinogenicity testing guidelines

~1000 animals per study

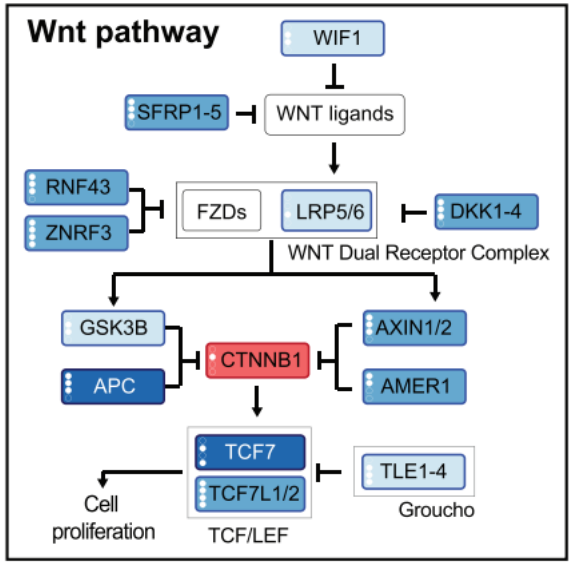
Advances in Science and Technology

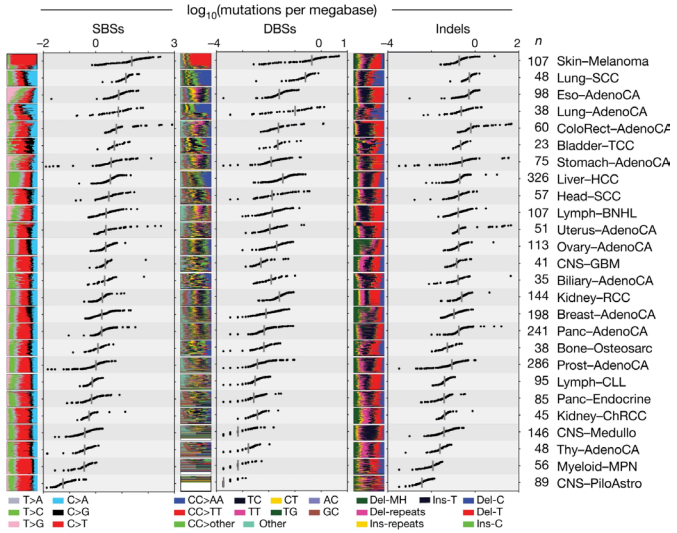
- In Vitro model systems (2D, 3D, MPS, iMPS)
- Collection and access to human cancer tissue samples
- Metabolomics / Proteomics / Transcriptomics
- NextGen / Whole Genome Sequencing
- (Big) Data collection, warehousing, sharing and development of bioinformatic tools: Pan-Cancer Atlas, TCGA, COSMIC, ICGC-PCAWG, etc.…
- Machine Learning / Artificial Intelligence and Computational Modeling

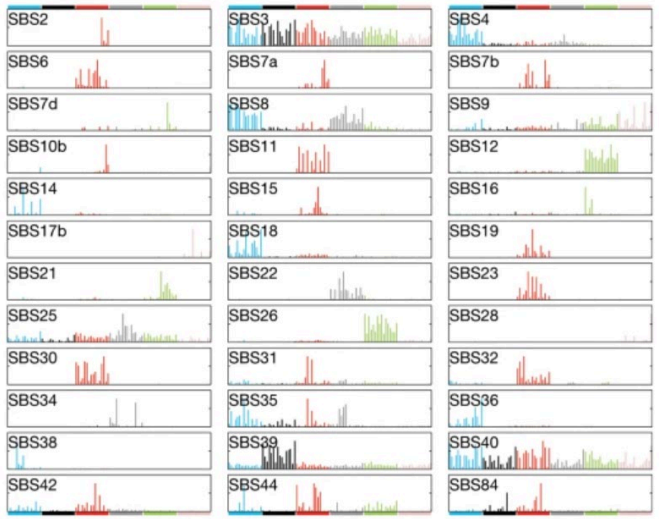
Advances in Understanding Human Cancer Biology

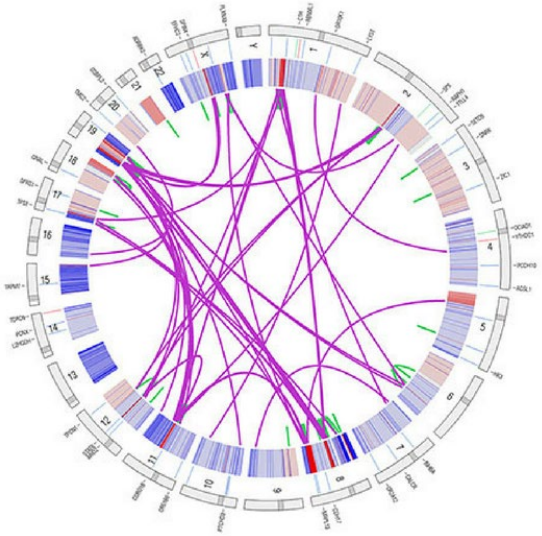
Improved understanding of human cancers (> > rodent)

- Oncogenic Signaling Pathways
- Hallmarks of Cancer / Key Characteristics of Carcinogens
- Cancer Driver Genes and Mutational Signatures







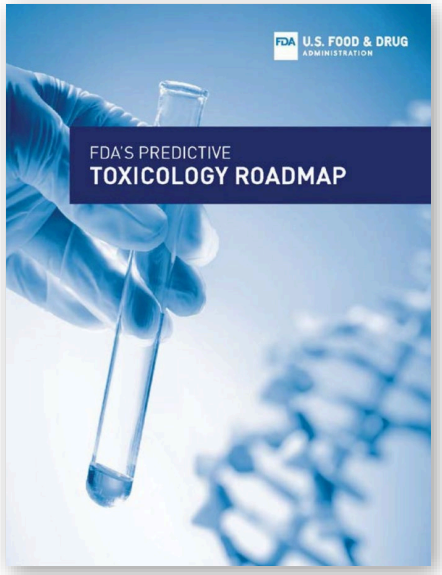


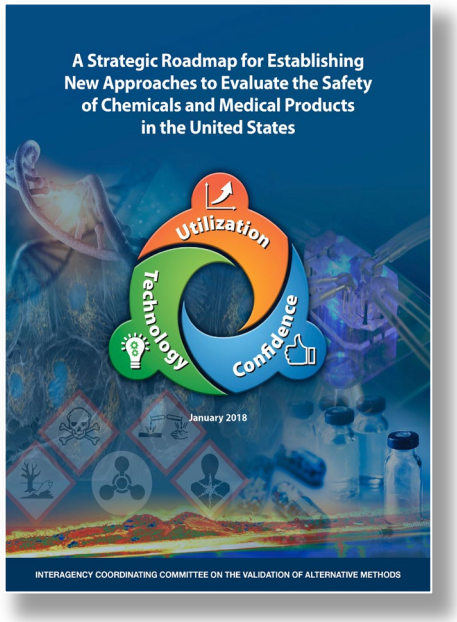
Adapted from Alexandrov et. al *Nature* **578**, 94–101(2020)

The Cancer Genome Atlas Mutations Circos Plot; Photo Source: NCI

New Regulatory Environment

- EPA initiatives
- FDA initiatives
- Interagency and International efforts

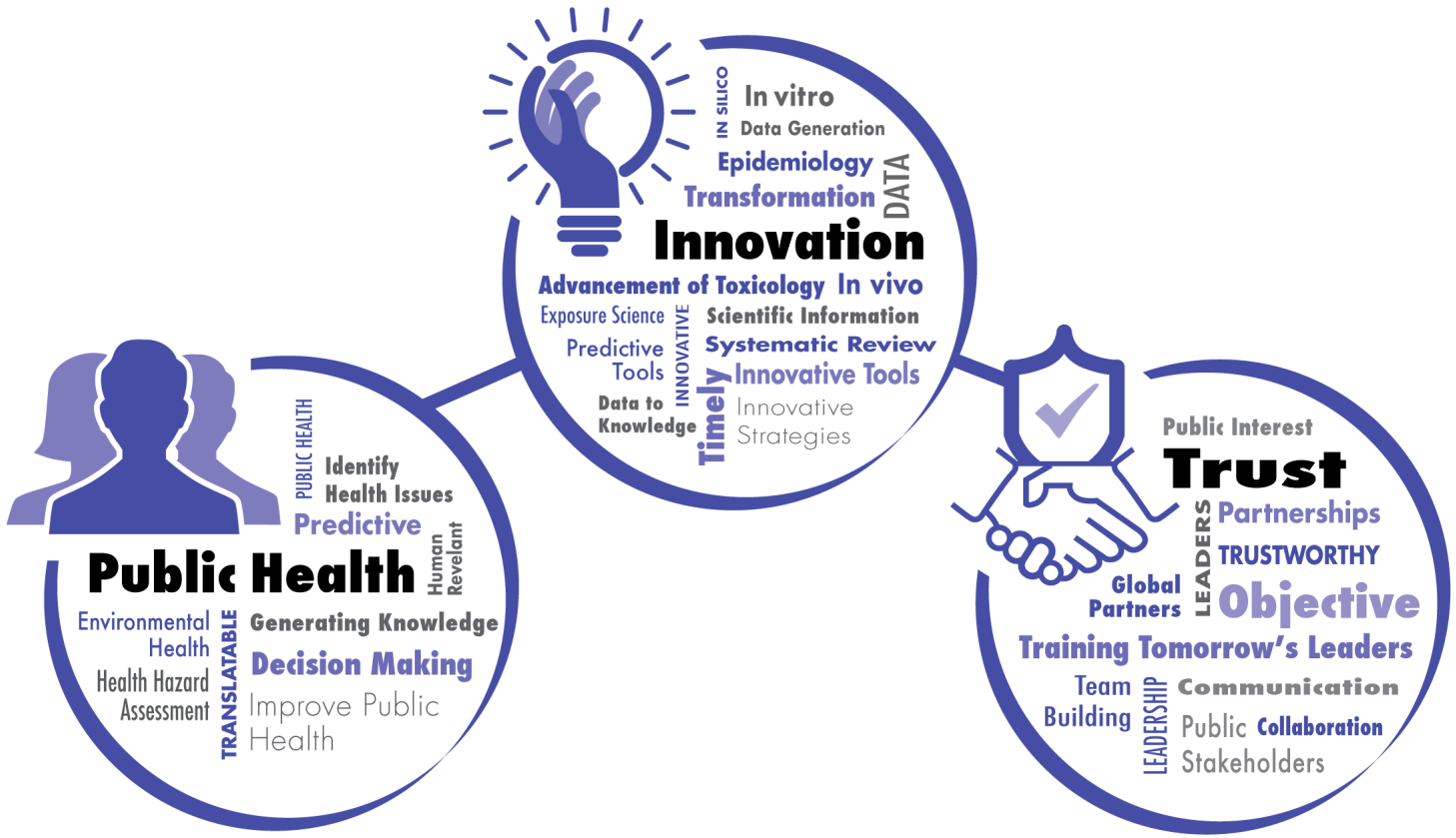




New DNTP Mission and Goals

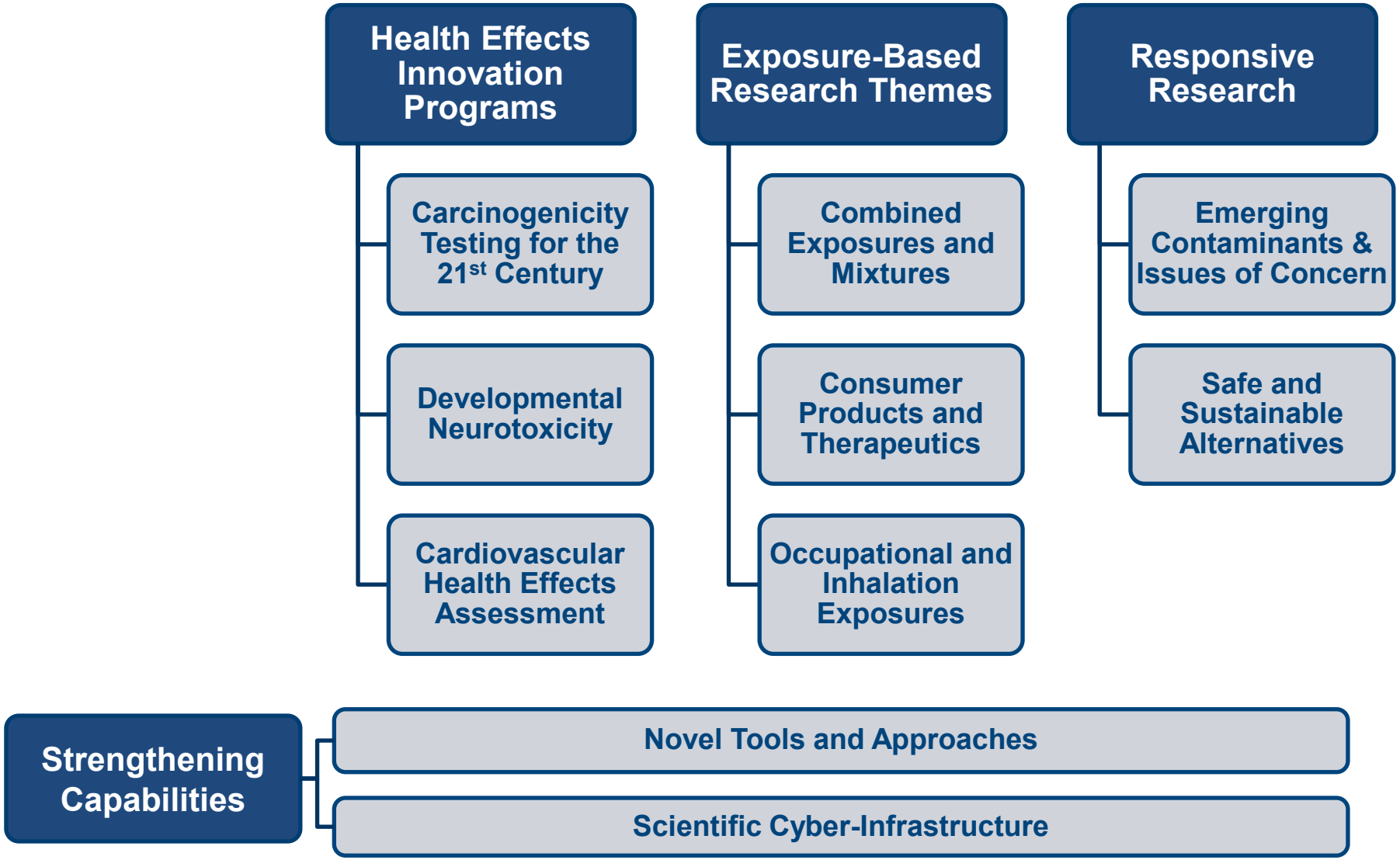
- **Mission**
  - To improve public health through the development of data and knowledge that are translatable, predictive and timely.
- **Goals**
  - Lead the transformation of toxicology through the development and application of innovative tools and strategies.
  - Collaborate with public stakeholders and global partners to identify and address public health issues.
  - Generate and communicate trusted scientific information to support decision making on environmental hazards of public interest.
  - Educating and training the next generation of translational scientists to be innovative leaders in the field.

Focus on Innovation



"Lead the transformation of toxicology through the development and application of innovative tools and strategies."

Strategic Areas of Focus



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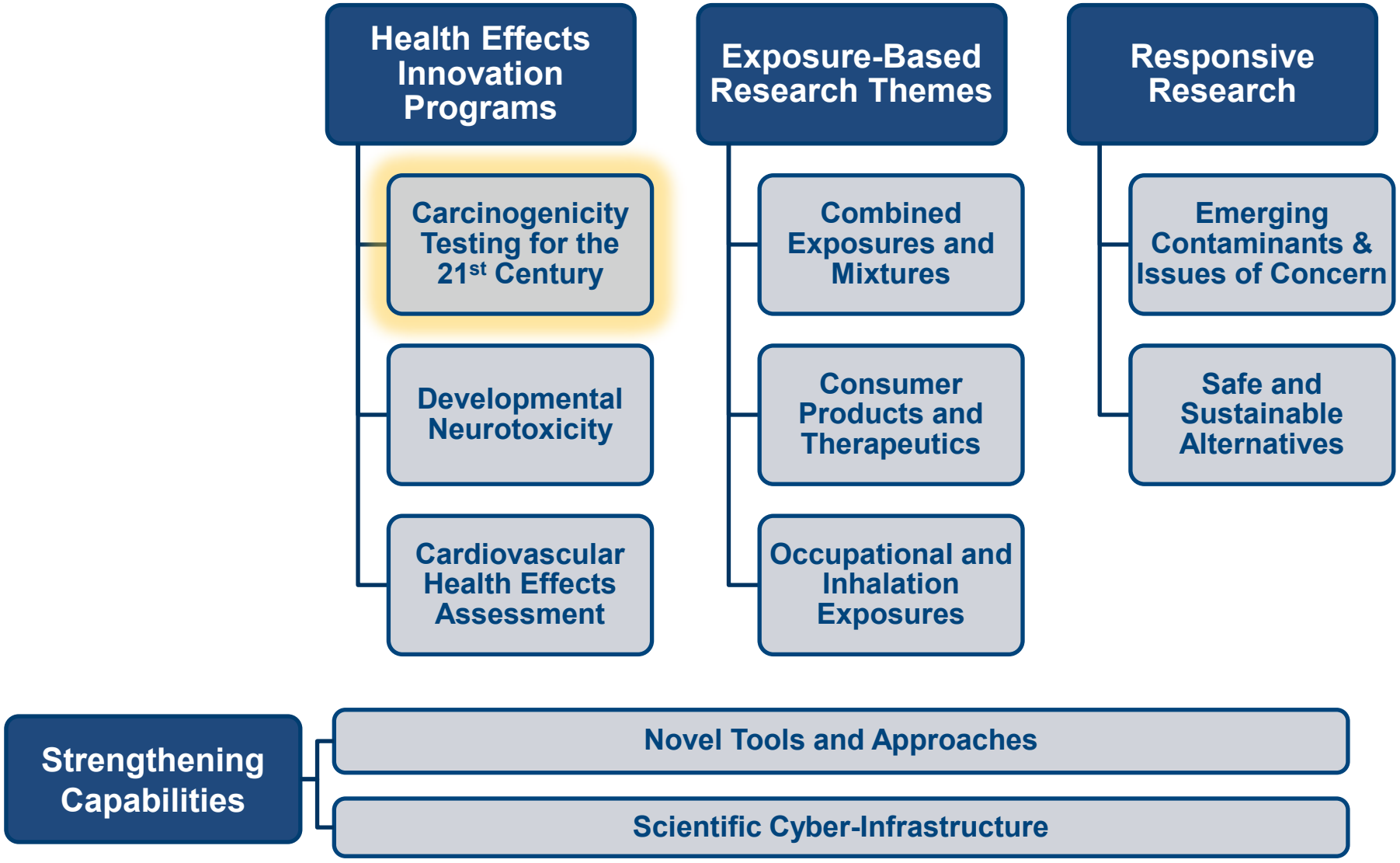
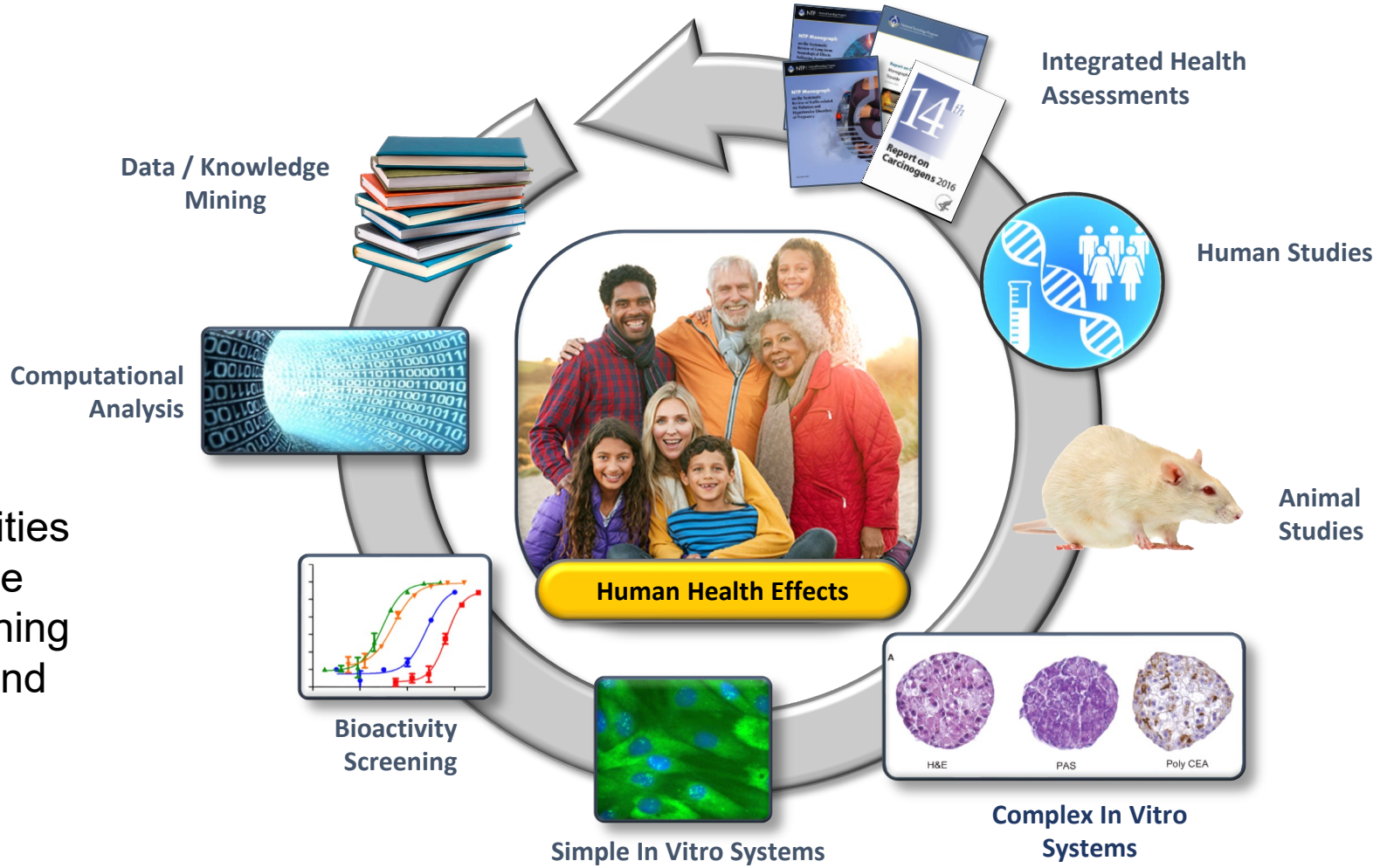


Goals of the Carci-HEI

- Shorten time to report trusted and actionable information
- Improve confidence in relevance to human health, especially in susceptible or disproportionately affected populations
- Reduce or eliminate reliance on animal models

Translational Toxicology Pipeline

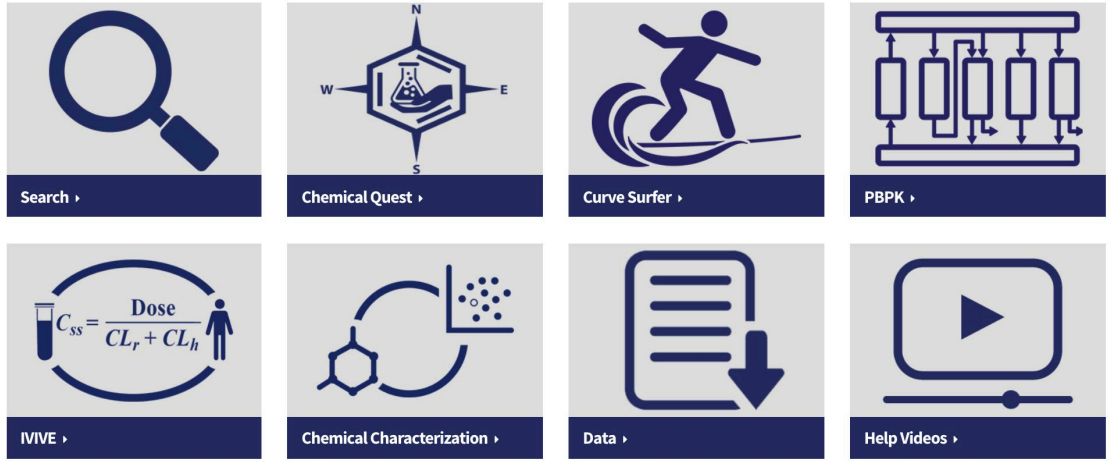
- Portfolio of technical capabilities
- Deliberate and integrated use
- Opportunity for iterative learning
- Focus on human condition and all it's complexities



Provide resources to make existing information on carcinogens Findable, Accessible, Interoperable and Reusable (FAIR)

- Curated data and search tools
  - Organized by toxicity endpoints
  - Standardized terminology, units, and formatting
- Curated chemical lists
  - Reference lists with classifications and bioactivity
  - In vitro assays linked with defined terminology
- Computational models
  - In vitro to in vivo extrapolation (IVIVE)
  - Quantitative structure-activity relationship (QSAR) models

Integrated Chemical Environment



https://ice.ntp.niehs.nih.gov/

Integrated Chemical Environment (ICE) database

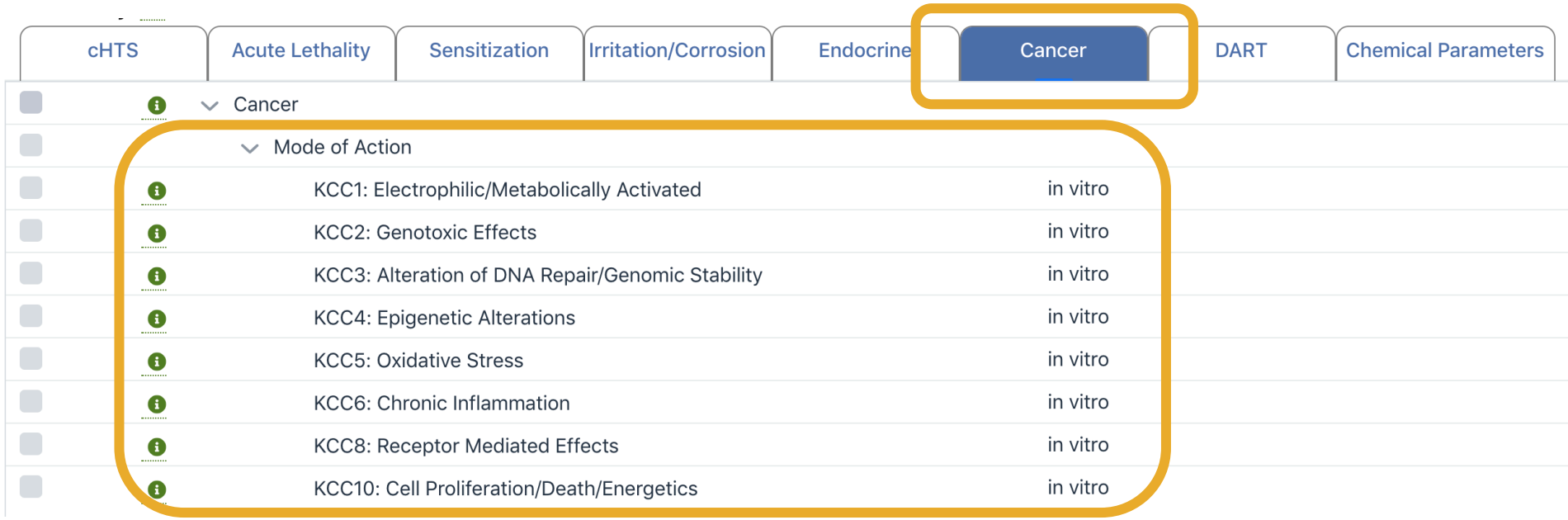
Chemical Lists

- Tox21
- AR In Vitro Agonist (R)
- AR In Vitro Antagonist (R)
- AR In Vivo Agonist
- AR In Vivo Antagonist
- EPA IRIS Carcinogenicity Classifications
- EPA Pesticide Active Ingredients
- EPA Pesticide Inert Ingredients, Food and Nonfood Use
- ER In Vitro Agonist (R)
- ER In Vivo Agonist (R)
- Eye Irritation-Corrosion (R)
- Genotoxicity (R)
- IARC Classifications
- NTP Cancer Bioassay Chemicals
- RoC Classifications
- Skin Corrosion (R)
- Steroidogenesis - Androgen
- Steroidogenesis - Estrogen
- Thyroid

CASRN	Chemical Name	DTXSID	Original SMILES	Original InChIKey	QSAR Ready SMILES	Technical Report No.	NTP Level Of Evidence Male Rats	NTP Level Of Evidence Female Rats	NTP Level Of Evidence Male Mice	NTP Level Of Evidence Female Mice	Tested in Tox21
67-66-3	Chloroform	DTXSID1020306	ClC(Cl)Cl	HEDRZPFGACZZDS-UHFFFAOYSA-N	ClC(Cl)Cl	TR-000	P	NE	P	P	Yes
143-50-0	Chlordecone (kepone)	DTXSID1020770	ClC12C(=O)C3(Cl)C4(Cl)C1(Cl)C1(Cl)C2(Cl)C3(Cl)C4(Cl)C1(Cl)Cl	LHHGDZSESBACKH-UHFFFAOYSA-N	ClC12C(=O)C3(Cl)C4(Cl)C1(Cl)C1(Cl)C2(Cl)C3(Cl)C4(Cl)C1(Cl)Cl	TR-001	P	P	P	P	Yes
79-01-6	Trichloroethylene	DTXSID0021383	ClC=C(Cl)Cl	XSTXAVWGXDQKEL-UHFFFAOYSA-N	ClC=C(Cl)Cl	TR-002	NE	NE	P	P	Yes

- genotoxicity data
- highest dose tested
- dose and tissue used for level of evidence call
- type of lesion

Tox21 HTS assays mapped to Key Characteristics of Carcinogens (KCC)



National Institute of Environmental Health Sciences
Division of the National Toxicology Program

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- Eye Irritation-Corrosion (R)
- Genotoxicity (R)
- IARC Classifications
- NTP Cancer Bioassay Chemicals
- RoC Classifications
- Skin Corrosion (R)
- Steroidogenesis - Androgen
- Steroidogenesis - Estrogen
- Thyroid

Search

Tox21 HTS assays mapped to Key Characteristics of Carcinogens (KCC)

cHTS | Acute Lethality | Sensitization | Irritation/Corrosion | Endocrine | **Cancer** | DART | Chemical Parameters

Cancer

Mode of Action

KCC1: Electrophilic/Metabolically Activated	in vitro
KCC2: Genotoxic Effects	in vitro
KCC3: Alteration of DNA Repair/Genomic Stability	in vitro
KCC4: Epigenetic Alterations	in vitro
KCC5: Oxidative Stress	in vitro
KCC6: Chronic Inflammation	in vitro
KCC8: Receptor Mediated Effects	in vitro
KCC10: Cell Proliferation/Death/Energetics	in vitro

Data

National Institute of Environmental Health Sciences
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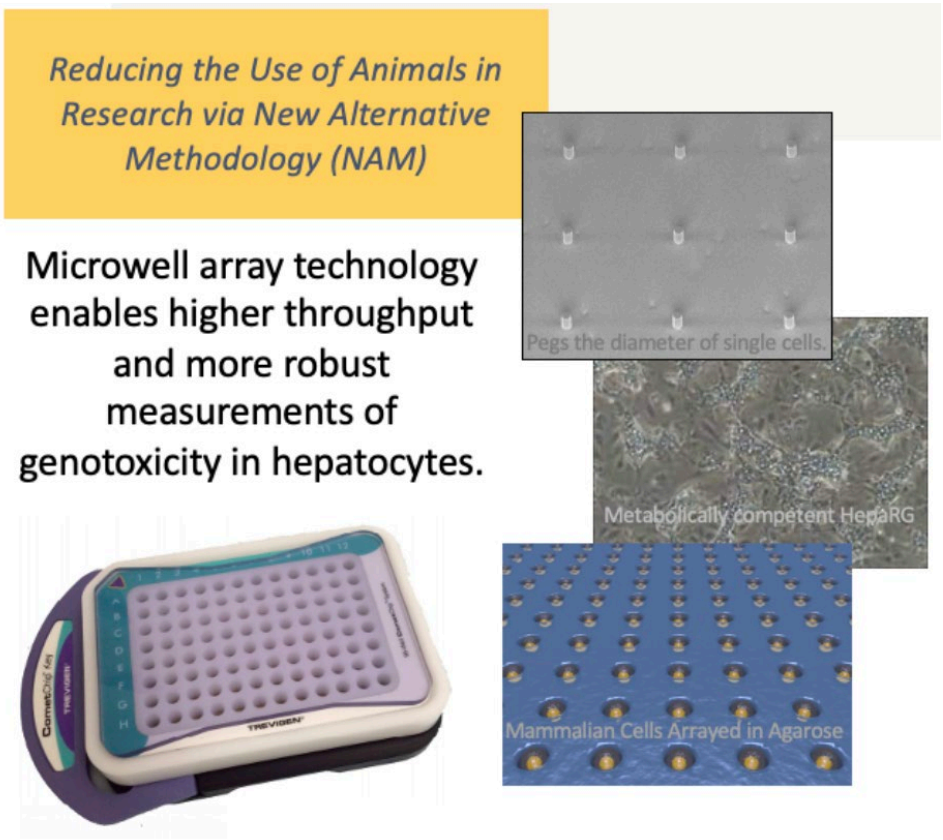
Replacing OECD TG489: In Vivo Comet Assay

HepaCometChip

NIEHS SBIR (U44): Development of a high throughput DNA damage assay in hepatocytes

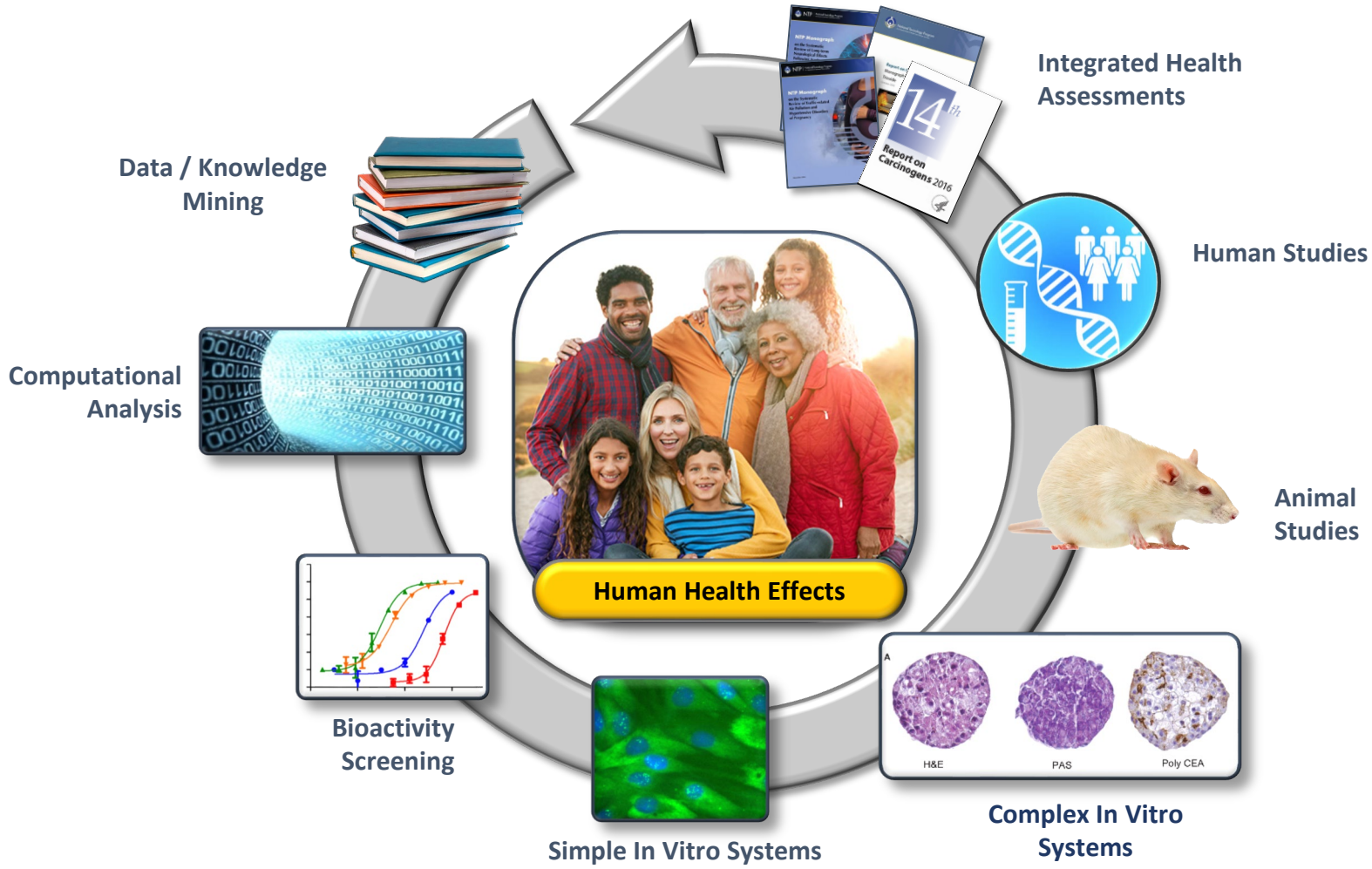


Prof. Bevin Engelward
Director, MIT Superfund Research Program
Dept. of Biological Engineering, MIT

Dr. Les Recio
Chief Scientific Officer
ScitoVation

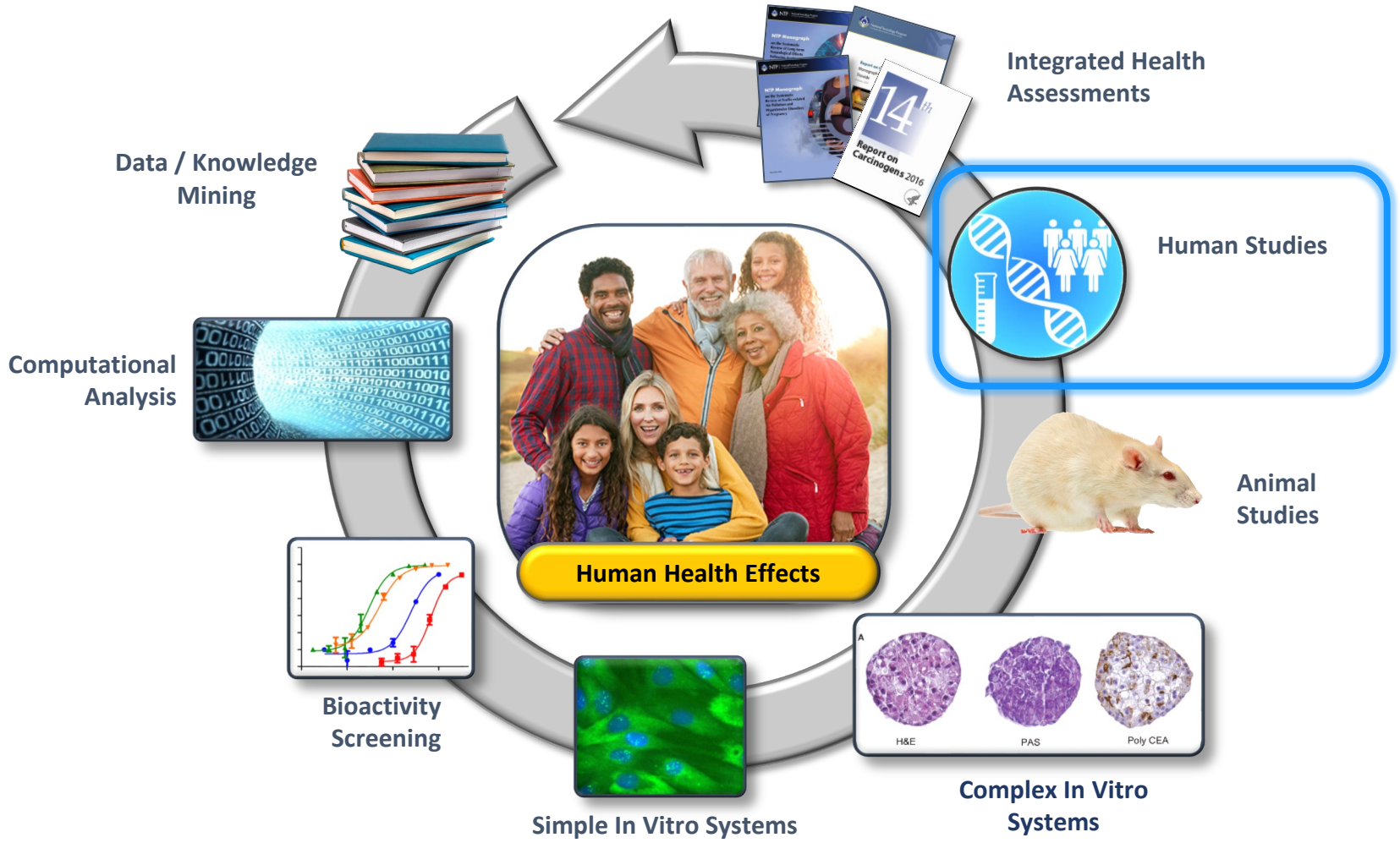
Leveraging capabilities to improve public health

Translational Toxicology Pipeline



Leveraging capabilities to improve public health

Translational Toxicology Pipeline



President Biden's Cancer Moonshot

THE WHITE HOUSE

Administration Priorities COVID Plan Briefing Room Español

BRIEFING ROOM

Fact Sheet: President Biden Reignites Cancer Moonshot to End Cancer as We Know It

FEBRUARY 02, 2022 • STATEMENTS AND RELEASES

"Biden-Harris Administration Sets Goal of Reducing Cancer Death Rate by at least 50 Percent Over the Next 25 Years, and Improving the Experience of Living with and Surviving Cancer"

President Biden's Cancer Moonshot

Goals include..

- **To diagnose cancer sooner** —Detecting and diagnosing cancers earlier means there may be more effective treatment options. Five years ago, detecting many cancers at once through blood tests was a dream. Now new technologies could put this within our reach.

- **To prevent cancer** — According to the WHO, Between 30-50% of all cancer cases are preventable. Prevention offers the most cost-effective long-term strategy for the control of cancer.

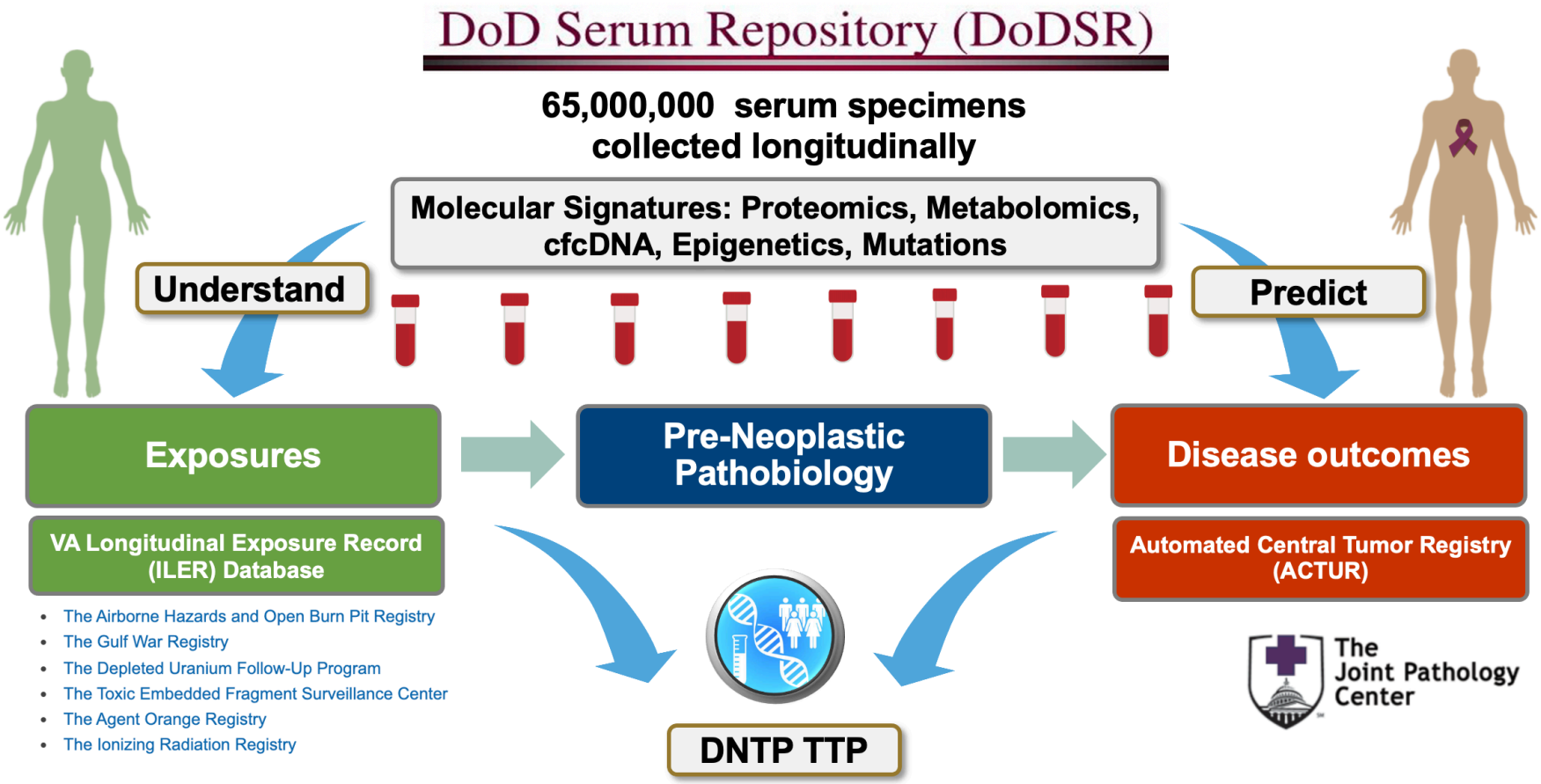
Colonel Craig D. Shriver, MD
Director of the Clinical Breast Care Project (CBCP) as well as the Director of the John P. Murtha Cancer Center at Walter Reed National Military Medical Center.

National Institute of Environmental Health Sciences
Division of the National Toxicology Program

Department of Defense Serum Repository

Pacific Northwest
NATIONAL LABORATORY

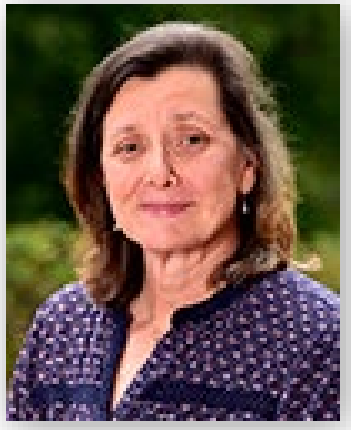
Translational Research: Linking Exposures to Disease



National Institute of Environmental Health Sciences
Division of the National Toxicology Program

Carci HEI Program Management Team Members

Amy Wang
Integrative Health Assessments Branch



Julie Foley
Mechanistic Toxicology Branch

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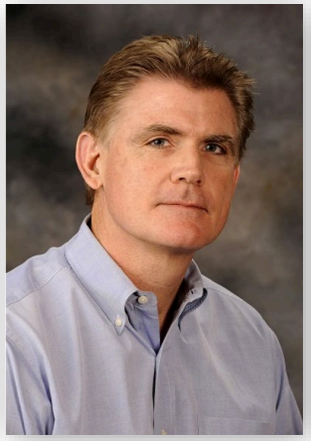
Comparative and Molecular Pathogenesis Branch

Dave Gerhold
National Center for Advancing Translational Sciences

Erik Tokar
Mechanistic Toxicology Branch



Warren Casey
Predictive Toxicology Branch

Kristine Witt
NIEHS Retired, Special Volunteer

Thank you!