Center for Cancer Research Overview

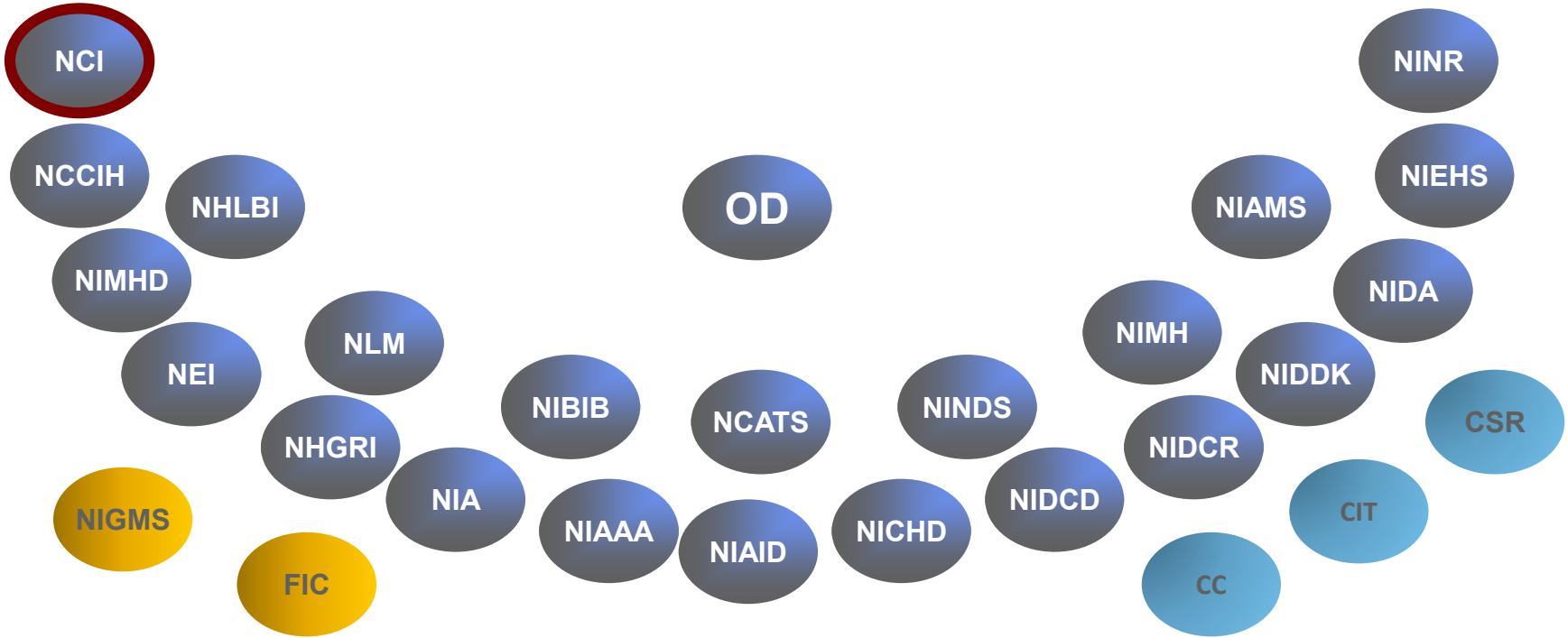
Glenn Merlino, Ph.D.

Scientific Director for Basic Research

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

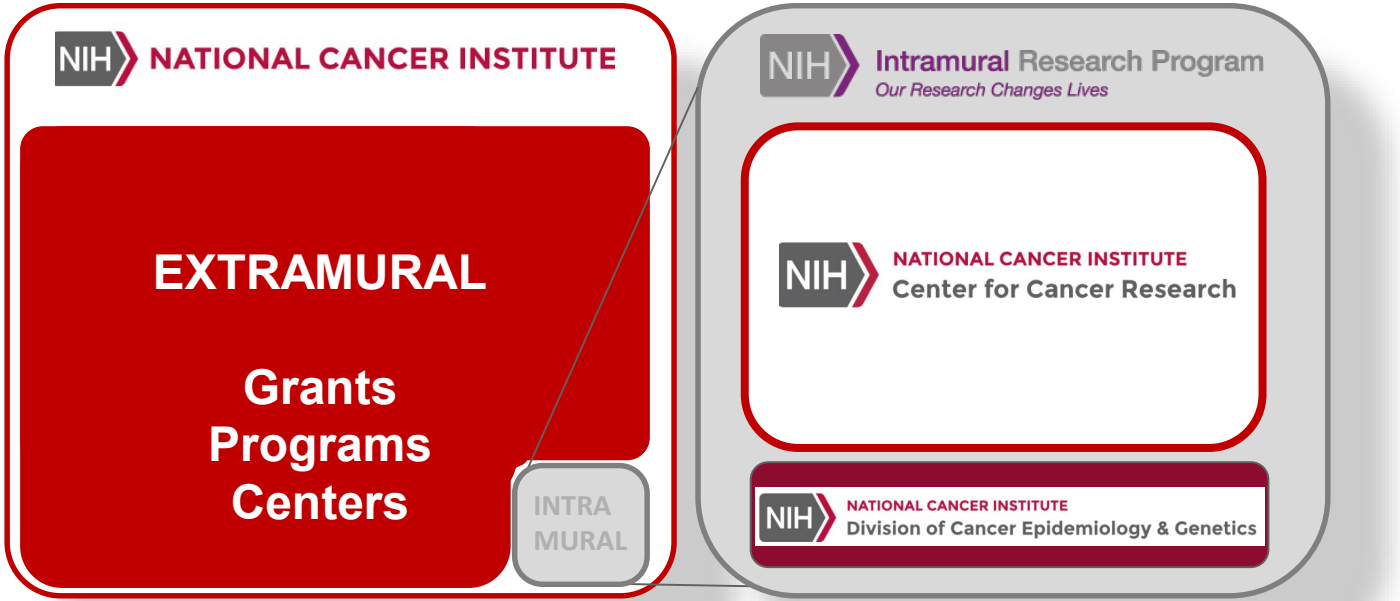
June 2018

The National Institutes of Health



27 Institutes

CCR is part of the Intramural Research Program (IRP) of NIH



Our MISSION

To improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research, prevention and patient care

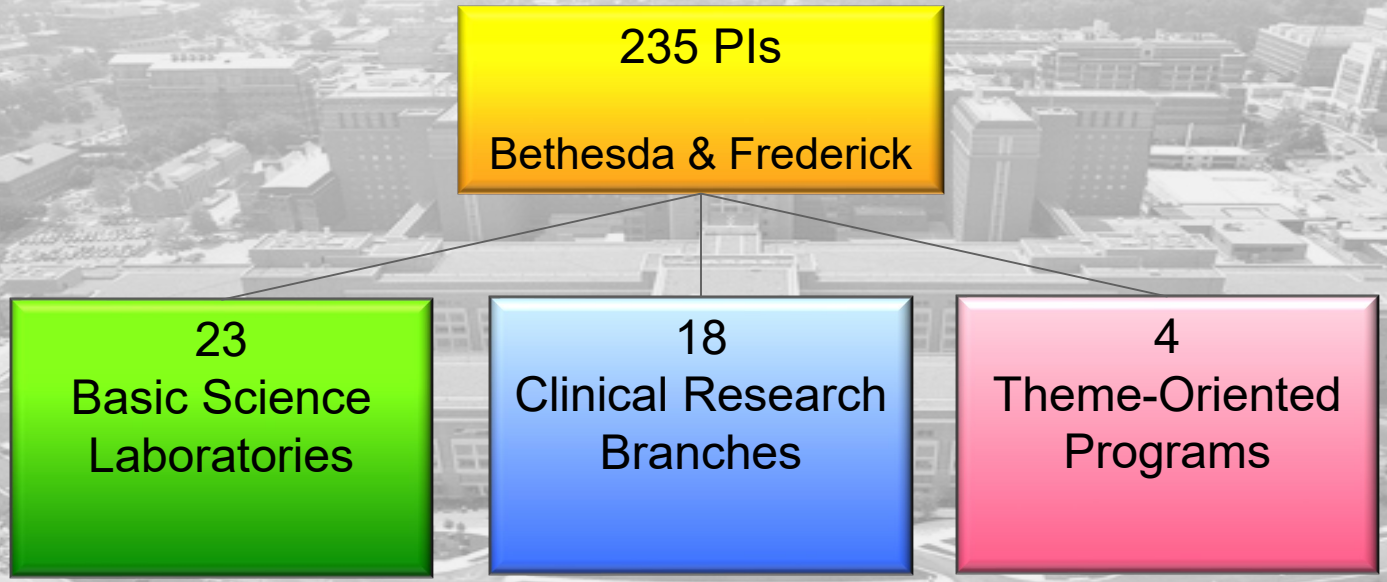
Our VISION

To be the world's leading catalyst for tomorrow's cancer research and patient treatments

Our Strategic Goals

- Be a world-leader in basic, translational and clinical research and patient care
- Maintain an institutional focus on high-risk and long-term projects, unmet needs, and pursuit of unexplored ideas
- Translate our discoveries into novel therapeutic interventions
- Take full advantage of the NIH Clinical Center
- Lead and coordinate national disease networks and development of technology resources for the cancer community
- Partner with academic institutions, commercial entities and patient advocacy groups
- Train the next generation of the biomedical workforce

The CCR in numbers



226 staff scientists/staff clinicians

430 technical lab staff

767 postdoctoral/ clinical fellows

190 postbaccalaureate/ predoctoral students

335 summer students

Cancer Research With A Purpose

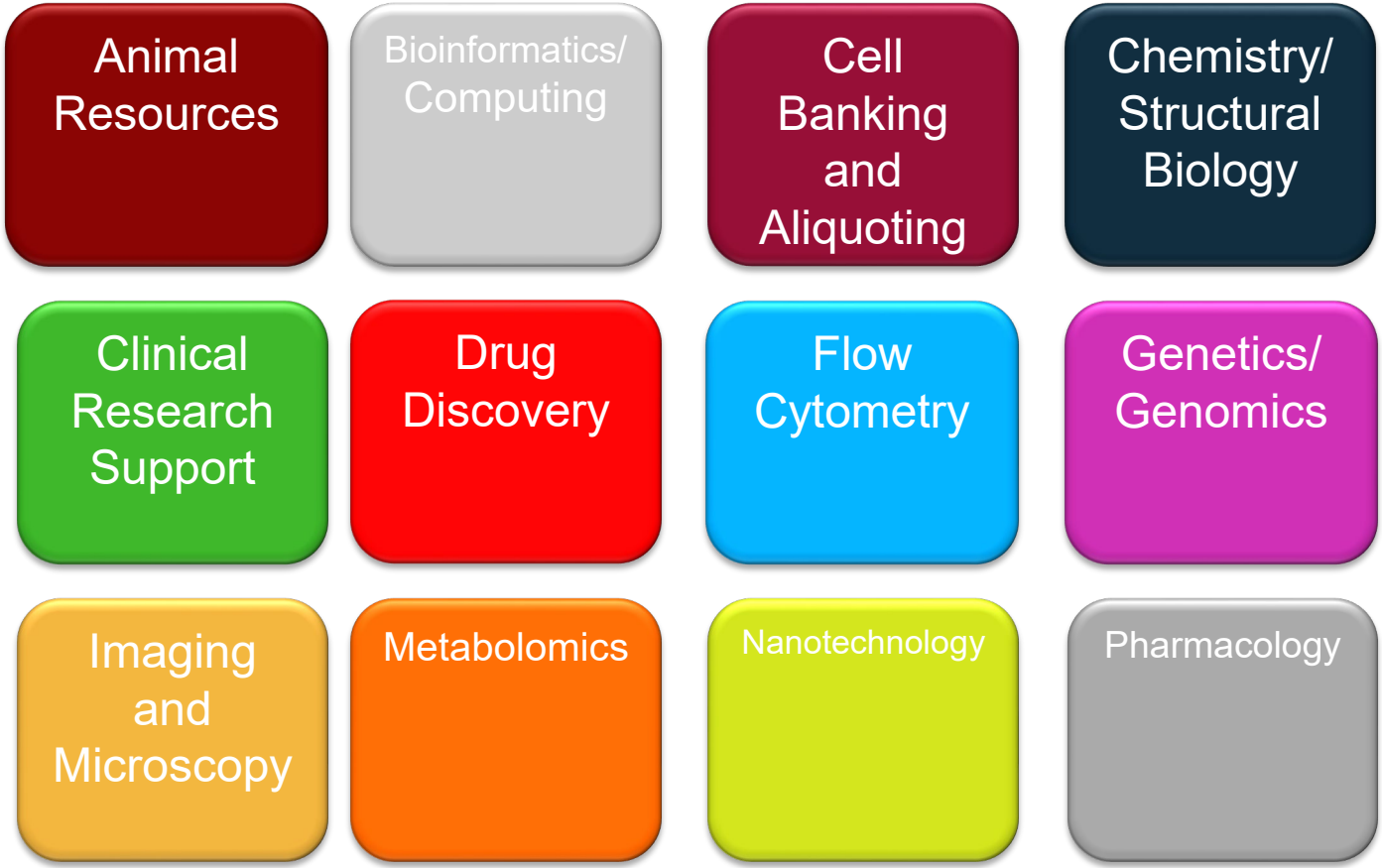
- **Secure resources:** Freedom to pursue most important problems
- **Risk-taking:** We do what others may not do
- **Long time window**: Difficult problems need time
- **Technology development** is encouraged
- **Full spectrum of basic to patient care**
- **Work that might not be possible in the extramural environment** due to limitations in funding, infrastructure, patient populations, “en vogue” topics

The NCI Intramural Clinical Research Program

- The NIH is home to the largest clinical research center in the world
- The NCI is one of its major users
- The NIH clinical center is not a regular hospital

  It is dedicated to patient-intensive clinical research and to develop new approaches for prevention, diagnosis, and treatment of cancer
- The NCI intramural clinical program is a resource for both basic and clinical scientists
- Translate basic discoveries to the point of first-in-human use

CCR Cores


Animal Resources
Bioinformatics/ Computing
Cell Banking and Aliquoting
Chemistry/ Structural Biology
Clinical Research Support
Drug Discovery
Flow Cytometry
Genetics/ Genomics
Imaging and Microscopy
Metabolomics
Nanotechnology
Pharmacology

Examples of groundbreaking CCR research

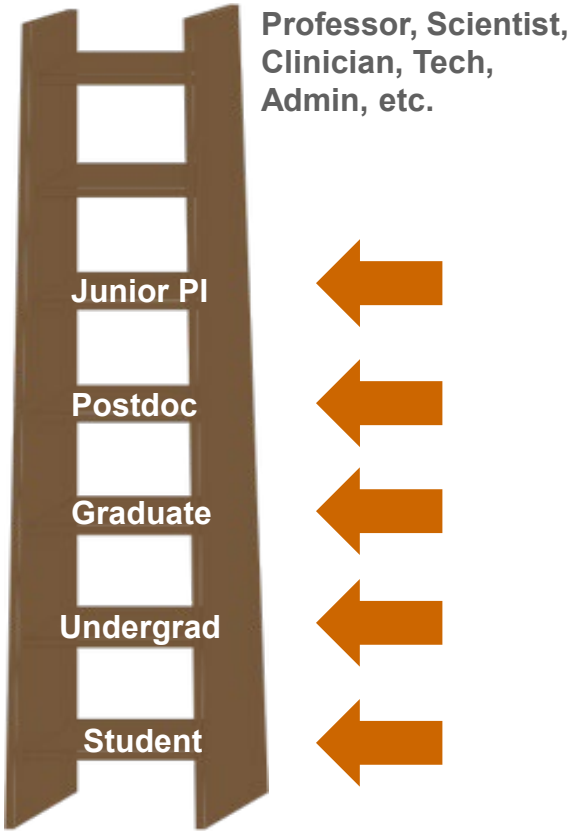
- Human Papilloma Virus
- Gene therapy
- Immunotherapy
- Imaging methods (basic and clinical)
- Chromatin biology

CCR Training

CCR offers training to young scientists at several levels of education:

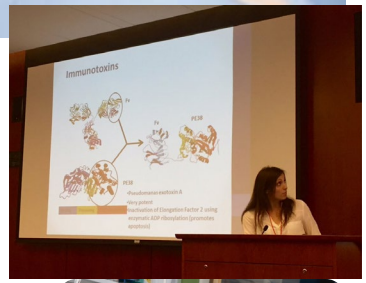
Training programs exist for:

- High School students
- College students
- Post Baccalaureate students
- Veterinary School students
- Medical and Dental School students
- Post Doctoral Training -- Ph.D. / D.V.M.
- Post Doctoral Training -- M.D.
- Clinical Fellowship Program



Why Train at the NIH?

- State-of-the-art laboratory facilities, technology, and equipment
- Scientific and professional skills workshops and training
- Lectures and courses by eminent scientists
- Mentoring in a collaborative, team-focused environment
- Competitive stipends, paid leave, and medical insurance



Specialty CCR Programs

- Johns Hopkins University partnership in Drug Discovery Technologies
- Associate Clinical Investigator Development Program
- NCI/FDA Interagency Oncology Task Force (IOTF) Research and Regulatory Review Fellowship
- Summer Cancer Research Interns (CRI) Program for students from underrepresented groups or disadvantaged backgrounds
- Comparative Molecular Pathology Research Training Program
- Sallie Rosen Kaplan fellowship program to retain women in independent science careers
- Center for Cancer Training, Intramural Workforce Diversity Branch to increase scientific workforce diversity

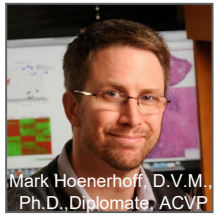
https://ccr.cancer.gov/training

Graduates

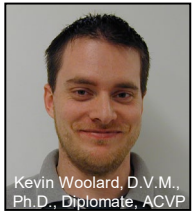
CBTP NIH

Comparative Biomedical Scientist Training Program

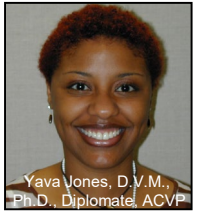
NCI / Univ. of Maryland
Associate Director of The Center for Comparative Medicine Research
Wake Forest University



NCI / Michigan State Univ.
Tenure Track,
Asst. Professor
University of Michigan



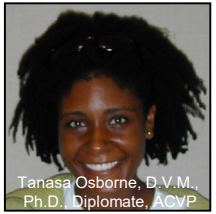
NCI / NC State University
Tenure Track,
Asst. Professor
UC, Davis



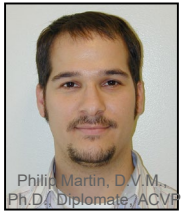
NCI / Michigan State Univ.
Tenured,
Assoc. Professor
Purdue University

NIDDK/ Michigan State Univ.
Veterinary Pathologist
Charles River CRO

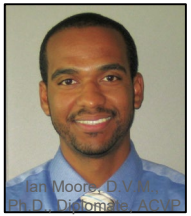
NCI / Univ. of Maryland
Tenure Track,
Asst. Professor
North Carolina State Univ.



NCI / Univ. of Illinois
Project Pathologist
Novartis



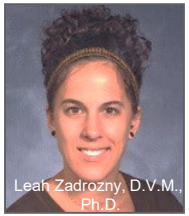
NCI / Univ. of Maryland
Investigative Pathologist
MedImmune/
AstraZeneca, Inc.



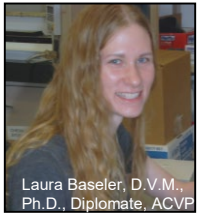
NIAID/ Michigan State Univ.
Staff Scientist
NIAID

NIAID/ NC State University
Tenure Track,
Asst. Professor
Kansas State University

NCI / Michigan State Univ.
Veterinary Pathologist
Center for Disease Control

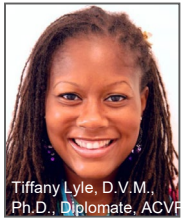


NHLBI/ NC State University
Staff Fellow /
Veterinary Pathologist
Food & Drug Administration



NIAID / Purdue University
Veterinary Pathologist,
Univ. British Columbia and
Asst. Professor,
MD Anderson Cancer Ctr

NCI / Michigan State Univ.
Pathologist /
St. Jude Children's
Research hospital



NCI / Purdue University
Tenure Track,
Asst. Professor
Purdue University

NCI / Univ. of Maryland
Veterinary Pathologist
ToxPath Specialists, LLC

Global Impact on Science

Harold Varmus
Former Director NIH, NCI

Distinctive NCI alumni are contributing across the globe

- Three Nobel laureates
- Department chairs for over 100 U.S. medical centers and universities
- Leaders of many biotechnology companies
- Leaders at NCI-cancer centers (21% of current directors)

Doug Lowy & John Schiller
Lasker awardees

Kenneth Olden
Former Director NIEHS

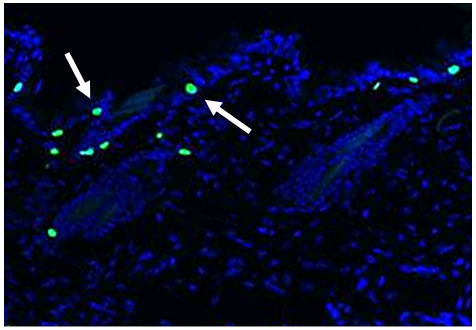
Modeling the Genesis, Progression and Treatment of Human Melanoma in the Mouse

Reproduce human oncogenic drivers by genetically engineering

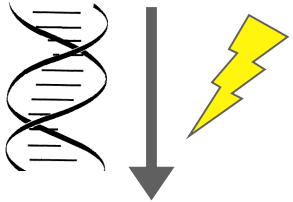
- $BRAF^{V600E}$ – 50% patients
- $NRAS^{Q61K}$ – 20% patients
- wt BRAF/NRAS – 30% patients

↓

Aberrant MET activation in HGF^{tg} mice (human relevance)



Humanized Mouse Skin
(HGF^{tg} ; Dct-rtTA^{tg}/TRE-GFP^{tg})



Cutaneous Malignant Melanoma

Reproduce human environmental insults using a UV lamp

Intermittent burning doses of UV during childhood

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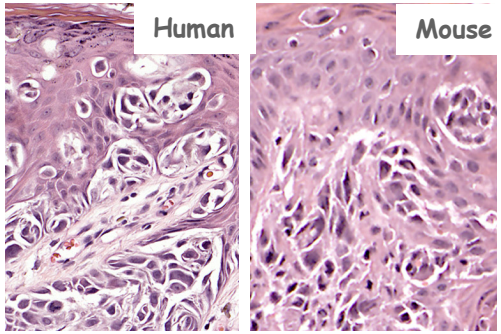
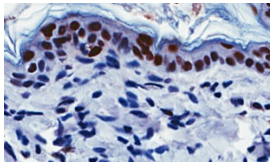
Mouse tumors arise resembling human melanoma



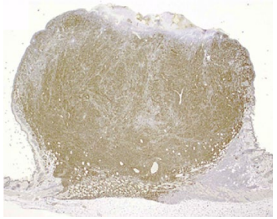
RGP Pagetoid Spread
(HGF^{tg} + UV)

Study of the genesis and progression of mouse lesions resembling human melanoma

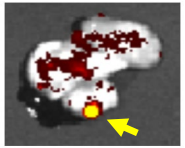
Nevi (GFP)

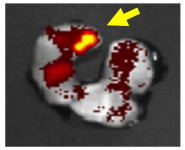


RGP melanoma (GFP)

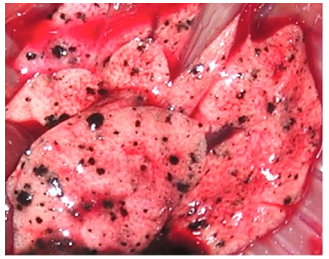


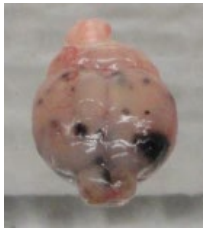
Nodular melanoma (DCT)



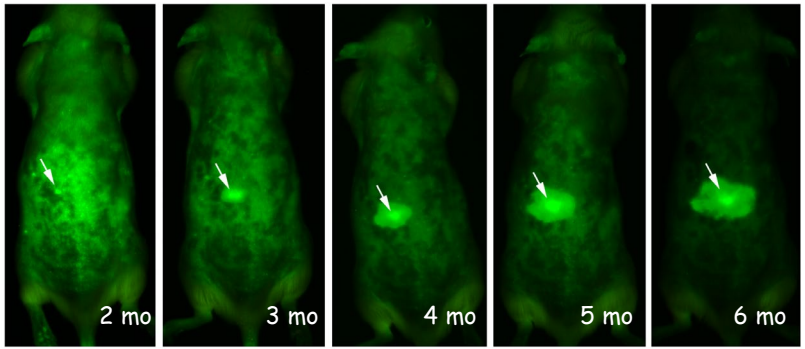


Lung & liver metastases





Recent identification of cell lines with high propensity for brain metastasis



RGP superficial spreading melanoma (GFP)

Helen Michael

Chi-Ping Day

Modeling diversity in melanomas and their responses to immune checkpoint inhibitors for mechanistic insight and preclinical analysis

Tumor Model	GM1	GM2	GM3	GM4
Cell line	**M114433**	**9013B**	**HM1274**	**B2095**
Mouse strain	Albino C57BL/6	C57BL/6	C57BL/6	C57BL/6
Genotype	$Braf^{CA/+}$; $Pten^{flox/+}$; $Cdkn2a^{flox/+}$; Tyr-Cre^{ERT2}-tg	$Braf^{CA/+}$; HGF-tg; $Cdkn2a^{flox/+}$; Tyr-Cre^{ERT2}-tg	HGF-tg; $Cdk4^{R24C}$	HGF-tg
Dominant driver genes	$Braf^{V600E}$ and PI3K (Pten deletion)	Braf and HGF/Met	HGF/Met and $Cdk4^{R24C}$	HGF/Met
Tumor Induction	UV	UV	DMBA	UV
Anti-CTLA-4 Response	**Non-responder**	**Non-responder**	**Partial responder**	**Sensitive**
Collaborators	Martin McMahon & Marcus Bosenberg	Martin McMahon & Marcus Bosenberg	Thomas Tueting	Frances Noonan & Ed DeFabo

- Different platforms for the study of immunotherapies in immunocompetent mice
  - ✓ Tumor pieces (never in culture) implanted in syngeneic mice
  - ✓ Cell lines derived from original tumors
  - ✓ Tumors generated from cell lines implanted in syngeneic mice
- Molecular characterization of the melanoma mouse models
- Comparative analysis of the responses to anti-CTLA-4
- Identification of factors/pathways influencing response to anti-CTLA-4
- Compare and contrast mouse model data with human clinical experience

Chi-Ping Day
Eva Perez
Cari Graff-Cherry
CAPR

Summary of our preclinical findings compared to the clinical observations

Clinical findings	Mouse melanoma models
• T cell infiltration in tumors during ICI (Anti-PD-1) correlates to better responses (but not predictive)	• CD8 T cell profiles in the tumors were not predictive of α-CTLA-4 response
• High mutational and neoantigen load is associated with clinical benefit of ICI (controversial)	• Tumor immunogenicity, but not mutational and neoantigen load, was correlated with α-CTLA-4 response
• Alterations in antigen presentation and IFNg pathways have been found in patients resistant to immunotherapies	• Antigen presentation pathway was functional and similarly induced in the four models
• Induction of immunosuppressive microenvironment in patients not responding to ICI	• Immunosuppressive profiles were markedly higher in non-responder models (e.g., M2 macrophages and induction of immune checkpoints)

How to start your career with us

@NCIResearchCtr

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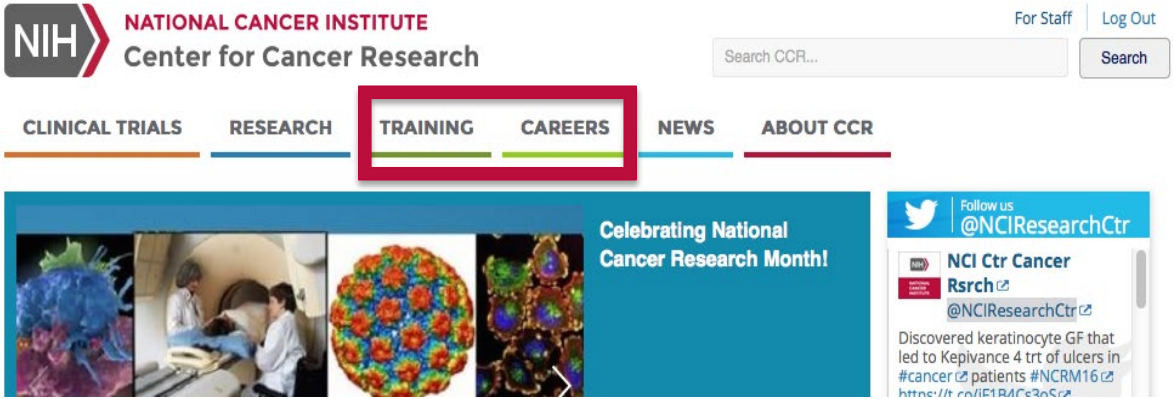

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https://ccr.cancer.gov/careers