Professional Development and Mock Review Workshop

*Training for Independence: Academic Job Search Success*

Graduate Student Special Session
NCI Intramural Investigator Flash Talk Presentations
United We Stand, Divided We Fall: Mitosis and Disease in Human Cells

Poster Number 2
Udayan Guha, MD, PhD

Center for Cancer Research
Thoracic and GI Malignancies Branch
Investigator
Head, Cancer Signaling Networks Section

Tumor Heterogeneity and Targeted Therapy Resistance

Poster Number 5
Most common EGFR mutations and EGFR-tyrosine kinase inhibitors (TKIs)

EGFR TKIs

1\textsuperscript{st} generation:
- gefitinib
- erlotinib

2\textsuperscript{nd} generation:
- afatinib
- dacomitinib

3\textsuperscript{rd} generation:
- osimertinib
- BI 1482694
- rociletinib

- EGFR TKI-sensitizing mutations
  - L858R
  - Del EGFR

- EGFR TKI-resistant mutation
  - T 790 M (60% of resistance)

\textbf{C797S}
\textbf{L718Q, L844V}
Influence of tumor heterogeneity on targeted therapy resistance

Resistance Mechanisms: A and "others"

Resistance Mechanism: A

What are A & Others??
A multipronged approach from the bench to bedside- multi-"omics" approach and disease modeling to study targeted therapy resistance

Lung adenocarcinoma cells in culture → Mouse models in vivo (GEM and orthotopic) → Human tissues-biopsy, surgery and rapid autopsy

Genomics

Quantitative mass spectrometry-based proteomics
Christian S. Hinrichs, MD

Center for Cancer Research
Experimental Transplantation and Immunology Branch
Investigator
Lasker Clinical Research Scholar

Adoptive T Cell Therapy for Cancer

Poster Number 6
Transgenes to enhance function

TCR discovery and enhancement

Single-cell genomics to identify effective cells

Target discovery for new treatments

Investigation of tumor genomics and the tumor microenvironment to understand response/resistance

Study of therapeutic T cells in vivo

Rational therapeutic combinations to improve treatment

Jing Huang, PhD

Center for Cancer Research
Laboratory of Cancer Biology and Genetics
Senior Investigator
Head, Cancer and Stem Cell Epigenetics Section

p53 in Mesenchymal Stem Cells and Osteosarcoma

Poster Number 7
Osteosarcoma Is a Devastating Cancer for Children and Young Adults

- Osteosarcoma (OS) is one of the leading causes of cancer-related death in pediatric patients.

- Challenges of OS treatment
  1) No FDA-approved targeted therapy.
  2) Current standard of care is the same as 30 years ago.
  3) Metastasis decreases 5-year survival to around 25%.
  4) Current immune checkpoint inhibitors are not effective.

- Osteosarcoma is included in the Rare Tumor Initiative at CCR in NCI.
Study p53 in Mesenchymal Stem Cells to Understand Osteosarcoma

Stresses: UV, IR, Hypoxia, Oncogene overexpression, UPR, Virus

Targets: p53, Tumor suppression and development, Differentiation, Apoptosis, Senescence, Metabolism, DNA repair

MSCs: Osteocytes, Chondrocytes, Adipocytes, Abnormal p53

Osteosarcoma cells
Jennifer C. Jones, MD, PhD

Center for Cancer Research
Laboratory of Pathology
NIH Earl Stadtman Investigator (Pending)

Extracellular Vesicles for Precision Medicine: A New Frontier, New Challenges, and Revolutionary Potential

Poster Number 8
Extracellular Vesicles (EVs): Multidimensional Packets

**KEY**
- Tetraspanin (CD9, CD63, CD81)
- microRNA
- Uptake signal (ligand, antigen, etc.)
- Receptor (cell surface receptors, MHC, etc.)

**Stimuli**
- γ-irradiation
- Hypoxia
- Heparanase
- Calcium ionophores
- Statins
- Low pH
- Detachment

**MVB**
- Exocytic MVB
- Exosomes
- Rab27A
- Rab27B

**ESCRT**
- Lysosome

**ILVs**
- Ceramide

**Endocytosis**
- Exosome Release
- microRNAs
- let-7 family
- miR-92a
- miR-141
- miR-223
- miR-494
- miR-542-3p
- miR-21
- miR-29a
- miR-101?

**Target mRNA 3’UTR**
- Translational Repression/ mRNA Degradation

**Effects**
- Growth/Proliferation (TAK1)
- Inflammation/Immune Response (Toll-like receptors-MAPK, NFκB)
- Epigenetic Reprogramming (EZH2)
- Angiogenesis/Endothelial Cell Activation (VEGF, VEGFR, MMPs)
- Invasion (β-catenin)
- Pre-Metastatic Niche (ECM remodeling proteins)
- Metastasis (MMPs)
Translational Exosome, EVs Analysis Pipeline

A. Sample

B. Isolation

C. General EV Size, Concentration, and Cargo Assays
- Protein Concentration
- Western Blot (Tsg101, Alix)
- Nanoparticle Tracking Analysis

D. Multiplex EV Assay: > 20 Epitope Survey

E. High Resolution EV Analysis

F. nanoFACS Sorting

G. mRNA, miRNA
Daniel W. McVicar, PhD

Center for Cancer Research
Deputy Director for Basic Science, Cancer and Inflammation Program
Head, Leukocyte Signaling Section
CCR Deputy Director

Identification of Macrophage Irg-1 as Possible Target in Ovarian Cancer

Poster Number 9
Sharon Savage, MD

Division of Cancer Epidemiology and Genetics
Chief, Clinical Genetics Branch
Senior Investigator
DCEG Clinical Director

Research Opportunities in Clinical Cancer Genetics

Poster Number 11
The Clinical Genetics Branch
“Saving lives & improving quality of life for individuals at increased genetic risk of cancer”

**Discovery** in High Risk Individuals
- Clinical
- Genetic
- Epidemiology

**Clinical Translation** to Different Populations
- High-Risk Individuals
- General Population

**Direct Application** to Clinical Care
- Clinical Care
- Clinical Guidelines

**Cross-Cutting Collaborations**
The Clinical Genetics Branch
“Saving lives & improving quality of life for individuals at increased genetic risk of cancer”

Family Studies

• Inherited Bone Marrow Failure Syndromes
• *DICER1*-related Pleuropulmonary Blastoma Cancer Predisposition Syndrome
• Li-Fraumeni Syndrome
• Familial Testicular Cancer
• Neurofibromatosis Type 1
• Familial Melanoma
• Lymphoproliferative Diseases
• Familial Chordoma
• Psychosocial studies across all syndromes

Molecular Epidemiology

• Transplant outcomes in aplastic anemia and leukemia
• Pediatric cancer genetic susceptibility
• Upper gastrointestinal malignancies
• Myotonic dystrophy and cancer susceptibility
• Rare tumors
• Viral genomics

savagesh@mail.nih.gov
Allan M. Weissman, MD

Center for Cancer Research
Chief, Laboratory of Protein Dynamics and Signaling
Senior Investigator

Functions of the Ubiquitin-Proteasome System in Health and Disease

Poster Number 13
Ubiquitin-Proteasome System (UPS)

Tumor suppressors
Proto-oncogenes
Cell cycle regulators
Receptors
Transporters
Channels
Transcription factors
Kinases
Histones

All of the basic UPS components represent potential therapeutic targets!

E1: ubiquitin-activating enzyme; E2: ubiquitin-conjugating enzyme; E3: ubiquitin ligase; DUB: deubiquitinating enzyme
Weissman Lab: Areas of Focus in the Ubiquitin-Proteasome System

E2-E3 structure-function relationships

ER-associated degradation (ERAD)

Mitochondria-associated degradation (MAD)

---

Characteristic | Significance (p value)
---|---
Race (Black>White) | .013
Low 3 yr. survival | <.001
Lymph node positive | <.050
Triple negative | <.001

High gp78 levels in breast cancer....

---

Poster #13 – M. Iveth Garcia
Nicolas Wentzensen, MD, PhD, MS

Division of Cancer Epidemiology and Genetics
Deputy Chief, Clinical Genetics Branch
Senior Investigator
Head, Clinical Epidemiology Unit

Clinical Epidemiology: Translating Etiologic Discoveries to Clinical and Public Health Applications

Poster Number 14
Translating evidence to clinical practice

- Translating evidence to clinical practice is a long process, most discoveries do not make it
- Careful assessment of clinical implications is necessary before implementation of public health and clinical guidelines
- Areas of work:
  - Biomarker discovery and translation
  - Risk prediction
  - Big data from epidemiologic studies and electronic health records
  - Methods development
  - Development of clinical guidelines

Identify key questions

Individual Studies
- Clinical Trials
- High-quality observational studies
- Medical record data

Synthesis
- Systematic Reviews
- Meta-Analyses

Models
- Cost-effectiveness
- Clinical effectiveness

Implementation
## A Clinical Epidemiology Framework

<table>
<thead>
<tr>
<th>Component</th>
<th>Important Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health burden</td>
<td>- Prevalence, incidence and mortality rates and trends</td>
</tr>
<tr>
<td></td>
<td>- Demographics</td>
</tr>
</tbody>
</table>
Bríd M. Ryan, PhD, MPH

Center for Cancer Research
Laboratory of Human Carcinogenesis
Investigator
NIH Earl Stadtman Investigator

Integrative and Translational Epidemiological Studies of Lung Cancer Health Disparities