# Cancer Pharmacology (CP) Program

X.F. Steven Zheng, PhD
Stephen K. Burley, MD, DPhil

April 26, 2023


RUTGERS Cancer Institute of New Jersey
RUTGERS HEALTH

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

RUTGERS

PRINCETON UNIVERSITY

RWJBarnabas HEALTH

# Cancer Pharmacology Program Leadership

## XF Steven Zheng, PhD

University Professor

- NCI R01
- NIDDK R01

### Zheng's Role in Program

- Lead activities among basic science Members
- Lead CP seminar series
- Organize Program retreats

## Stephen K Burley, MD, DPhil

University Professor and Henry Rutgers Chair
Director, RCSB Protein Data Bank (PDB)

- NIGMS R01
- NSF
- NCI PDB

### Burley's Role in Program

- Lead activities among applied science/engineering Members
- Build drug-discovery eco-system
- Organize joint IQB Crash Courses and Boot Camps

### Shared Program Responsibilities

- Collaborate with AD Basic Research (Shen) and AD Translational Research (Ganesan) in translation
- Foster consortium-wide collaborations, especially with CETI and CIPT program to enhance bi-directional translational efforts
- Enable research activities that address CINJ Catchment Area Priorities
- Promote IDEA (Inclusion, Diversity, Equity, and Access) throughout the membership
- Recruit and mentor new Members across the Consortium

# Program Aims

AIM 1

To **understand the biology of key molecular targets** in cancer that drive cell growth, proliferation, and survival so that they can be effectively targeted for cancer therapy

## AIM 1

Baker
Burley
Cartegeni
Chen
Dutta
Goodsell
Herranz
Hou
Jang
Kleiner
H. Li
Muir
Rameshwar
Sadoshima
Scotto
Tao
Vallat
Wuhr
Yan
Zheng
Zamudio

# Program Aims

AIM 1

To **understand the biology of key molecular targets** in cancer that drive cell growth, proliferation, and survival so that they can be effectively targeted for cancer therapy

AIM 2

To determine **mode of action and mechanisms of resistance** for anticancer agents

## AIM 2

An
Burley
Cartegeni
Chen
Glytsou
Hatefi
Herranz
Hou
Jin
Kaelber
Minko
Muir
Pasqualini
Staquicini
Scotto
Vallat
Wuhr
You
Zheng

# Program Aims

AIM 1

To **understand the biology of key molecular targets** in cancer that drive cell growth, proliferation, and survival so that they can be effectively targeted for cancer therapy

AIM 2

To determine **mode of action and mechanisms of resistance** for anticancer agents

AIM 3

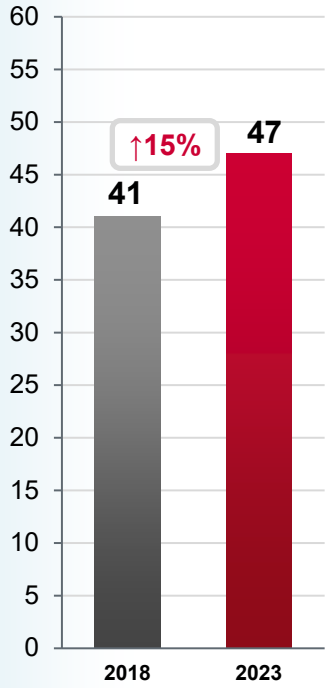
To **discover and develop novel therapies and enabling technologies** for more effective cancer treatment

## AIM 3

Burley
Gormley
Groves
Hatefi
Herranz
Javanmard
Jin
Lee
Kagan
Khare
Kim
Laskin
Minko
Moghe
Rabitz
Sinko
Skezely
Tromp
Tyagi
Wang
Yarmush

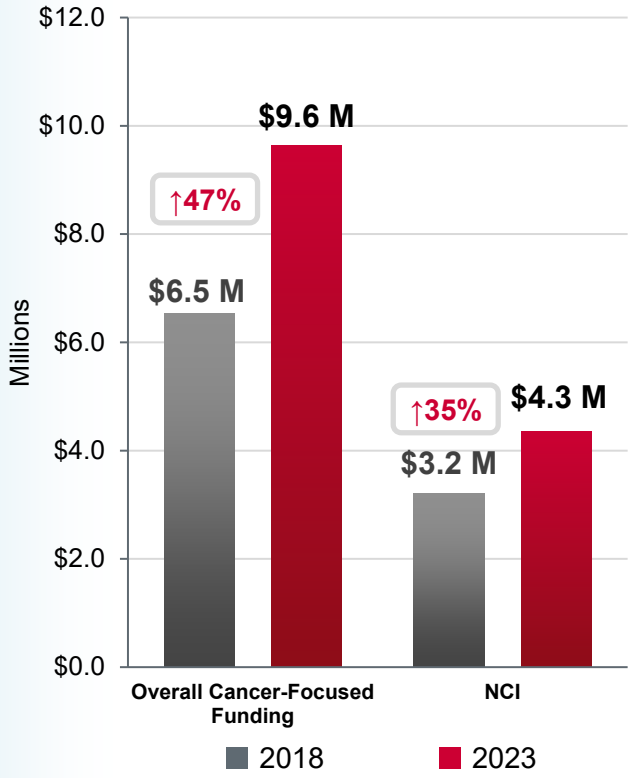
# Program Membership Profile

## Membership

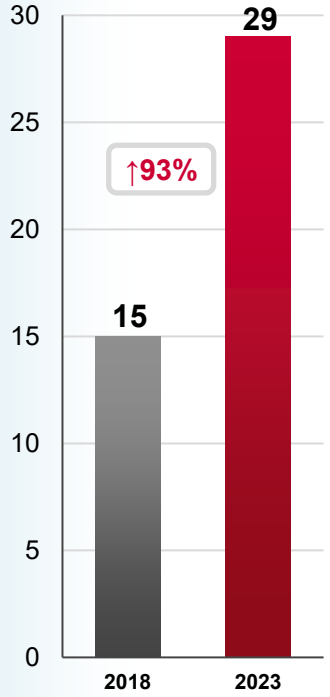



**2023**
23 Departments
7 Schools
2 Universities
16 New Members

## Total Cancer Relevant Funding



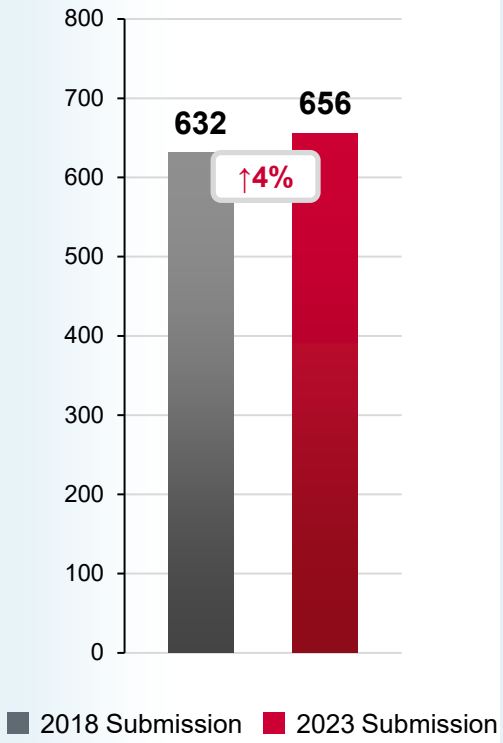

## R01 Equivalents



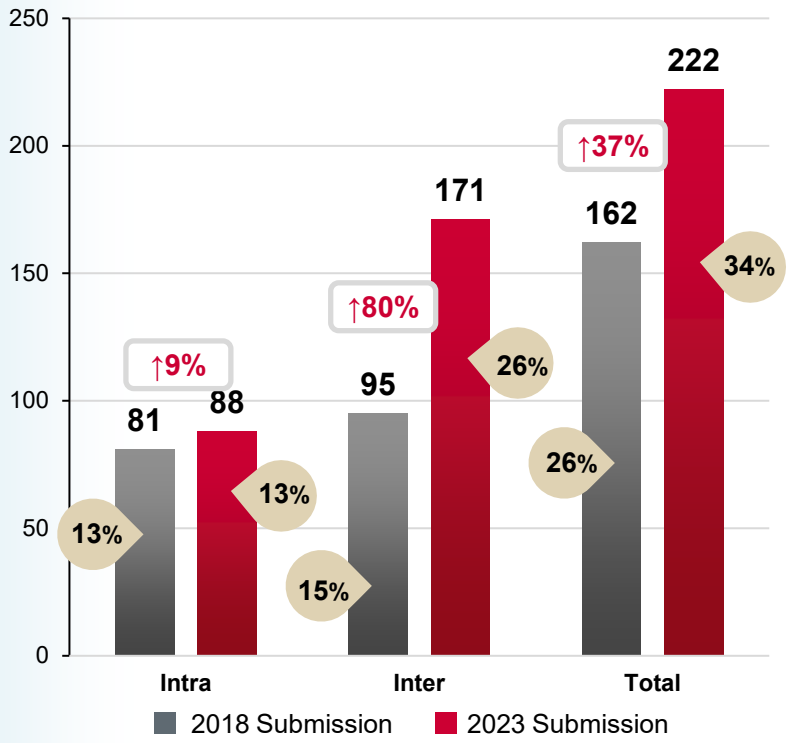

2018: 14 PIs/PDs
**2023: 21 PIs/PDs**

# Program Productivity and Collaborations

## Total Publications

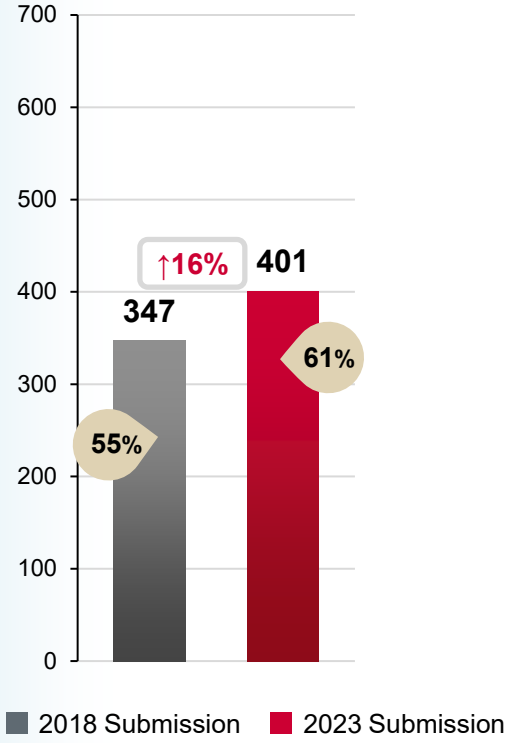



## Collaborative Publications




**High impact publications (IF ≥ 10): 36%** (236)
**Publications with citations ≥ 10: 41%** (271)

## Collaborative Publications with Other Institutions



# Response to Prior Critique

**Scored Outstanding to Excellent**

## Increased Princeton Representation, Collaborations

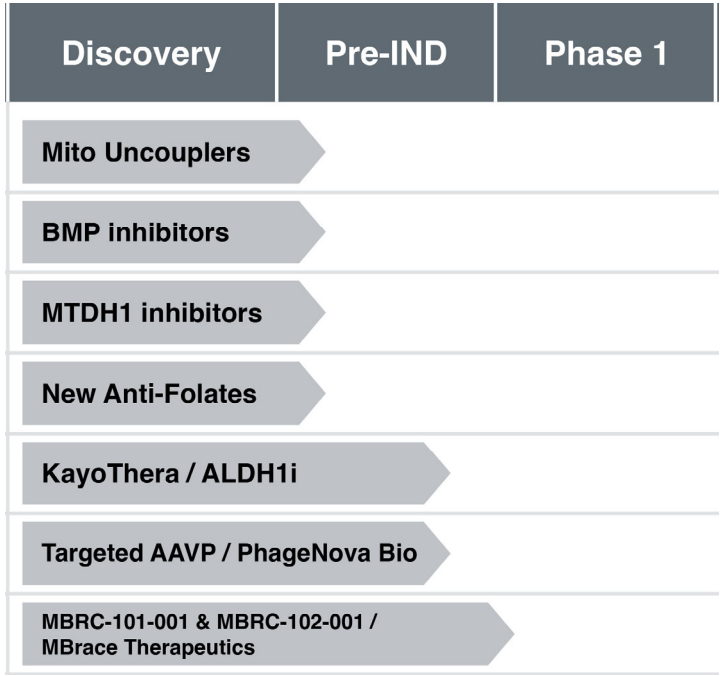
- Membership increased from 3 to 7
- Multiple intra/inter-programmatic collaborations

## Increased Multi-PI and Program Project Grants

- Multi-PI grants increased
- 5 P01/P01-equivalent grants

## Enhanced Drug Discovery Efforts

- SHIN2 for leukemia: Kim, Rabinowitz, Herranz
- MB1-47 for leukemia and liver metastases of colorectal and pancreatic cancers: Jin, Herranz
- CSSTRESAC peptide for TNBC: Pasqualini, Staquicini, Burley, Arap, Libutti




## Expanded Translation Scope and Commercialization

- Close interactions with CETI/CIPT and Biopharma Alliance AD
- RGD4C-AAVP-TNF in advanced solid tumors – Pre-IND: Pasqualini, Arap, Libutti; Related Co: PhageNova Bio
- High-resolution ultrasound diagnostic imaging technology for breast cancer, NSF funded: Tromp, Ganesan, Haffty
- Bench discovery to clinical trials (Troriluzole, Chen: CINJ Phase I ***NCT03229278***; International GBM AGILE Multi-center Phase II/III ***NCT03970447***)

# Scientific Impact of Program

## Advances in Scientific Knowledge

- Landscape of cancer epigenetics and chromatin remodeling: Muir
- mTOR inhibitor response/resistance: Zheng, Burley, Vallat, Su
- Structural basis of cancer painkiller action: Yan (former Member)
- Resistance to EGFR inhibitors: Burley, Vallat, Ganesan

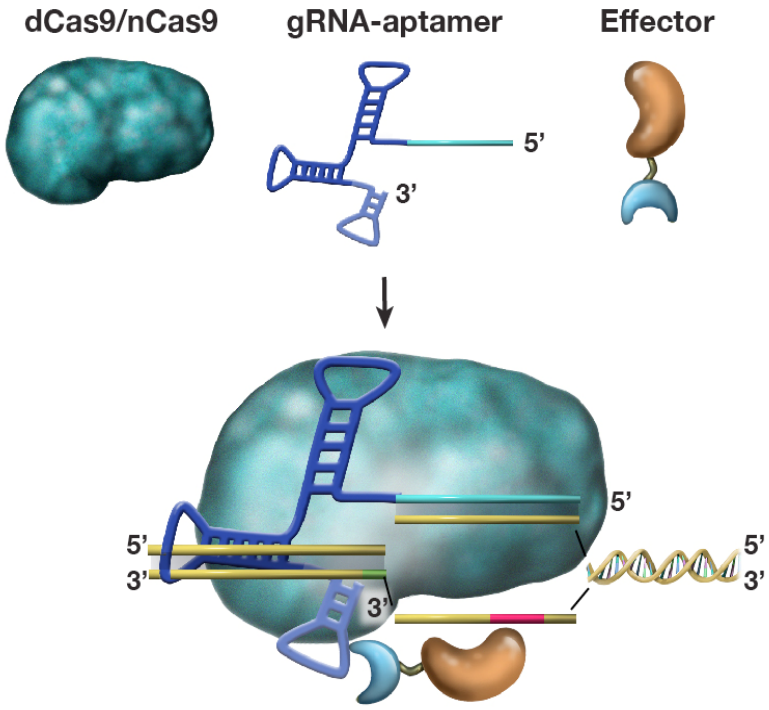
## Innovative Technologies

- Precision CRISPR single-base editing for CAR-T engineering: Jin
- AI-driven design, engineering and synthesis of nanomaterials: Gormley
- Chemical biology of epigenetics and chromatin remodeling: Muir
- Multiplex quantitative proteomics: Wuhr

## Novel Therapeutics

- Targeting mitochondria in leukemia and colorectal cancer: Jin, Herranz
- Targeting SHMT in leukemia: Herranz, Kim, Rabinowitz
- Targeting PDIA3 in TNBC: Pasqualini, Staquicini, Burley, Arap, Libutti

**Precision CRISPR Single-Base Editing**




Jin and colleagues

# Understanding the Biology of Molecular Targets

AIM 1

Muir | Kadoch (Dana Farber) | Sadoshima | Li

Jang | Baker | Cole (CIPT)

**Shared Resources**
- Biomedical Informatics
- Comprehensive Genomics
- Genome Editing
- Biostatistics

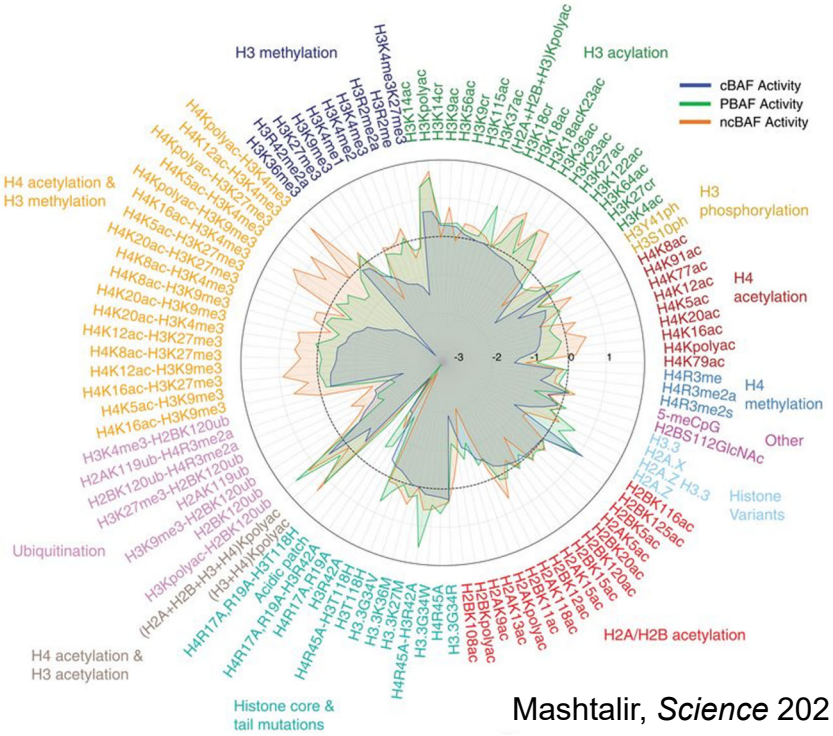
**Grants**
- P01CA196539
- R01CA259365
- R21CA262491
- R01CA242158
- R01HL138720

**Publications**
- Mashtalir, *Science* 2021
- Valencia, *Cell* 2019
- Oliveros, *PNAS* 2022
- Nagarajan, *J Clin Invest* 2022
- Kashihara, *J Clin Invest* 2021

## Major Discoveries

- Muir: Landscape of cancer chromatin remodeling and epigenetics
- Jang, Baker, Cole (CIPT): Molecular mechanisms of chemo brain
- Sadoshima, Li: Understand cancer targets in the heart

**Epigenetic Marks Dictate Activity of Chromatin Remodeling Complexes**




Mashtalir, *Science* 2021

## Impact

Global understanding of epigenetics/chromatin remodeling
Understand and reduce adverse effects of chemo brain

## Catchment Priority

Breast and Lung Cancers

# Understanding the Biology of Molecular Targets

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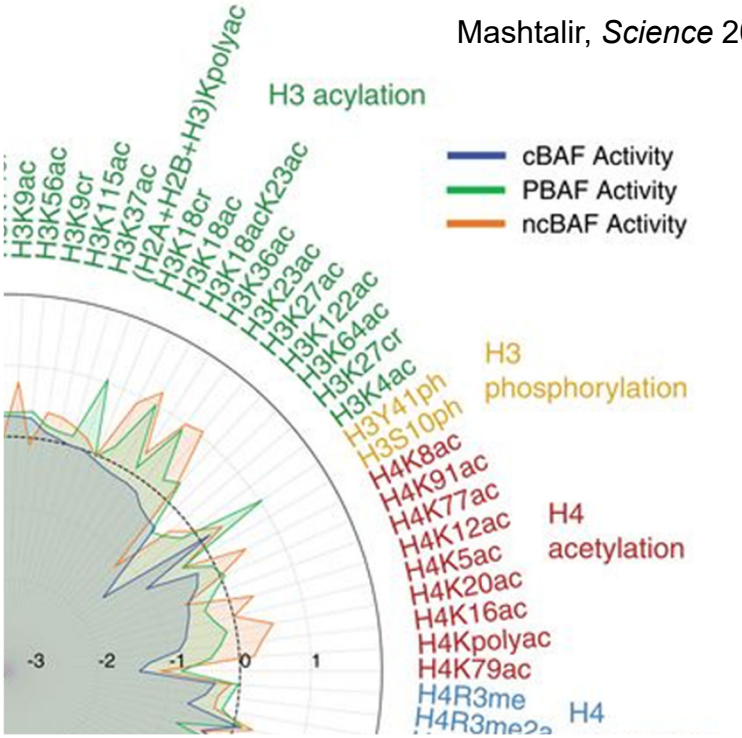



**Impact**

Global understanding of epigenetics/chromatin remodeling
Understand and reduce adverse effects of chemo brain

**Catchment Priority**

Breast and Lung Cancers

# Drug Action and Resistance Mechanisms

AIM 2


Zheng


Su (CMI)


Burley


Vallat


Ganesan (CIPT)


Pine (former GICG)


Pasqualini


Arap (CIPT)

**Shared Resources**
- Biomedical Informatics
- Comprehensive Genomics
- Genome Editing
- Biostatistics

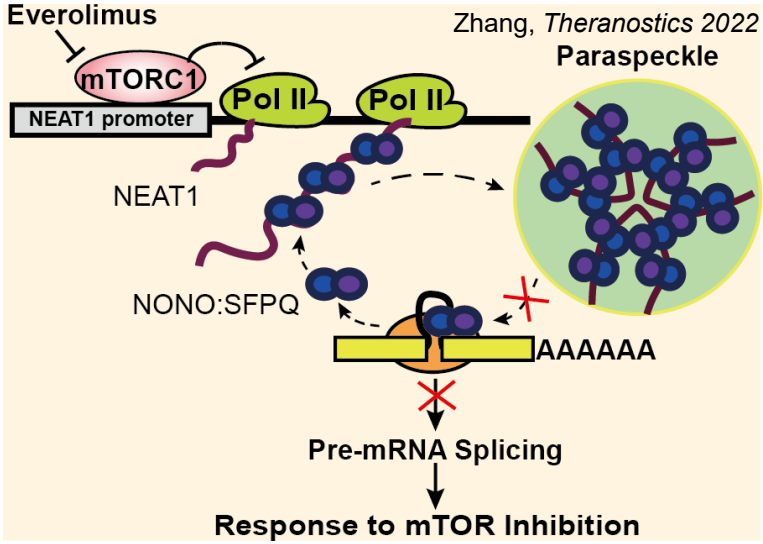
**Grants**
- R01CA260006
- R01DK124897
- R01GM133198
- R01CA226537
- R01CA240516

**Publications**
- Zhang, *Theranostics* 2022
- Zhang, *Cancer Res* 2021
- Wang, *Nat Comm* 2021
- Tsang, *Mol Cell* 2018
- Castellano, *J Thoracic Oncol* 2019
- Butner, *Sci Adv* 2021
- Butner, *eLife* 2021

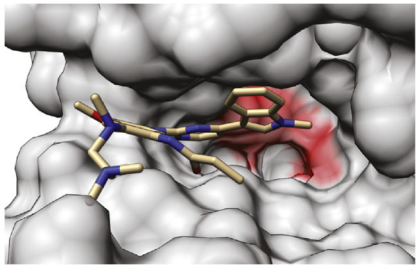
## Major Discoveries

- Zheng, Vallat, Burley, Su (CMI): Mechanism of Response to mTOR Inhibitors and Chemotherapy
- Vallat, Burley, Ganesan (CIPT), Pine (former GICG): Mechanism of Acquired Osimertinib Resistance
- Pasqualini, Arap (CIPT): Computational Prediction of Responses to Immune Checkpoint and Chemotherapies

**Mechanism of Response to mTOR Inhibitors**




**Osimertinib Resistance in NSCLC**



Castellano, *J Thoracic Oncol* 2019

**Impact**
Understand and overcome resistance to targeted agents

**Catchment Priority**
Breast, Colorectal, Lung, and Prostate Cancers

# Novel Therapies and Drug Delivery

AIM 3


Kim


Rabinowitz (CMI)


Herranz


Jin


Pasqualini


Staquicini


Arap (CIPT)

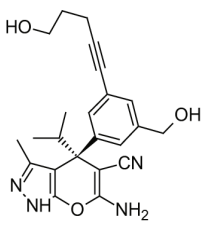
**Shared Resources**
- Biomedical Informatics
- Comprehensive Genomics
- Genome Editing
- Biostatistics

**Grants**
- R01CA236936
- R00CA197869
- ACS133916
- R01CA163591
- R01CA204517
- R01CA240516

**Publications**
- García-Cañaveras, *Leukemia* 2020
- Ghergurovich, *Nat Chem Biol* 2020
- da Silva-Diz, *Blood* 2021
- Alasadi, *Oncogene* 2021
- Staquicini, *PNAS* 2021
- Staquicini, *eLife* 2021
- Suwan, *PNAS* 2019

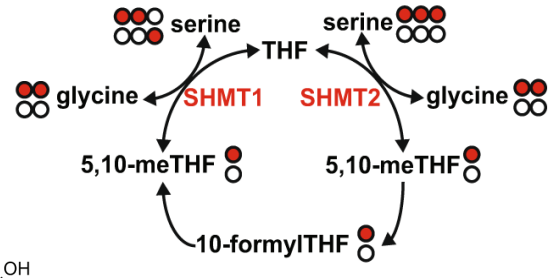
## Major Discoveries

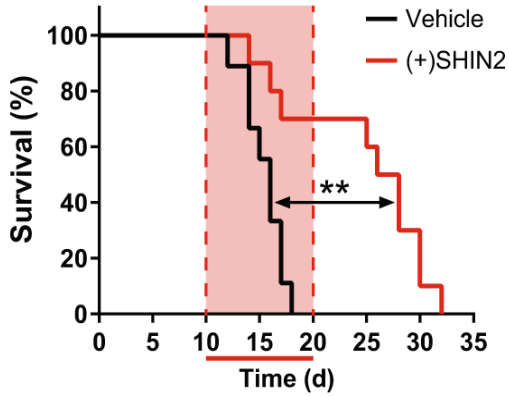
- Kim, Rabinowitz (CMI), Herranz – Small-Molecule: First-in-class SHMT inhibitor SHIN2 with activity in adult and pediatric acute leukemia models
- Jin, Herranz – Small-Molecule: 2nd generation mitochondrial uncoupler MB1-47 with activity in T-cell acute lymphoblastic leukemia, colon, and pancreatic cancer
- Pasqualini, Staquicini, Arap (CIPT) – Biologics: Cyclic nona-peptide targeting PDIA3 for triple-negative breast cancer; Monoclonal antibody targeting GRP78 for breast and prostate cancers



(+)SHIN2

**SHIN2 Anti-leukemic Activity**




García-Cañaveras, *Leukemia* 2021

**Impact**
First-in-class targeted agents SHIN2 and Biologics

**Catchment Priority**
Breast, Colorectal, and Prostate Cancers

# Translational Research

## In collaboration with CIPT and CETI and AD for Biopharma Alliances Molloy

### Small-Molecule Drugs

- Troriluzole: Drug discovery and demonstration of anti-cancer efficacy by CP Member Chen; CINJ Phase I led by Saraiya (CIPT) (***NCT03229278***, completed 2020); BioHaven Ltd. – International GBM AGILE Phase II/III Multi-center, Interventional Trial (***NCT03970447***, ongoing)
- SHIN2: Adult and pediatric anti-leukemic activity; Barer Institute – IND-enabling studies
- MB1-47: Activity against T-cell acute lymphoblastic leukemia and metastatic colorectal carcinoma; Mito BioPharma, Inc. - IND-enabling studies

### Biologics Drugs and Cell Engineering

- CSSTRESAC cyclic peptide targeting PDIA3 for triple-negative breast cancer; PhageNova Bio, Inc. – IND-enabling studies
- Monoclonal antibody targeting GRP78 for breast and prostate cancers; MBrace Therapeutics, Inc. – IND-enabling studies
- Antibody-Drug Conjugate XCN-010 targeting activated matriptase (Warhead: monomethyl auristatin-E ); Xiconic Pharmaceuticals, Inc. – IND-enabling studies
- Precision CRISPR technology for CAR-T cell engineering; Horizon Discovery, Ltd. – Pre-clinical development

**Commercialization: 43 Innovation Disclosures, 31 Patents Filed, 21 Patents Issued, 8 License Agreements**

# Research Responsive to Catchment Area

Herranz
(COE Liaison)

Tromp

Ganesan
(CIPT)

Haffty
(CIPT)

Minko

Kagan

Pine
(former GICG)

**Shared Resources**
- Biomedical Informatics
- Genome Editing
- Biostatistics
- Metabolomics

**Grants**
- R01CA238871
- R01CA209818
- R01CA269513
- R01GM124046
- NSF1941241
- NSF1906883

**Publications**
- Shen, *J Control Release* 2020
- Garbuzenko, *Theranostics* 2020
- Garbuzenko, *Theranostics* 2020

## Major Discoveries

### Novel Ultrasound Imaging Technology

- Tromp, Ganesan, Haffty: High-resolution ultrasound technology for precision diagnosis of breast cancer
- Reducing diagnostic imaging costs to lower barrier for early detection and treatment of breast cancer among underrepresented and economically-disadvantaged groups

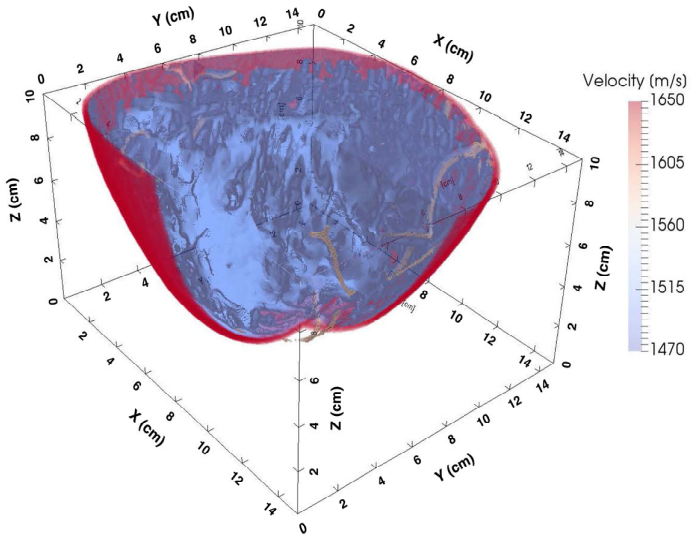
### Targeted Delivery of Lung Cancer Therapies

- Minko, Kagan, and Pine (former GICG): delivery technology for inhaled nano-formulated anti-lung cancer drugs
- Reducing systemic side effects

### Catchment Area Responsive Research

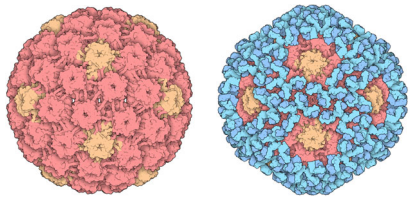
- A majority of CP publications and most CP grants are relevant to Catchment Area priorities
- Addresses diagnosis, and therapeutic development and resistance in breast, colorectal, and lung cancers, and melanoma

### High-Resolution Ultrasound Detection of Early Breast Tumors

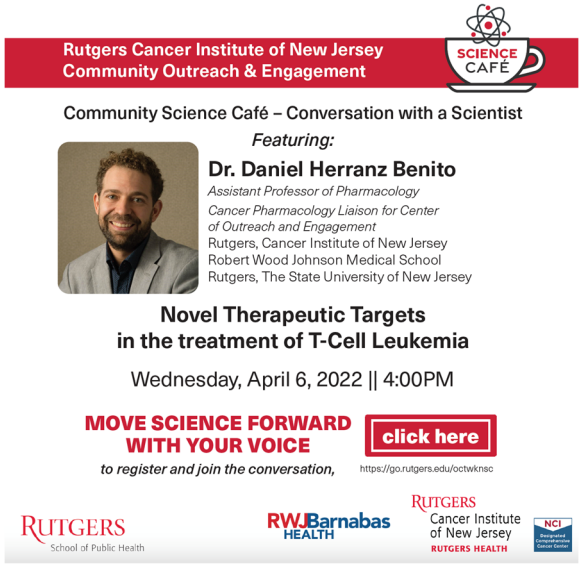



Tromp and colleagues

# Additional Examples of Catchment Area Responsiveness



HPV Vaccine 3D Structures
PDB IDs: 3j6r, 6bt3




## Collaboration with Cancer Health Equity Center of Excellence

- CP Program Leaders and Program Liaison meet quarterly with the Internal Catchment Advisory Committee
- Rameshwar engaged the **Community Cancer Action Board** in discussion of research
- Herranz and Zheng participated in Science to Sidewalk


## Bidirectional Community Engagement

- Herranz and Jang discussed leukemia therapies and chemo brain, respectively, at the **Community Science Cafés** (**COE sponsored**)
- Community feedback led to new focus on developing therapeutic interventions for chemo brain
- Burley, Dutta, and Zheng organized and judged the 2022 RCSB Protein Data Bank Video Challenge on “Molecular Mechanisms of Cancer” for High School Students across the US

# Education and Training over Grant Period

## Peer-Reviewed Training Grants

- NIH NRSA Training Grant for the New Jersey Alliance For Clinical Translational Science (Scotto)
- NIH Rutgers Biotechnology Training Program (Yarmush)
- NIH Summer Research and Education Program for Health Professional Students (Rameshwar)

## Faculty Development Awards

- NCI Award K22CA251491 (Hou)
- NCI Award K99CA252602 / R00CA252602 (Glytsou)
- American Cancer Society Scholar Award 133916-RSG-19-161-01-TBE (Herranz)

## Specialized Training Courses

- 2022, 2023 IQB Winter Boot Camp on cancer biology and mechanisms of cancer drug action for **Underrepresented Minority undergraduate students**
- 2022 RCSB PDB High School Video Challenge on Molecular Mechanisms of Cancer
- 2022 IQB Crash Courses on “Intrinsically Disordered Biological Macromolecules in Cellular Signaling/Regulation” and “Cancer Immunology and Metabolism”


# Value Added: Program to Center

- **Paradigm-Shifting Science**: Breakthroughs driven by Program aims
- **Translation**: Clinical trials; Biopharma startups; Drug discovery infrastructure; and the Protein Data Bank
- **Addressing Catchment Area Priorities and COE**: Research and development for breast, lung, and colon cancers, and melanoma; Bidirectional community engagement

- **Education and Training**: Undergraduate Boot Camps; Crash Courses for Graduate Students and Postdocs; Mentoring new CINJ faculty and Rutgers basic and applied researchers in Cancer Biology
- **Diversity Enhancement**: Working closely with members and their Schools/Departments to enhance CP-related diversity recruitment of faculty/trainees
- **These activities demonstrate CP Program roles in supporting the Comprehensiveness of the Cancer Center Consortium**

**Glytsou**
Co-recruited with CMI

**Zamudio**
Co-recruited with GICG

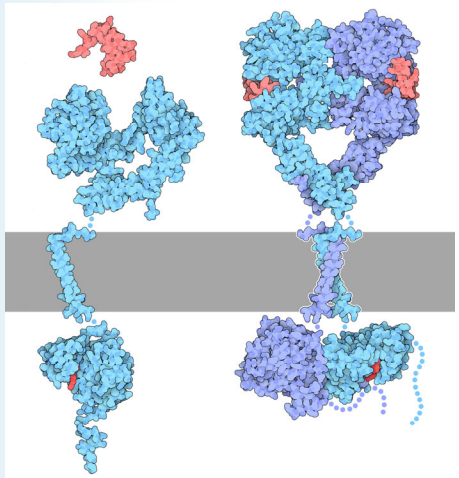
# Future Plans

## 1 Enhance Collaborative Drug Discovery and Translation

- Pilot Awards to stimulate P01, U01 and MPI-R01 submissions
  - 3D-Stucturalyzer for Oncology Drug Discovery: Burley, Zheng, Ganesan (CIPT)
  - Higher-Resolution Ultrasound Diagnostics: Tromp, Ganesan (CIPT), Haffty (CIPT)
- Work with CETI and CIPT Program to advance preclinical candidates to human trials
  - *e.g.,* SHIN2, MB1-47, and cyclic-nonapeptide CSSTRESAC
- Work with AD BioPharma Alliances to develop strategic industry collaborations

## 2 Leverage Artificial Intelligence and Protein Data Bank to Accelerate Research

- Develop the Protein Data Bank as a global resource for basic and applied oncology research
- Build upon multi-PI NSF DMREF grant to promote AI-based design and synthesis of small molecules and nanomedicines



**280 EGF/EGFR PDB Structures Enable Studies of Targeted Drug Action and Resistance**

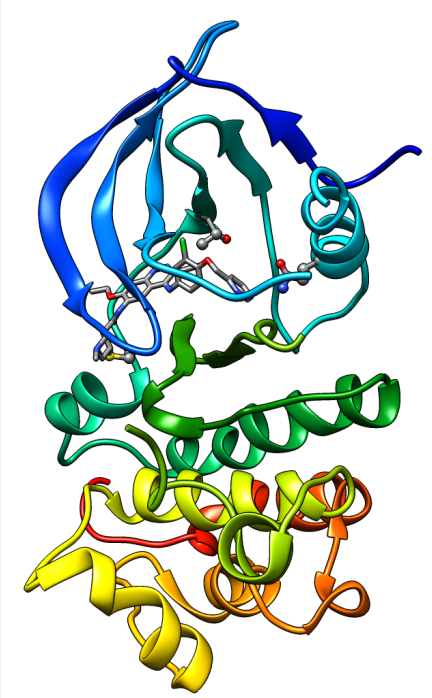
# Future Plans

## 3 Enhance Integration of Princeton Members and Build Team Science

- Explore molecular targets of cancer pain: Tao, Kim, Baker, Wang
- Advance quantitative proteomics technology in drug response and resistance: Wuhr, Zheng, Li

## 4 Recruit to Strengthen Diversity and Catchment Area Priority Research

- Rutgers Cancer Institute of New Jersey
- Medicinal Chemistry – Rutgers School of Pharmacy
- Chemical Biology – Princeton University and Rutgers School of Arts and Sciences



**L858R/M766Q EGFR Inhibited by Neratinib Modeled using PDB ID 2JIV Castellano *et al.* (2019)**

# Thank You

Q&A Segment

RUTGERS
Cancer Institute
of New Jersey
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RUTGERS

PRINCETON UNIVERSITY

RWJBarnabas HEALTH