Genomic Instability and Cancer Genetics

Chang Chan, PhD
Cristina Montagna, PhD

April 26, 2023

RUTGERS
Cancer Institute
of New Jersey
RUTGERS HEALTH

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

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PRINCETON UNIVERSITY

RWJBarnabas HEALTH

Genomic Instability and Cancer Genetics

Cristina Montagna, PhD

Professor
Radiation Oncology

- NCI R21
- NCI U54 Subproject
- NIA RF1
- DoD (3)

Montagna's Role in Program

- Aims 1 and 2
- Experimental Sciences

Chang S. Chan, PhD

Associate Professor
Medicine

- NET ResFndtn

Chan's Role in Program

- Aim 3
- Computational Sciences

Shared Program Responsibilities

- Co-leaders share responsibilities in all aspects of the program, while each has a leading role in certain aspects of the program
- Translational and team projects
- Monthly Program meetings
- Pilot awards
- NIA nominations
- Education, DEI, catchment
- Membership
- Interactions with PU

Program Aims

AIM 1

To elucidate the **core mechanisms that provoke genomic instability**, including imprecise repair of DNA damage, DNA replication infidelity, and chromosome segregation errors

AIM 1

Bunting
Ganesan
Gartenberg
Georgopoulos
Herbig
Madireddy*
McKim
Patel
Petry*
Schindler
Shen
Tischfield
Xia
Zaratiegui

*New Member

Program Aims

AIM 1

To elucidate the **core mechanisms that provoke genomic instability**, including imprecise repair of DNA damage, DNA replication infidelity, and chromosome segregation errors

AIM 2

To understand the **coordination between genome maintenance machinery and intrinsic cellular homeostasis**, and their contribution to tumor initiation and progression

AIM 2

Copeland
Feng
Gu
Hu
Levine
Libutti
Montagna*
Perekatt*
Pestov*
Rasin
Roth
Verzi
Zamudio*
Zhou*

*New Member

Program Aims

AIM 1 — To elucidate the **core mechanisms that provoke genomic instability**, including imprecise repair of DNA damage, DNA replication infidelity, and chromosome segregation errors

AIM 2 — To understand the **coordination between genome maintenance machinery and intrinsic cellular homeostasis**, and their contribution to tumor initiation and progression

AIM 3 — To characterize the **cancer genome landscape** and gene expression signatures to reveal therapeutic vulnerability

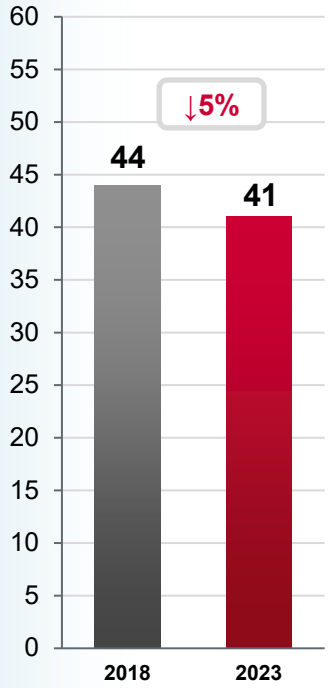
AIM 3

Adamson*
Bhanot
Chan, C
Chan, M*
De
Grigoriev*
Kreimer*
Mitrofanova*
Raphael
Shah*
Singh
Troyanskaya

*New Member

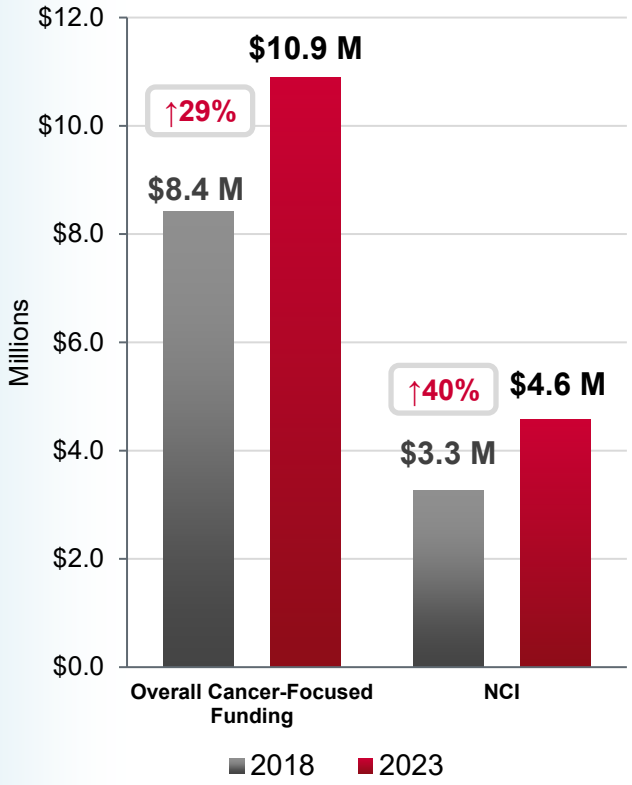
Program Membership Profile

Membership

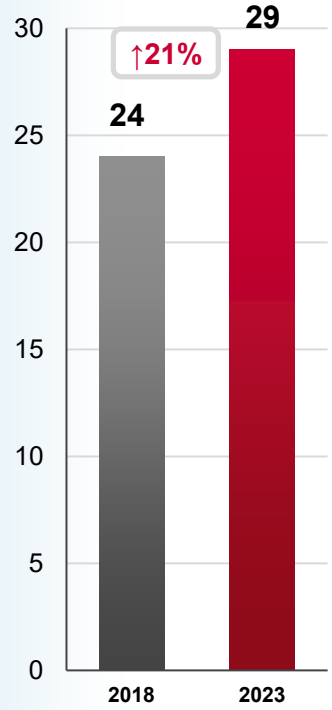


2023
20 Departments
8 Schools
3 Universities
1 Institute
12 New Members

Total Cancer Relevant Funding



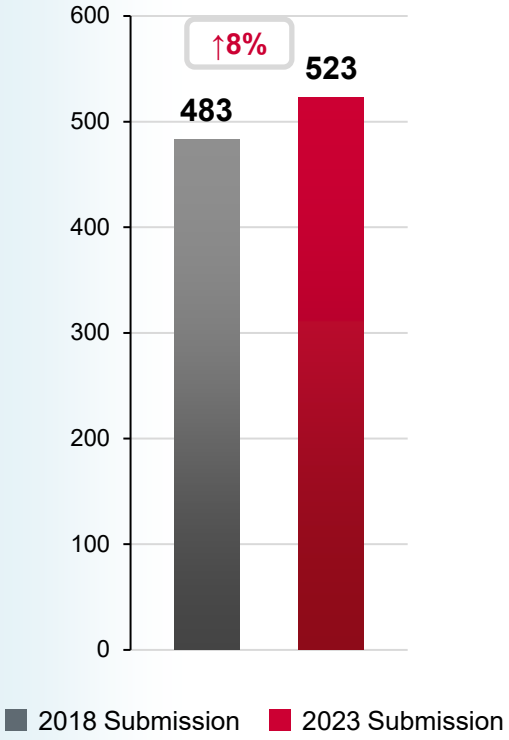
R01 Equivalents



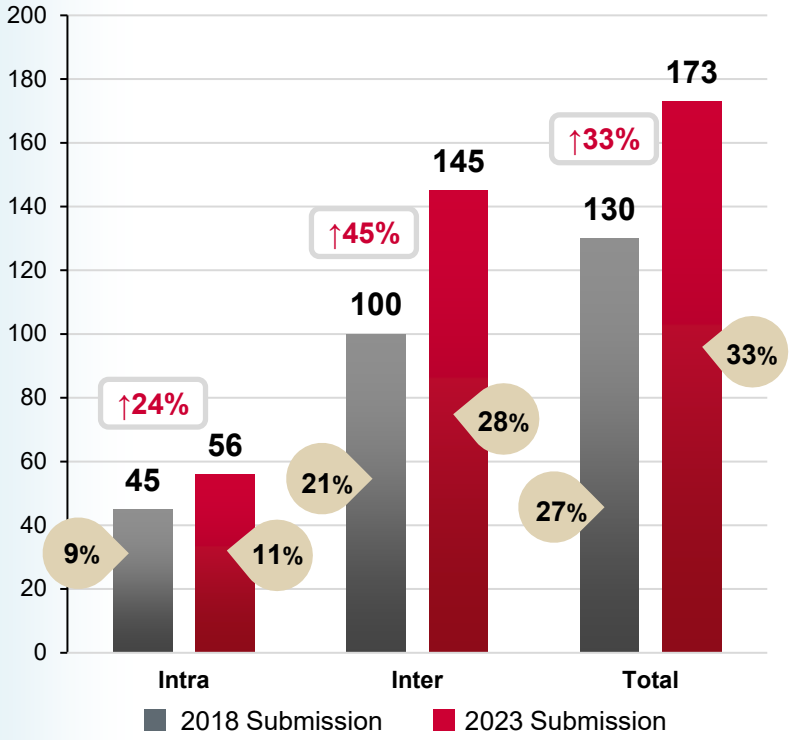
2018: 18 PIs/PDs
2023: 19 PIs/PDs

Program Productivity and Collaborations

Total Publications

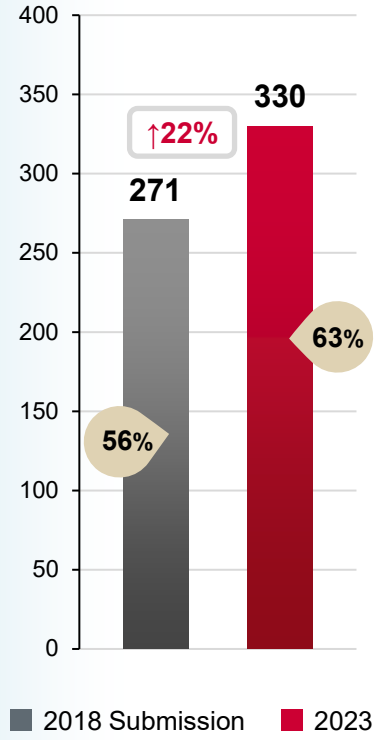


Collaborative Publications



High impact publications (IF ≥ 10): 38% (198)
Publications with citations ≥ 10: 38% (201)

Collaborative Publications with Other Institutions



Response to Prior Critique

Scored Excellent

- Improved clinical translation of cancer genomics studies
  - Developed LOHGIC and All-FIT, routinely used by Molecular Tumor Board
  - Identified truncated form of FGFR2 as an oncogenic driver targeted in clinical trials
  - Calculated HRD scores and applied to breast cancer therapeutic trials
  - Defined a genomic signature of CHIP and used to evaluate potential AEs in breast cancer therapy
- Improved collaborations among members from Consortium institutions
  - CINJ pilot awards (Verzi/Toettcher, and De/Raphael)
  - NJACTS award (Petry/Shen)
  - Mutational variants of unknown significance (Singh, C. Chan, Ganesan)
  - Single cell-based synthetic lethality/viability screen for DNA repair genes using PerturbSeq (Adamson, Xia, Shen, Ganesan)
  - Targeting spindle-formation factors in mitosis (Petry, Shen)

Scientific Impact of Program

Fundamental mechanisms

- Centrosome-independent branching microtube nucleation during mitotic spindle formation
- New cellular origin of colorectal cancer due to ectopic crypt formation resulting from villi de-differentiation
- Non-canonical roles of the Trp53 in tumor progression
- Microbial signatures in colorectal and pancreatic cancers

Tools and drivers for precision oncology

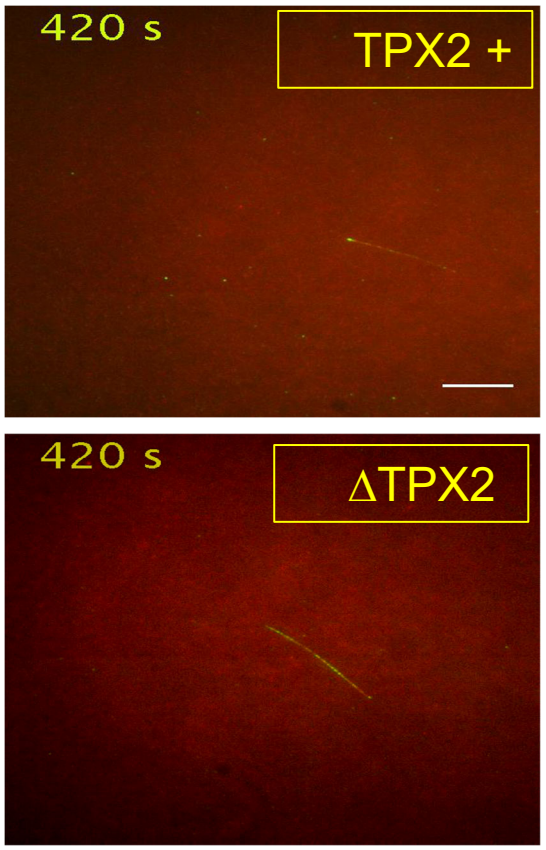
Grants:

- R01GM141100 (Petry)
- R01DK121915 (Verzi)
- R01DK126446 (Verzi)
- R01CA229257 (Feng)

Publications:

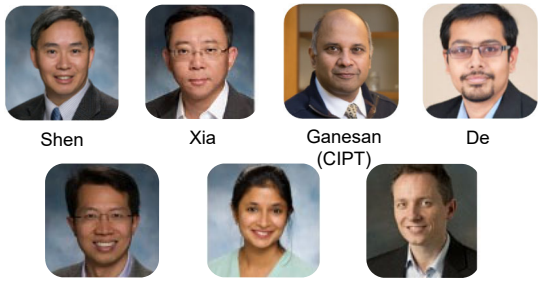
Petry, *Nat Cell Biol* 2018
Petry, *Nat Commun* 2020
Verzi, *Cancer Res* 2018
Verzi, *Nat Genet* 2019
De, *Cancer Cell* 2022

Branched Microtube Formation Without Centrosome (Petry)



BRCA Network in DNA Damage Response, Tumor Development, and Therapeutic Response

AIM 1



Shared Resources

- Genome Editing
- Biospecimen Repository and Histopathology
- Comprehensive Genomics
- Immune Monitoring

Grants

- P01CA250957
- R01CA138804
- R01CA195612
- R01CA262227
- R01CA260724
- R01GM129066

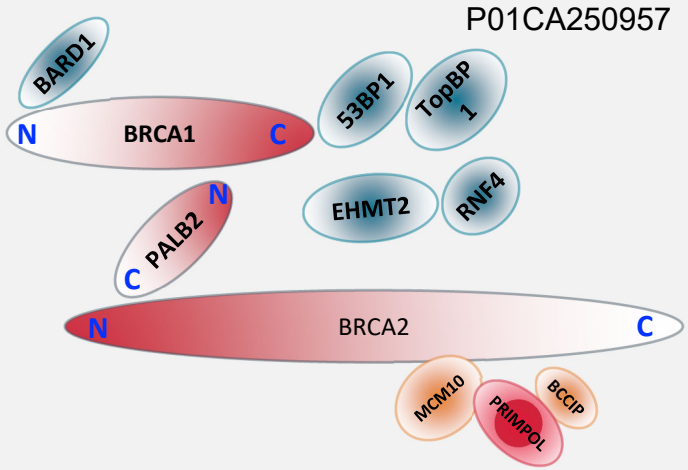
Publications

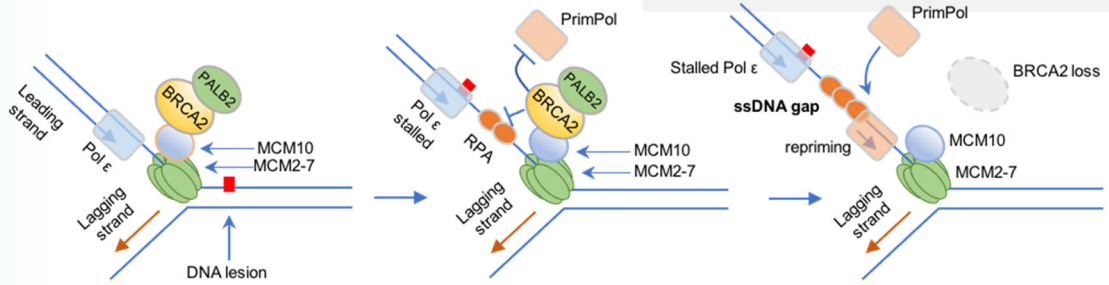
Bunting, *Mol Cell Biol* 2018
Xia, *Oncogene* 2019
Xia, *Nat Commun* 2021
Xia, *Cancer Res* 2021
Shen, *Cell Reports* 2022

Major Discoveries

- BRCA2-MCM10 interaction suppresses PRIMPOL-mediated ssDNA gap formation upon DNA damage
- Inter-tissue difference in DNA damage response revealed in *Brca2* and *Palb2* KO mice
- Structural basis of PALB2 homo-dimer
- Differential roles of BRCA1-PABL2 and PALB2-BRCA2 interactions in G2/M checkpoint activation and maintenance

P01CA250957





Impact

Investigate DNA damage response (DDR) networks across cell types and conditions to reveal new therapeutic vulnerabilities

Catchment Priority

Breast Cancer
Hereditary Cancer

Tissue Homeostasis Dictates the Susceptibility to Colorectal Cancer

AIM 2


Verzi


Perekatt


Gao (CMI)


White (CMI)


Ganesan (CIPT)


Montagna

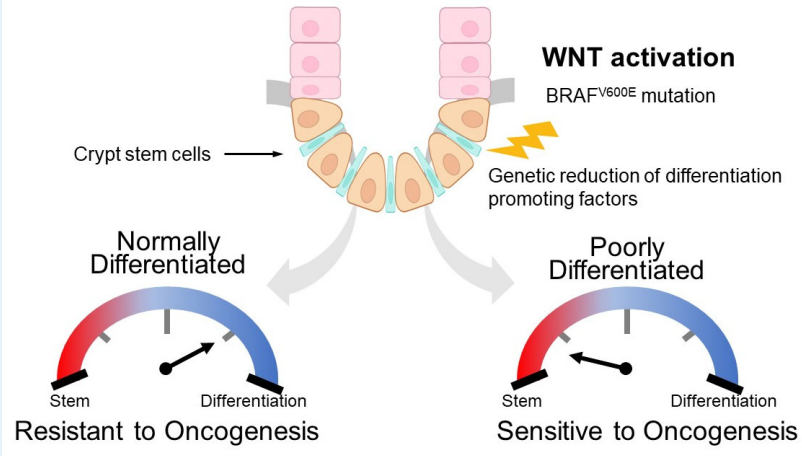
Shared Resources
- Genome Editing
- Comprehensive Genomics

Grants
- CINJ pilot award
- R01DK121915
- R01CA190558
- K22CA218462

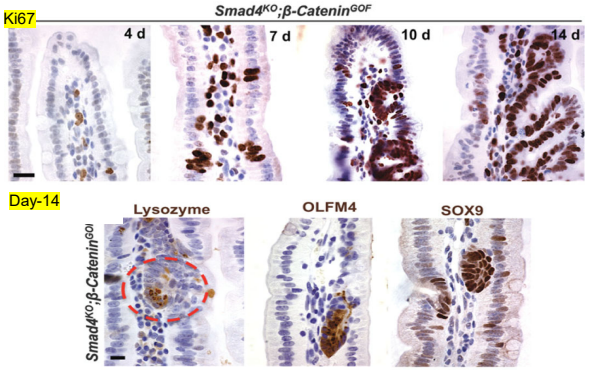
Publications
Perekatt/Verzi, *Can Res* 2018
Chen/Verzi, *Nat Genet* 2019
Kumar/Verzi, *Development* 2019
Chen/Verzi, *Gastroenterology* 2020
Chen/Verzi, *Cell Reports* 2021
Verzi, *Oncogene* 2022

Major Discoveries

- SMAD4 dampen epithelial differentiation and enhance BRAF and WNT oncogenic functions
- Dedifferentiation expands cells of origin for WNT-driven oncogenesis
- SMAD4 and HNF4 maintain tissue homeostasis via feed-forward loop



Ectopic crypt formation from villi upon SMAD4 deletion and expression of GOF b-catenin



- Montagna/Jabbour: U54 Radiation Oncology-Biology Integration Network (ROBIN) (1U54CA274291)

Impact
Paradigm shifting theory of new cellular origin for colorectal cancer

Catchment Priority
Colorectal Cancer

New Insights into the Landscapes of Cancer Genomes: Reconstruction of Clonal Evolution

AIM 3


Raphael


Khiabanian (former GICG)


Riedlinger (CIPT)


Ganesan (CIPT)


De

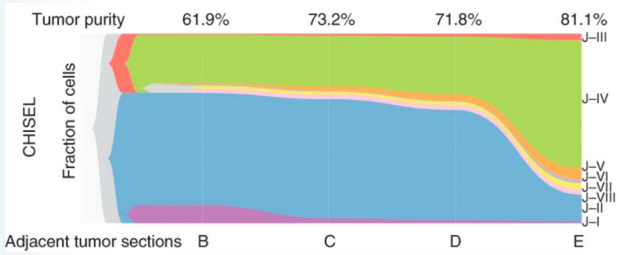
Shared Resources
- Biomedical Informatics

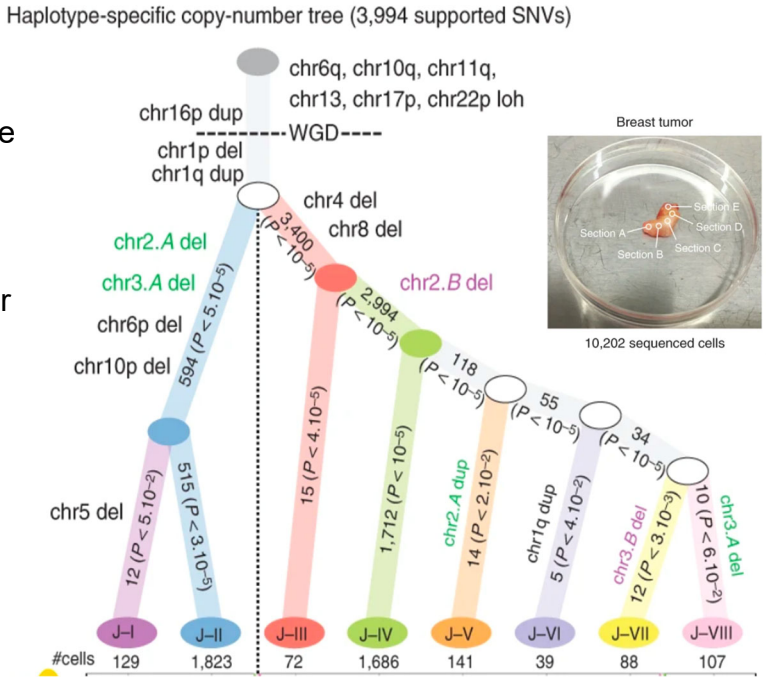
Grants
- U24CA211000
- R01CA233662
- R01GM129066
- R21CA248122

Publications
Khiabanian, *JCO Prec Oncol* 2019
De, *Cell Rep* 2019
Raphael, *Genome Res* 2020
Raphael, *Nat Comm* 2020
Raphael, *Cell Syst* 2020
Raphael, *Nat Biotech* 2021

Major Discoveries

- CHISEL: characterizing allele and haplotype specific copy number alterations in single cells
- SCARLET: single-cell tumor phylogeny inference with copy number-constrained mutation losses
- Detection of distinct clonal populations in cell-free DNA
- Non-genetic intra-tumor heterogeneity is a major predictor of phenotypic heterogeneity and evolutionary dynamics in lung tumors





Impact
Breakthrough in knowledge of how cancers evolve and respond to treatment

Catchment Priority
Relevant to all catchment priority cancers

Clonal Hematopoiesis of Indeterminate Potential (CHIP) in Solid Tumor Microenvironment: Translational Research

AIM 3


Khiabanian (former GICG)


Ganesan (CIPT)


Toppmeyer (CIPT)


Riedlinger (CIPT)

Shared Resources
- Biospecimen Repository and Histopathology
- Biomedical Informatics

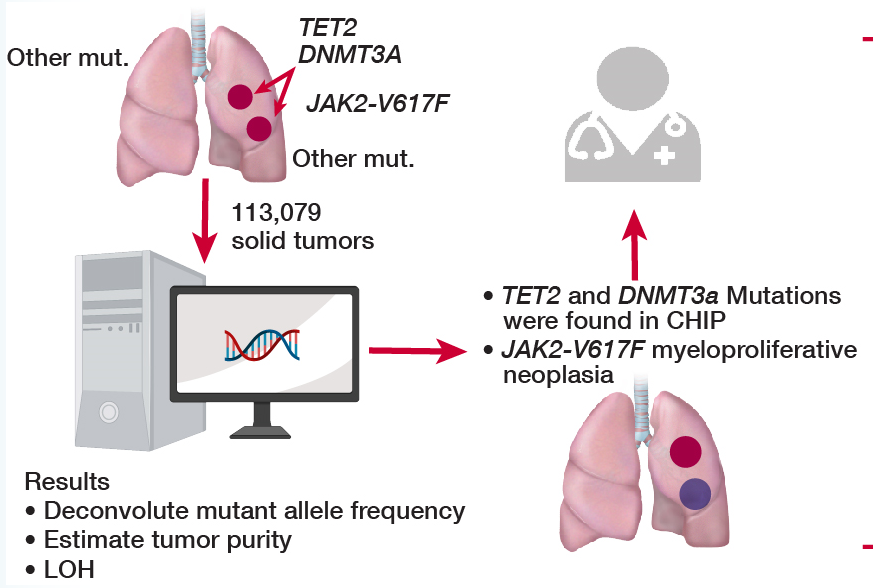
Grants
- R01CA233662

Publications
Severson/Khiabanian, *Blood* 2018
Riedlinger/Khiabanian, *JAMA Oncol* 2019

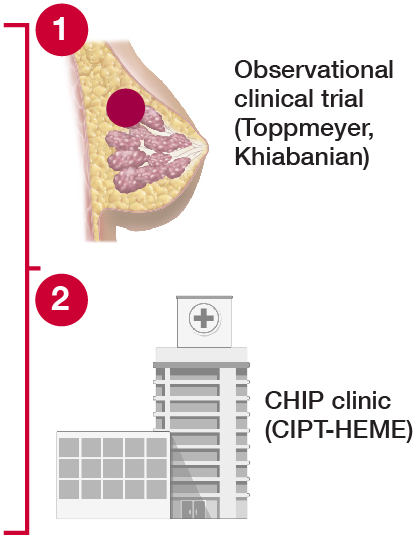
Clinical Challenges

Molecular Tumor Board (MTB) faces challenges in utilizing sequencing data for clinical management of cases with multiple mutations at varying frequencies.

Reverse and Forward Translation



Clinical Translation (CIPT, GICG)



Impact
Analytical tools implemented in the MTB to interpret mutational variants

Catchment Priority
Relevant to all catchment priority cancers

Research Responsive to Catchment Area

Xia
(COE Liaison)

De

Madireddy

Ganesan
(CIPT)

Shared Resources
- Genome Editing
- Biomedical Informatics
- Comprehensive Genomics

Grants
- R01GM129066
- R00HL136870

Publications
De, *Cell Rep* 2019
De, *NAR Cancer* 2021
De, *JCO-PO* 2022
De, *Cancer Cell* 2022
Madireddy, *Nature Medicine* 2022

Major Discoveries

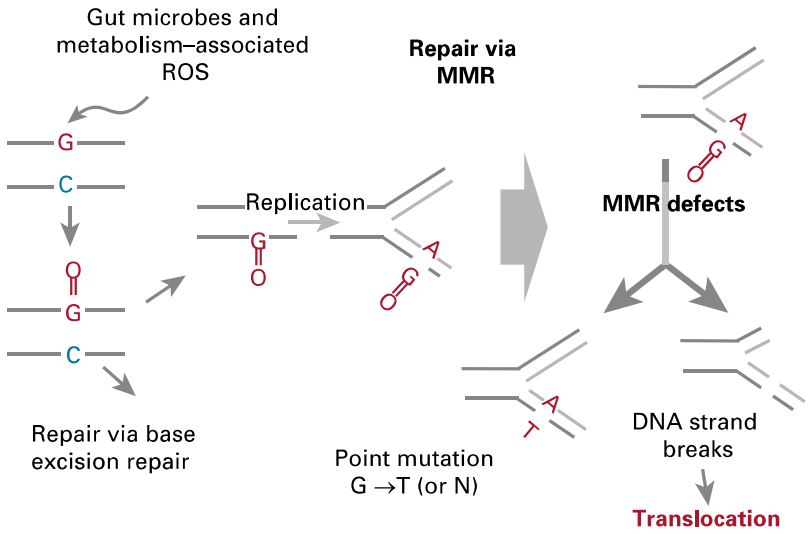
Cancer Types with High Mortality
- Distinct oncogenic fusions associated with clustered oxo-G linked to potential exposure to microbial metabolism in colorectal cancer

Environmental Risk Factors
Dust exposure
- Some NJ and Tri-state area first responders and residents have higher cancer rates from 9-11 fallout dust exposure; dust increased mutation and replication fork speeds (**Madireddy**)

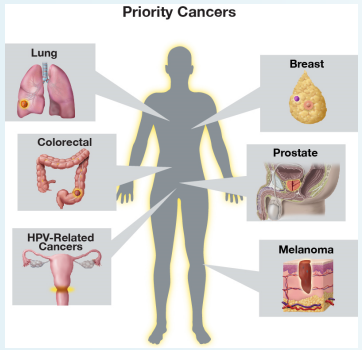
Plastic exposure
- Microplastic pollutants (MPP) were found in NJ river water, which is concerning given the state's long and dense coastline population
- Unique mutation signature found in cells exposed to main components of MPP, as well as in kidney and gastrointestinal cancers of elderly patients **(De)**

Catchment Priority
Colorectal Cancer

Contribution of Gut Microbes in Oncogenic Fusions of Mismatch Repair Defective CRC

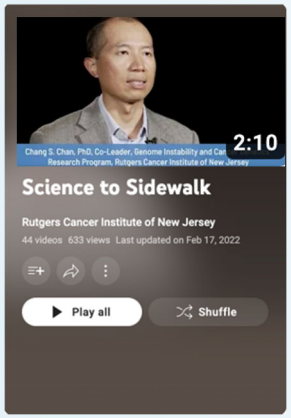


Additional Examples of Catchment Area Responsiveness



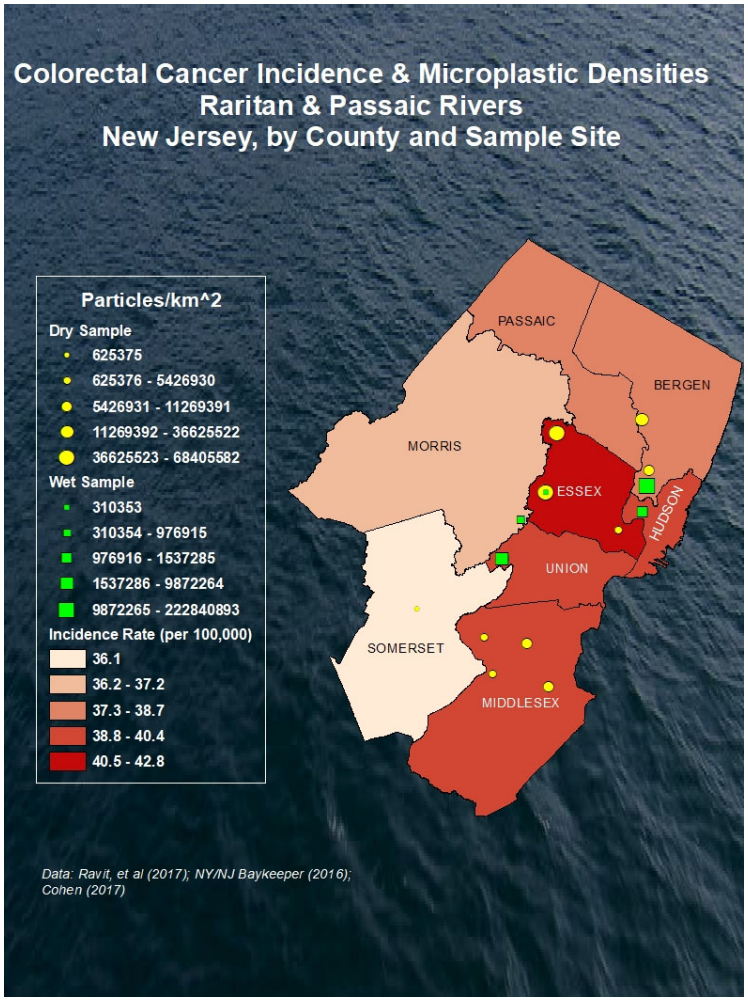
Catchment Area Responsive Research in the Program

- 43% publications and 45% of grants are directly relevant to catchment priorities
- Involves the basic mechanisms of multiple cancer types: breast, colon, lung, etc.
- Addresses multiple cancer risk factors: hereditary, environmental exposure, HPV, etc.



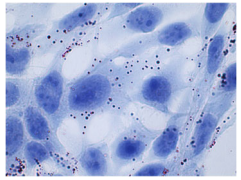
Collaboration and Communication with COE and Community

- COE provided the microplastic pollutant and colorectal cancer data for New Jersey
- Xia, Zhou, Pine, and others participated in COE's Community Science Cafés
- Hu, Madireddy hosted trainees from the community outreach and training program (RUYES)

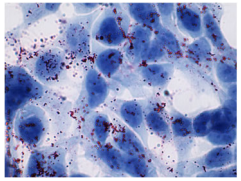


Education and Training within Program

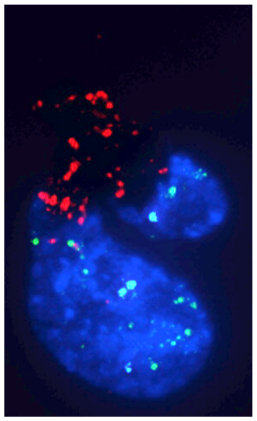
MCF shCtrl + Dox



MCF sh56 + Dox



Shaimaa Hussein
PhD trainee



Eleanor Agosta
MD/PhD candidate

RUYES Field Trip

RUYES community outreach: Linden High School (Hu)

Training Award Mentors/PIs

- NCI-K22 and NCI-K99
- NIH F30, F31 fellowships
- 41 NJCCR postdoctoral/pre-doc fellowships
- Mentors for the CMI T32 postdoc training award
- Hosts for the RUYES program

Research Training

- Graduate students and postdocs: 118 current and 122 new recruits since 2018
- 12% URG trainees (14 current and 15 since 2018)

Directors and Lectures for Major Classes

- Radiation Cancer Biology (2 semesters/ year), req. for Rad Onc residents (Shen/Xia/Hu/Feng)
- Molecular Biosciences graduate program
  - Mini-Course in Molecular Biosciences: p53 (Hu/Feng)
  - Spec Top Cell Mol Pharm: Mol Response Therapeutic DNA Damage (Xia/Shen)
- Guest lectures (Shen, Hu, Feng): NYU Env Carcinogenesis

Value Added: Center to Program

Development Funds

One New Investigator Award
$50,000

REACH Award

Pilot awards including CETI and Cancer Health Equity Awards
$350,000

RWJF Award
(contributed to P01)

Shared Resources

- Genome Editing
- Comprehensive Genomics
- Immune Monitoring/ Flow Cytometry
- Biospecimen Repository and Histopathology Services
- Biostatistics
- Biomedical Informatics

Meetings and Retreats

- Program
- DNA Repair Working Group
- Cancer Genomics Working Group
- PU-RU joint symposia
- Annual Retreats

Center Administration

- Central Laboratory Services
- Grants Office
- Faculty Recruitment
- IST
- Multi-Project Application Support
- Medical Writer Services
- Specialized Research Administrative Support
- Strategic Planning Facilitation
- Workforce Development

Member Recruitment

- 12 new members
- 7 consortium members

PED

Guidance to diversify research teams

COE

Educational sessions and updates on relevant issues at Program meetings

Value Added: Program to Center

Providing foundation for team science

- P01 offers a platform for DNA repair collaborations
- MPI projects
- Multiple inter-institutional teams

Fueling forward and reverse translation and supporting clinical projects

- Rational Neoadjuvant Rx targeting HRD in TNBC
- LIF1 to modulate radiation effects and to protect from GvHD pathologies
- Imputation of tumor purity and CHIP from high-depth clinical sequencing data
- Detection of actionable driver mutations
- Multiple preclinical therapeutic studies under development

- **Addressing multiple catchment priorities:** cancer types and risk factors
- **Education:** mentorship to trainees in R25, T32, and residency programs

PED

12% URG trainees

COE

Multiple community outreach bidirectional communication activities

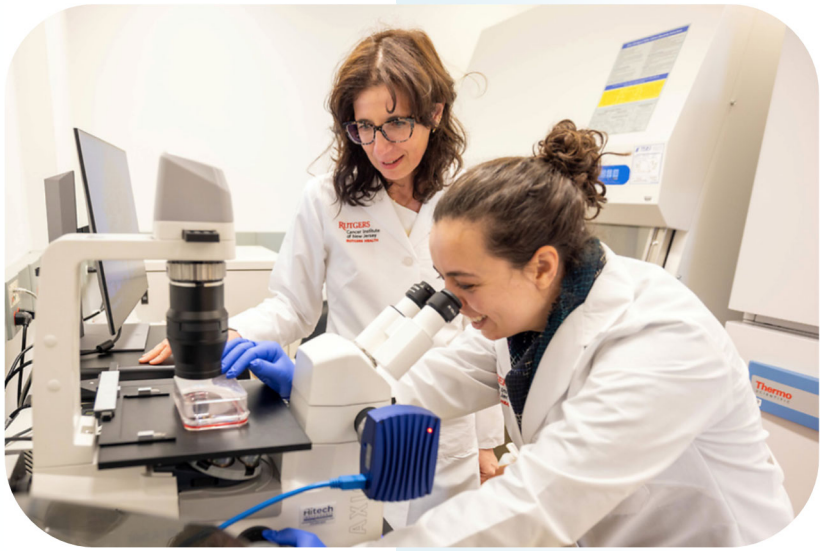
Future Plans

1 Establish new areas of scientific excellence and technological advancement

- Chromosomal instability and tumor microenvironment
- Advanced genomic technologies

2 Promote synergistic team science

- Pilot awards to teams that strengthen consortium collaborations
- Multidisciplinary studies: SPORE in NET; new functions of TP53; additional MPI R01s



3 Expand scope of translational science

- Work with CETI to promote pre-clinical studies
  - Validating new mechanism of mitotic spindle formation as a target for cancer therapy
  - Truncated form of FGFR2 as a therapeutic target
  - DNMT1 inhibitor in MEN1 deficient tumor
  - TOP1, PARP1, G9a inhibitors in BRCAness medulloblastomas and breast cancer
  - CDK6 and aromatase inhibitors in combination with radiotherapy
- Forward- and reverse-translational studies: characterizing new driver variants identified by Precision Oncology

Thank You

Q&A Segment

RUTGERS
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PRINCETON UNIVERSITY

RWJBarnabas HEALTH