Professional Development and Mock Review Workshop

Training for Independence: Academic Job Search Success

Graduate Student Special Session
NCI Intramural Investigator Flash Talk Presentations
Yamini Dalal, PhD

Center for Cancer Research
Laboratory of Receptor Biology and Gene Expression
Senior Investigator
Group Director, Chromatin Structure and Epigenetic Mechanisms Group

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
- dacominib

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

\begin{itemize}
  \item \textbf{EGFR TKI-sensitizing mutations}
    \begin{itemize}
      \item L858R
        \begin{itemize}
          \item (85%)
        \end{itemize}
      \item Del EGFR
    \end{itemize}
  \item \textbf{EGFR TKI-resistant mutation}
    \begin{itemize}
      \item T 790 M (60% of resistance)
    \end{itemize}
\end{itemize}
Influence of tumor heterogeneity on targeted therapy resistance

Resistance Mechanisms:
- A and “others”
- L858R

Erlotinib

6 weeks

13 months

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**

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2018 Professional Development and Mock Review Workshop
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

Rational therapeutic combinations to improve treatment

Study of therapeutic T cells in vivo

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

Target discovery for new treatments

T-Cell Infusion

Tumor Targeting

Manipulation of TCR

Retrovirus

TCR Gene

Engineered TCR

Apheresis Product

T Cell

Natural TCR

Patient

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: Differentiation, Apoptosis, Cell cycle arrest, Senescence, Metabolism, DNA repair
- MSCs
- Tumor suppression and development
- Abnormal p53
- Osteosarcoma cells
- Adipocytes
- Chondrocytes
- Osteocytes
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

**ESCRT**
- Lysosome
- ILVs
- MVB
- Ceramide
- Rab27A
- Rab27B

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

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

PSMA PET (DCFBC)
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

26S proteasome

- E1: ubiquitin-activating enzyme
- E2: ubiquitin-conjugating enzyme
- E3: ubiquitin ligase
- DUB: deubiquitinating enzyme

- lysosomal degradation
- autophagy
- DNA repair
- kinase activation
- transcription
- etc.

All of the basic UPS components represent potential therapeutic targets!
Weissman Lab: Areas of Focus in the Ubiquitin-Proteasome System

E2-E3 structure-function relationships

ER-associated degradation (ERAD)

Mitochondria-associated degradation (MAD)

High gp78 levels in breast cancer....

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Significance (p value)</th>
</tr>
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<tbody>
<tr>
<td>Race (Black&gt;White)</td>
<td>.013</td>
</tr>
<tr>
<td>Low 3 yr. survival</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>&lt;.050</td>
</tr>
<tr>
<td>Triple negative</td>
<td>&lt;.001</td>
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</tbody>
</table>

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>

Wentzensen and Clarke Cancer 2017
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Investigator
NIH Earl Stadtman Investigator

Integrative and Translational Epidemiological Studies of Lung Cancer Health Disparities