Recent Advances in Cancer Research and Therapeutic Approaches

Leonidas C. Platanias, MD, PhD
Cancer

Edwin Smith Papyrus
1600 BC - Ancient Egypt

Hippocrates of Kos
460-370 BC

“Athe veins stretched on all sides as the animal the crab has its feet”

Aulus Cornelius Celsus
25 BC- 50 AD
Advances in Cancer Research and Treatment - Past

Radiation Therapy – late 1800s

Wilhelm Conrad Röntgen

Pierre and Marie Curie

Niels Ryberg Finsen

1900 – Finsen Lab
Advances in Cancer Research and Treatment - Past

Chemotherapy – 1940s

Sidney Farber

Combination Chemotherapy – 1960s

George Canellos-Vincent DeVita-Robert Young (1971)
Advances in Cancer Research and Treatment - Past

Stem Cell Transplant – 1970s

Georges Mathé

E. Donald Thomas
Advances in Cancer Research and Treatment

Precision Medicine
Nanotechnology
Epigenetics
Immunotherapy
Precision Medicine and Therapeutic Targeting
One Size does not fit all

<table>
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<tr>
<th>Medicine Type</th>
<th>Failure Rate</th>
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<td>Antidepressants (SSRIs)</td>
<td>38%</td>
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<td>Asthma drugs</td>
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<td>Diabetes drugs</td>
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<td>Arthritis drugs</td>
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<td>Alzheimer's drugs</td>
<td>70%</td>
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<td>Cancer drugs</td>
<td>75%</td>
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Lung Cancer - Molecular Abnormalities
Current Approach

Patients with a "type" of cancer

Standard Therapy
Few patients respond to therapy
Most patients fail therapy
Inadequate response
No response
Develop resistance
Future Approach
# Integrative Genomic Analysis of Wilms Tumor


## The genetic landscape of Favorable Histology Wilms Tumor

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**Genomic Core**

ARRA TARGET; U10CA98543
Integrative Genomic Analysis of Wilms Tumor


The combination of two rare mutations results in poor clinical outcome

E. Perlman

miRNAPG and SIX
miRNAPG only
others
SIX only

Disease Free Survival

Logrank Test p = 0.0001

Years

SIX 1/2
DROSHA
XPO5
DICER1
DGCR8
Increased HoxA9/10 correlates with Fgf2-dependent cytokine hypersensitivity in AML

Clinical trial: 5-Azacitidine + Nintedanib

mRNA expression: CD34+ bone marrow cells (control versus AML\textsuperscript{low} versus AML\textsuperscript{high})

Flow Cytometry, Developmental Therapeutics, Mouse Histology and Phenotyping, Proteomics, High Throughput Analysis, ChemCore
Advances in Cancer Research and Treatment

Epigenetics and Nuclear Dynamics
Histone H3 Lysine to Methionine Mutants in Malignancies

Nature Genet 2017; Science 2014; | Nature Med 2017; Genes Dev 2017

A. Shilatifard

N. Kelleher (MOM)  C. D. James (TRIST)

S. Goldman (TRIST)

R01CA089455; P41GM108569; R35CA197569

Proteomics Core Facility, Developmental Therapeutics Core, Quantitative Data Sciences
Advances in Cancer Research and Treatment
Nanotechnology
Nanotechnology - From the lab to the treatment of solid tumors

First in Human - Phase 0 clinical trial
BCL2L12- targeting SNAs
NCT03020017 - ongoing - 3 patients enrolled so far
Anticipated accrual 8 patients and then move to Phase I

Crossing the blood brain-barrier in animal models
siRNA-based SNAs

Tumor weight (mg)
Co
siCo
siBcl2L12

P<0.001

miRNA-based SNAs
Co-miR
miR-182

P<0.013

U54 CA151880, R01CA208783, the American Cancer Society Research Scholar Award
Flow Cytometry, Mouse Histology and Phenotyping, Pathology, Center for Advanced Microscopy

Tumor Environment and Immunotherapy
Coley's toxin

Sometimes referred to as MBV for mixed bacterial vaccine, Coley's toxin was the first attempt to use immunotherapy and hyperthermia against cancer. William D. Coley, MD, a bone surgeon at MSK from 1893 to 1936, developed interest when his first patient, a young girl died from metastatic carcinoma.

New York Times - July 29, 1908

ERYSIPelas GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Lou's that two men have been cured of cancer in the City Hospital there by the use of a fluid 'discovered by Dr. William B. Coley of New York. It came out yester-
TIME
INTERFERON
The IF Drug For Cancer
The Case for Cancer Cellular Therapy

- Immunotherapy is a “living drug”
- Immune system can evolve to treat the tumor
- Immunotherapy can cure some cancers

http://www.cancerresearch.org/
Checkpoint Inhibitors

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
CAR T cells

CAR T-cell Therapy

1. Remove blood from patient to get T cells
2. Make CAR T cells in the lab
   - Insert gene for CAR
   - Chimeric antigen receptor (CAR)
3. Grow millions of CAR T cells
4. CAR T cells bind to cancer cells and kill them
5. Infuse CAR T cells into patient

https://www.cancer.gov/
CAR T manufacturing and administration

*large range on timing for processing

Future Approaches in Cancer Therapy

• New Immunotherapeutic Modalities
• New Targeted Agents
• Combinations of Therapeutic Approaches

We are still missing something significant in order to develop definitive curative treatments for all cancers
Thank You